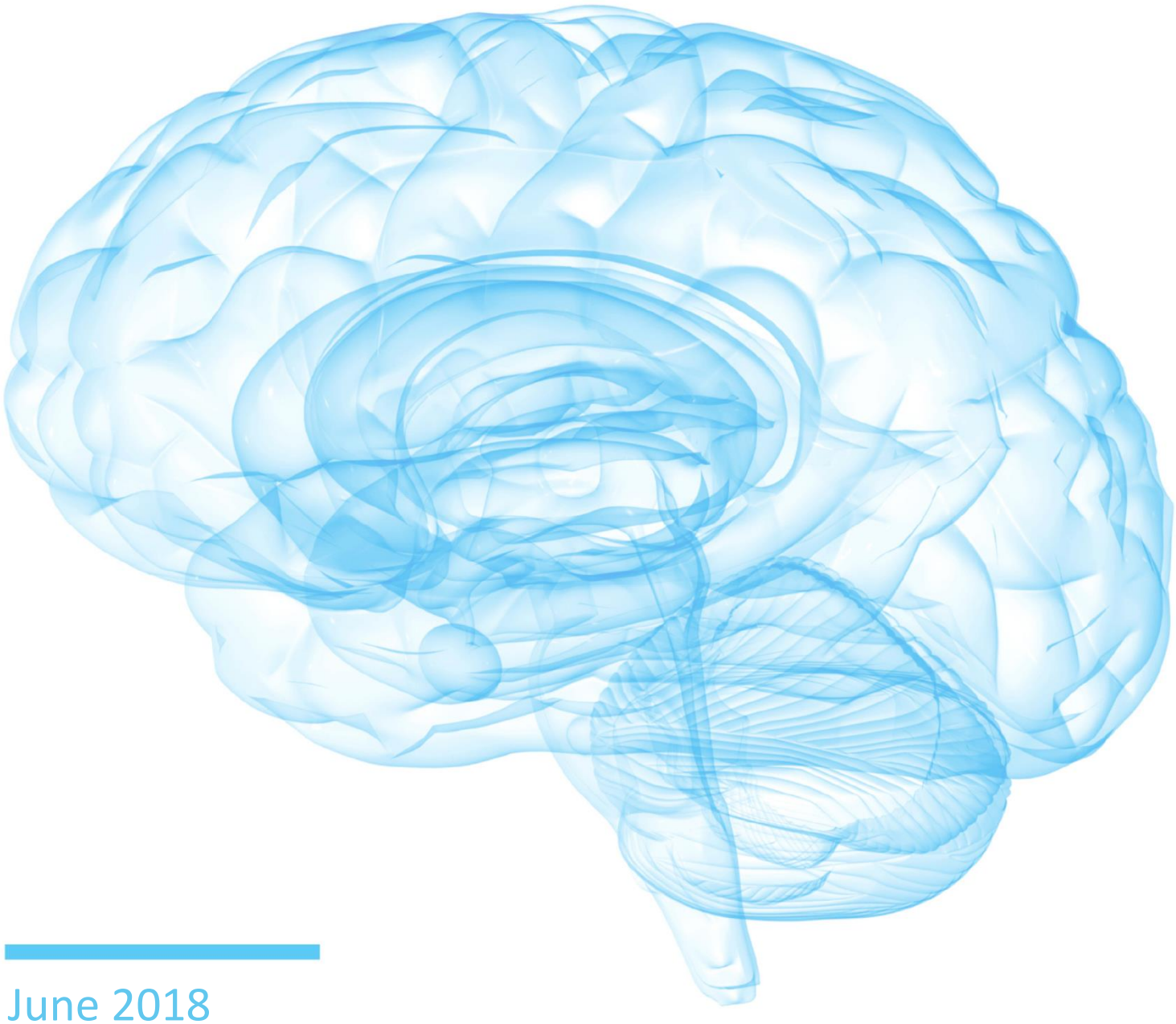

June 2018

EXABLATE MODEL 4000 TYPE 1.0

APPLICATION: BRAIN Tremor Dominant Parkinson's Disease

INFORMATION FOR PRESCRIBERS

INSIGHTEC

INSIGHTEC Ltd.

5 Nachum Heth St. PO Box 2059,
Tirat Carmel 3912001
Israel

Website: www.insightec.com/us

Revision: 06/2018

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CHAPTER 1: LABELING AND CLINICAL RESULTS

1.1 Device Description

1.1.1 Device Name and Configuration

The device full name and configuration is summarized in the table below:

DEVICE NAME	
Generic Name	MRgFUS
System	Exablate
Model	4000
Type	1.0
Application	Brain
Clinical SW Ver.	6.6 for Windows-XP 7.0 for Windows-7

The Exablate System for this indication is also marketed under

- "Exablate Neuro" with the following logo:

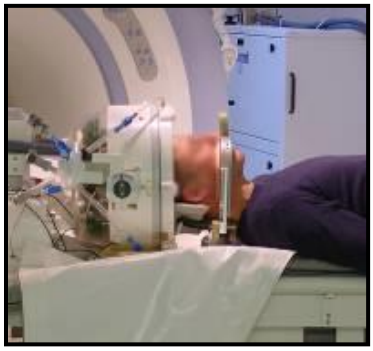
Exablate Neuro

The treatment for this indication using the Exablate Neuro System is marketed as

- "Neuravive Treatment" with the following logo:

Neuravive™

1.1.2. Overview



The Exablate® Model 4000 Type 1.0 (“Exablate ”, “Exablate Neuro” or “the system”) that is designed for the non-invasive ablation of brain tissue for the treatment of medication-refractory tremor in patients with
(TDIPD), is a transcranial, magnetic resonance, image-guided focused ultrasound (MRgFUS) system. The treatment goal of the Exablate Neuro system is to accurately guide the focus of the ultrasound energy to the target region. Focused ultrasound energy is then repeatedly transmitted to the target until the desired outcome is achieved. Targeting is accomplished using magnetic resonance (MR) images taken during the treatment. The treatment process is constantly monitored by real-time closed-loop thermal feedback under full control of the treating physician. Once the targeting is complete, the treatment outcome is confirmed with MR imaging sequences immediately after the treatment. The Exablate Neuro can be utilized in either 3T MR scanner or 1.5T MR Scanner with its dedicated MR 1.5T Head Coil.

The MR thermometry feedback information during treatment is analyzed by the physician to monitor patient safety, and to control and adapt system parameters for optimal results. This is performed via an interactive operator’s workstation interface application.

Treatments begin when the patient is positioned on the Exablate treatment table. The positioning includes attachment of a stereotactic frame and a patient membrane seal that is fitted over the patient’s head. The patient is then guided on top of the base plate and the frame is locked in position.

A series of standard diagnostic MR images is taken to identify the location and shape of the structure to be treated. These images are loaded to the Exablate workstation and are used to graphically determine the intended target region. A computed tomography (CT) scan of the patient is also loaded into the workstation, to allow reconstruction of the skull geometry.

Based on the loaded information and the target definition, the system automatically prepares a simulation of the treatment process. This plan may be edited and its parameters can be controlled by the operator. During this time, the system circulates cool water within the interface between the transducer and the skull.

The next step is to deliver low energy sonications to verify targeting accuracy and the patient’s reaction. First, the operator marks the target on the acquired MR images. Then, sub-lethal energy is transmitted to the prescribed location. The thermal rise is then identified on MR thermal images, and the location of the thermal spot is confirmed to be on target. If the thermal spot is observed to be off target, the system corrects for the misalignment in the subsequent sonications. This verification procedure also enhances the safety of the treatment by confirming the location of the target before producing thermal ablation of the target tissue.

Once targeting accuracy is confirmed, the energy is gradually increased, until the measured thermal rise is sufficient for treatment-level sonication. The online thermal feedback gives the operator the needed input to react to local variability in tissue properties and to modify system parameters as needed. The system provides an interface to allow parameter modifications prior to each sonication.

Importantly, each sonication is confirmed, executed and analyzed by the physician. This sonication cycle is repeated and edited by the operator according to the real-time thermal feedback. The MR thermal images are acquired every 3 to 5 seconds during the sonication. Various image analysis tools are available to aid in the analysis of the thermal rise over time. In addition, thermal measurements continue beyond the actual sonication time to evaluate the cool-down period and confirm that tissue has returned to baseline temperature. Furthermore, since the thermal imaging acquisition samples the entire Field-Of-View (FOV) of the imaging, the operator is also able to evaluate the non-focal temperature trend. This is another added safety measure that the operator may utilize during the course of the treatment.

The hardware and software components of the Exablate are described below.

1.1.3. Hardware

The Exablate Neuro for TDIPD is comprised of three main sub-systems:

- Patient Table: Contains the focused ultrasound (FUS) transducer with its positioning system.
- Console/Workstation: Allows the user to operate the Exablate Neuro system through the clinical application software.
- 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.
- The 1.5T Exablate setup utilizes a dedicated 1.5T MR Head coil (see **Figure 2**)

The complete system is shown below in **Figure 1**. Each of the sub-systems is further described in the sections that follow.

Patient Table:

During treatment, the patient lies on the patient table. The patient's head is fixated to the table, using a standard stereotactic head frame. The table also contains the FUS transducer located on a mechanical positioning system, so that transducer can be moved to the desired location relative to the patient's head. The table is docked to the MRI and the cradle located on top of it can move in and out of the MR Bore.

Workstation (WS) or Operator Console:

The WS is a 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.

Supporting Equipment:

Front End Cabinet (FE): The FE contains 1024 power amplifiers to drive the desired signal in each of the elements in the Exablate Neuro's 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.

Equipment Cabinet: The Equipment Cabinet contains the Control PC, running dedicated Software to manage the activation and monitoring of the sonications and the water system, control and data

Water System Cabinet:

Water is used as acoustic interface between the transducer and the patient's head. The water system cabinet contains the pumps, filters, etc., used for cooling, degassing, and circulating the water.

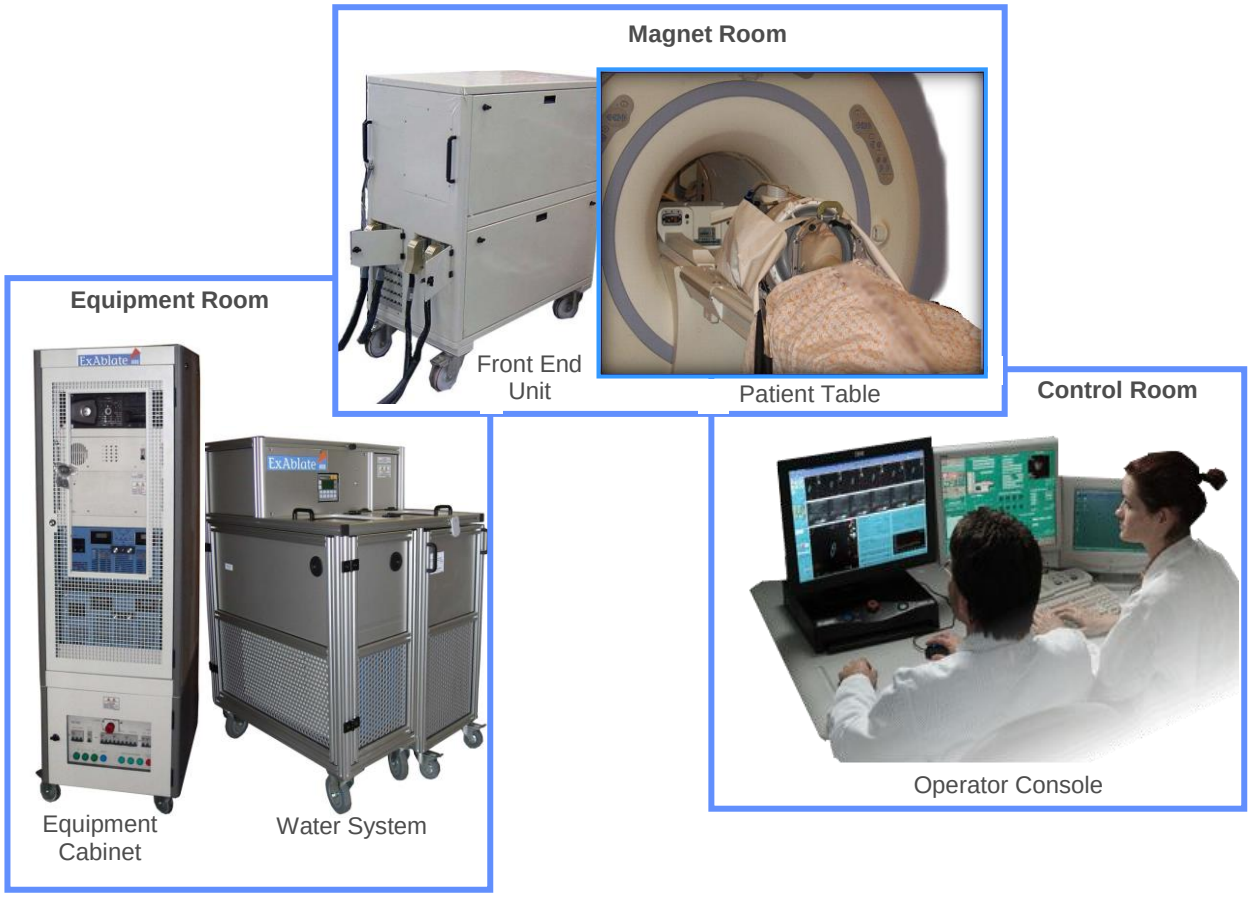


Figure 1: Exablate Neuro System Components

Figure 2 shows an illustration of the Tc MRgFUS Head Coil.

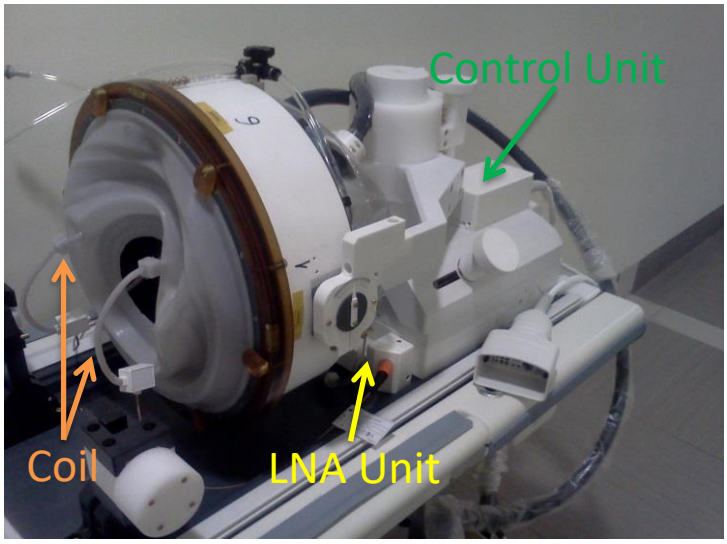


Figure 2: The 1.5T Transcranial (Tc) MRgFUS Head Coil

1.1.4. Exablate Neuro Accessories

The full list of Exablate Neuro accessories is provided in **Table 1** below.

TABLE 1: List of Key System Accessories		
NAME	P/N	DESCRIPTION
3.0T Neuro Patient Accessory Set	SET000936	The Accessory Kit includes the following items: A DQA gel, 1 helmet sealant tube, a cleaning kit , 4 protective frame pin caps, 4 long stereotactic frame pins set and a 3.0T silicone membrane.
1.5T Neuro Patient Accessory Set	SET000937	The Accessory Kit includes the following items: A DQA gel, 1 helmet sealant tube, a cleaning kit, 4 protective frame pin caps, 4 long stereotactic frame pins set and a Head Coil with 1.5T silicone membrane
Neuro Patient Accessory Kit	SET400186	The Accessory Kit includes the following items: A DQA gel, 1 helmet sealant tube, a cleaning kit and 4 protective frame pin caps.
Stereotactic Frame Set	SET400168	The stereotactic Frame Set includes the following items: The stereotactic frame, posts, screws, wrench and a case One set is supplied with the system
Long Stereotactic Frame Pins Set	MPR000444	Pair of long head frame pins for stereotactic frame fixation.

TABLE 1: List of Key System Accessories		
NAME	P/N	DESCRIPTION
Short Stereotactic Frame Pins Set	MPR000445	Pair of short head frame pins for stereotactic frame fixation
Protective Frame Pin Caps	MPR001164	Silicone protective cap used to cover the frame pin for membrane protection.
DQA Gel	SET000932	Tissue mimicking phantom gel, used for Daily Quality Assurance (DQA)
Helmet Sealant	BUY000180-AA	Tube containing sealant material for water-tight coupling to the transducer.
Cleaning Kit	SET000933	A set of products used for cleaning the system after each treatment
Silicone Membrane	ASM000355	For coupling of patient head to FUS helmet. For use only with a 3.0T MRI
1.5T Head Coil with Silicone Membrane	ASC002258-AA	The Head Coil is used with a 1.5T MRI.
Stereotactic Frame	ASM001399	Stereotactic head frame, including adapters to Exablate Neuro patient interface. One frame is supplied with the system.
Stereotactic Frame Screws Set	MPR001138	A set of spare stereotactic head frame screws (all types). One set is supplied with the system.
Stereotactic Frame Posts	ASM001395	A part of the stereotactic head frame set. Includes 4 Posts (with separate P/N). One set is supplied with the system.
	ASM001396	
	ASM001397	
	ASM001398	
Frame Attachment Strap	MEC001647	Assists with stereotactic frame placement.

1.1.5. Software

The Exablate Neuro clinical software is based on Graphical User Interface (GUI) that allows the user to perform the following principal functions common to all Exablate applications:

- Enslaving the MR operation (e.g., start/stop scan, image retrieval, change of scan parameters, etc.)
- Display of MR images for treatment planning
- Exablate hardware system operation and control through the Control PC (e.g. prescribing energy delivery, steering)
- Selecting the target or drawing of Region of Treatment (ROT) on diagnostic images
- Treatment planning (allowing manual editing) and dose prediction display
- Real time MR thermometry measurement, processing and display
- Calculation of accumulated thermal dose based on MR thermometry
- Spectrum monitoring: A graph displaying the frequency spectrum of acoustic emissions is displayed so it can be monitored for cavitation.

Use of the Exablate system begins by locking 2 independent coordinates systems into one single set of (MR) coordinates:

- The Exablate Transducer Coordinates
- MR Scanner Coordinates

Once these coordinates are translated into a single frame of reference, all treatment planning and system interactions are carried out in this reference frame. This is accomplished by using the MR to locate the four tracker coils attached to the frame of the transducer, and using their locations to determine the location of the transducer. The transducer location is shown by superimposing a template on top of planning MR images.

Treatment Envelope

The treatment envelope is the volume that can be safely covered by the transducer. A 3-dimensional representation of the treatment envelope is displayed to the user in all orientations. This is to help the user identify the region that can be covered by the transducer in its current mechanical location.

MRI Central Frequency Determination

Detecting the correct value of the MRI Central Frequency prior to the treatment can reduce thermal imaging shifts during sonications. The system automatically detects the correct MR Central Frequency values for the treatment and will use it in all future scans that are initiated by the WS.

Define Treatment Protocol

The operator selects a treatment protocol appropriate for the treatment. Choosing a treatment protocol is necessary to enable the system to adjust parameters according to the treatment specific target characteristics. Factory protocols with default values of the parameters of treatments are part of the system.

Planning Image Acquisition

The system enables the user to acquire planning images in two ways:

- AC-PC (Anterior Commissure – Posterior Commissure) Based anatomically aligned images – the operator acquires sagittal images and marks the AC and PC locations. The system will produce axial scan that will be taken aligned with the AC-PC plane and will ensure that one of the images will intersect with the AC-PC line. In addition, coronal scan will be produced perpendicular to the axial series.
- Manual prescription of planning images - the operator will prescribe three orthogonal sets of MR images along the 3 main axes; axial, coronal and sagittal. After prescription on the MR, the scan will be initialized from the Exablate workstation that will ensure the use of the same adequate MRI Central Frequency values for the scans throughout the treatment. The images are automatically retrieved from the MR system and displayed.

CT and Pre-Treatment MR Images

The operator will need to upload a set of CT images of the patient's head on the Exablate workstation. These CT images are used to determine the thickness and density of the skull to compute the required phasing of the FUS beam to enable accurate focusing through the skull.

If previously acquired MR images that can help with the treatment planning are available, then these MR images may also be uploaded on the Exablate workstation. These pre-treatment MR and CT images may also be used to identify areas that may need to be avoided (e.g. calcifications).

CT-MR Registration

The operator will inter-connect the CT and MR frames of coordinates by applying an automatic or manually controlled registration between the corresponding set of images. An appropriate graphical user interface for such a registration process, including the ability to manipulate CT-mask of the skull overlay on top of the MR images is provided for this purpose.

Define Target and No-Pass-Regions

Using the treatment day MR images, the operator can define a target location or can draw a region for treatment on the MR images.

In addition, the operator may also delineate sensitive anatomical structures (e.g. calcifications) as No-Pass-Regions (NPR). The system will tailor the acoustic beam to avoid undesired acoustic energy density on these areas.

Patient Movement Detection

A Movement Detection feature can assist the operator in detecting patient movement during the treatment. Movement detection reference images are taken automatically by the system, and the user places fiducials markers on the MR images at distinct anatomical locations to enable the system to identify and alert the user if a patient movement occurred.

Compute Treatment Plan

The system computes the treatment plan by taking into account the Treatment type that was defined in the Treatment Protocol form or the dimensions, location and shape of the Region of treatment that was drawn, as well as the transducer location and the shape, location and properties of the skull (as derived from the patient's CT images). The acoustic beam required to produce the sonication, is determined automatically by the system. Optimal electrical steering and enabling/disabling of individual transducer elements is employed to create the sonication within the treatment plan. Optimal phase and amplitude per element are calculated to compensate for skull aberration and to achieve uniform energy density on skull.

Edit Plan

The operator reviews the treatment plan and can decide to modify the treatment plan using a graphical system interface. The user may also decide to change protocol-defined treatment parameters, which triggers a re-planning computation.

Geometrical Alignment

The operator performs low power sonications to generate a low temperature thermal spot. This thermal spot is used to identify any mismatch between the actual thermal spot and the planned spot. This procedure allows fine tuning of the actual target of the system. If mismatch is identified, the operator can perform an adjustment and correct for this mismatch.

Treat

The system suggests initial parameters for the sonications at each stage of the treatment (Align, Verify, Treat Low and Treat High) based on the results from previous sonications in the treatment. Before sonicating, the operator can review and modify spot location, parameters and details of the planned thermal imaging. Once this is confirmed the operator presses the sonication button to actually initiate the treatment.

- As the sonication is executed, the system controls the MR to acquire thermal images. All thermal images are displayed to the operator during the actual sonication. This real-time thermal feedback can be used to determine whether the desired thermal rise was delivered to target tissue.
- Following the examination of the thermal measurements, the operator may choose to raise or lower the energy, adjust the spot location, and/or proceed to the next sonication spot. This adaptive process of sonicate/image, review the result, and adjust/proceed, continues until the desired temperature and clinical effect are achieved.

Final Review

After reaching ablation temperatures, the operator will evaluate the treatment results and choose whether to continue with the treatment by adding additional spots, or to exit the treatment. This decision is typically based on standard anatomical imaging (e.g. T2 weighted) to assess the location and shape of the treated area, and on assessment of patient symptoms.

For more detailed information about each of these functions, refer to the Exablate Operator's Manual.

1.1.6. Manual Graphical User Interface (GUI)

The GUI, shown in **Figure 3,** was designed to be user friendly, using mostly buttons, icons, graphical representations and annotations and overlays directly on the MR image. For example, the skin line, region of treatment, individual sonications and beam path overlaid on MR images in three perpendicular orientations. Most of the treatment operations can be performed using the mouse with minimal manual data entry.

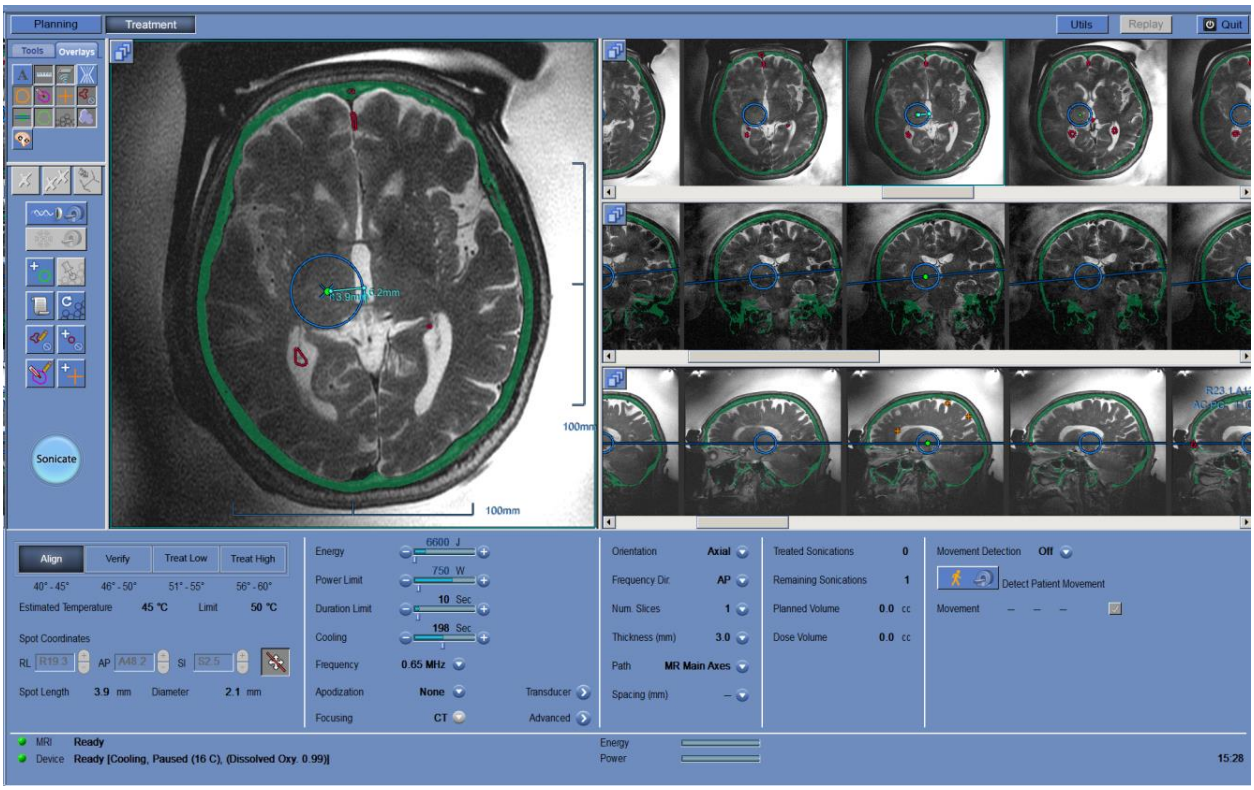


Figure 3: Exablate Software Graphical User Interface

Exablate software graphical user interface (GUI):

- Graphical user interface uses buttons and icons to identify functions during treatment,
- The software overlays graphical displays on MR image(s),
- Treatment parameters and treatment progress easily accessible for continuous tailoring and monitoring of the treatment. Dialogue boxes and tool tips that appear when the cursor hovers over a button assist the user at every stage.

Image acquisition

The software communicates with the MR-computer software to acquire planning images, and MR phase images during treatment.

Imaging tools

Image enhancing operations, such as zoom in/out, image contrast and measurement tools, can be used on MR images during the treatment planning and delivery.

Safety mechanisms

Safety mechanisms are built into the software preventing the physician from bypassing steps necessary for a safe treatment. For example, fiducial markers denoting anatomical structures must be placed before verification of treatment geometry and dosimetry.

Sonication parameters and status

Treatment parameters are set using pre-planned protocols. Within a limited range, the energy level, sonication and cooling duration, spot size, etc., may be adjusted during the course of the treatment. The software also keeps track of the status of each sonication (including energy delivered, elapsed time, and thermal dose volume).

Cavitation monitoring

During treatment, the software displays the thermometry monitoring graph and cavitation spectrum to the physician.

MR Thermometry

The software uses the MR images to calculate thermal maps. It then displays this thermal map as an overlay on the anatomic images. This provides both quantitative feedback, in the form of a time/temperature and thermal dose graph, and qualitative feedback, as a color map, to assist the physician in the management of the treatment.

1.2. Intended Use / Indications for Use

Unilateral Thalamotomy (*ventralis intermedius*) treatment of Tremor-Dominant Parkinson's Disease with medication-refractory tremor. Patients must be at least age 30. One of the brain areas responsible for the movement disorders symptoms of tremor is the *ventralis intermedius*. This target must be identified and accessible for targeted thermal ablation by the Exablate device.

CHAPTER 2: PATIENT SELECTION CRITERIA FOR TREATMENT WITH EXABLATE NEURO

2.1 Patient selection criteria

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

2.2. Contraindications

The Exablate treatment is contraindicated for use in:

- Patients with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, 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 anticoagulant 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 CT.

2.3. Warnings

- Prolonged immobilization may lead to increased risk of deep venous thrombosis (DVT) or pulmonary embolism (PE). In order to avoid this, the patient should be wearing **Thromboembolic Stockings (TEDs),** also referred to as **"anti-embolism"** stockings through the entire procedure time in the MRI.
- The transducer interface must be filled completely with water without air bubbles to provide adequate acoustic coupling.
- Ensure that the patient can activate the Stop Sonication button before initiating treatment. In the event of pain or patient motion, failure to do so may result in serious injury.
- Ensure that the subject's scalp is shaved well, and that any scars or scalp lesions (i.e., eczema or psoriasis) are marked for avoidance in the treatment beam path to minimize heating/burning at the scalp.
- Accurate calibration of the alignment of the transducer at the start of the treatment is critical to proper tissue targeting and to avoid injury to non-targeted tissue. Perform geometrical verification prior to treatment to ensure proper alignment before beginning treatment.
- Failure to monitor the MR thermal maps during the procedure may result in unintended heating of non-targeted tissues, which may cause permanent injury. Operator must cancel/abort the procedure if MR thermometry data are not available.
- Ensure that only degassed water is used in the circulating area between the transducer and the subject's skull to avoid air bubbles in the system which might result in skin burn.
- Prior to the delivery of each sonication throughout the treatment, the beam path should be evaluated to avoid scars or other irregularities in the skin which can cause pain or skin burns.
- Inadequate cooling time between sonications could lead to thermal build-up that may cause serious damage to normal tissues outside the targeted volume. The cooling time between sonications is automatically scaled according to the actual energy applied and sonication parameters, and should not be decreased.
- If the skull bone is heated significantly, tissue adjacent to the skull can also absorb heat and may be damaged. To prevent damage to this tissue, heating of the skull should be minimized – this is achieved both by circulating chilled water across the outer surface of the skull (avoid heating of outer skull-skin interface) and choosing target regions at a depth in the brain at least 2.5 cm from the skull (avoid heating of internal skull-tissue interface).

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

2.4. Precautions

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

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

Contact INSIGHTEC Technical Support at 1-866-674-3874

CHAPTER 3: SUMMARY OF CLINICAL STUDY

3.1. STUDY DESIGN

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

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

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

3.1.1 ELIGIBILITY CRITERIA

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

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

3.1.1.1. 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

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

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

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

3.1.1.2. EXCLUSION CRITERIA

- Subjects with unstable cardiac status including:
  1) Unstable angina pectoris on medication
  2) Subjects with documented myocardial infarction within six months of protocol entry
  3) Significant congestive heart failure defined with ejection fraction < 40
  4) Subjects with unstable ventricular arrhythmias
  5) 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:
  1) 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).
  2) 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)
  3) Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)
  4) 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 the upper weight limit the MR scanner table
- 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 disease.
- 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.
- Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia
- Subjects who have an Overall Skull Density Ratio of 0.45 (±0.05) or less as calculated from the screening CT.[1]

[1] Exclusion added to protocol amendment 1.

The Schedule of Events is shown in **Table 2.**

Table 2. Schedule of Events

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

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

β: See MR Table Schedule

3.1.4. STUDY ENDPOINTS

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

Safety Endpoint

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

Primary Effectiveness Endpoint

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

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

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

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

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

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

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

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

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

Secondary Effectiveness Endpoint

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

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

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

3.1.5. Study Analysis Population

The data analysis in this report involves three analysis populations **Table 3**:

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

Table 3. Number of Subjects in each of the Analysis Sets by Treatment Group

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

3.1.6. STUDY SUBJECT ACCOUNTABILITY

Fifty-three subjects were recruited for this trial. Out of these subjects, 19 were screen failures (**Table 4, Figure 4**) and an additional seven declined to participate prior to randomization. The remaining 27 subjects were randomized and treated accordingly.

Patient accountability for this study is presented in **Table 4**. Recruitment included screening of 53 subjects to arrive at a total of 27 eligible study participants (N=20 Active Exablate; N=7 Sham control). The study's actual random ratio became 3:1because the study was stopped early as the number of active subjects was reached at an earlier timepoint.

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

Table 4. Patient Disposition by Treatment Group and Scheduled Visit.

Category	Baseline		1 Month FU		3 Months FU		6 Months FU	12 Months FU
	ExAblate	Sham	ExAblate	Sham	ExAblate	Sham	ExAblate	ExAblate
Recruited	53							
SF 1[1]	19							
Discontinued for Reasons Other than SF (not yet randomized)	7							
Randomized[2]	20	7						
Discontinued for Reasons Other than SF (after randomization)	0	0	0	0	0	0	0	0
Theoretical[3]	20	7	20	7	20	7	20	20
Death	0	0	0	0	0	0	0	0
Failure[4]	0	0	0	0	0	0	2	3
Exited – Other Reasons[5]	0	0	0	0	0	0	1	3
Expected[6]	20	7	20	7	20	7	17	14
Actual[7]	20	7	20	7	20	7	16	14
Actual %[8]	100%	100%	100%	100%	100%	100%	94%	100%

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

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

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

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

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

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

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

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

Table 4. Patient Disposition by Treatment Group and Scheduled Visit.								
Category	Baseline		1 Month FU		3 Months FU		6 Months FU	12 Months FU
	ExAblate	Sham	ExAblate	Sham	ExAblate	Sham	ExAblate	ExAblate
[*]: Subjects 106125 and 106136 exited the study for alternative treatment of DBS following the 3 Month visit. Subject 106143 exited following the 6 Month visit to receive DBS. [2]An additional 3 subjects withdrew from the study for personal reasons unrelated to the study (2 subjects) or by subject's request due to health concerns (unable to travel due to feeding tube placement).								

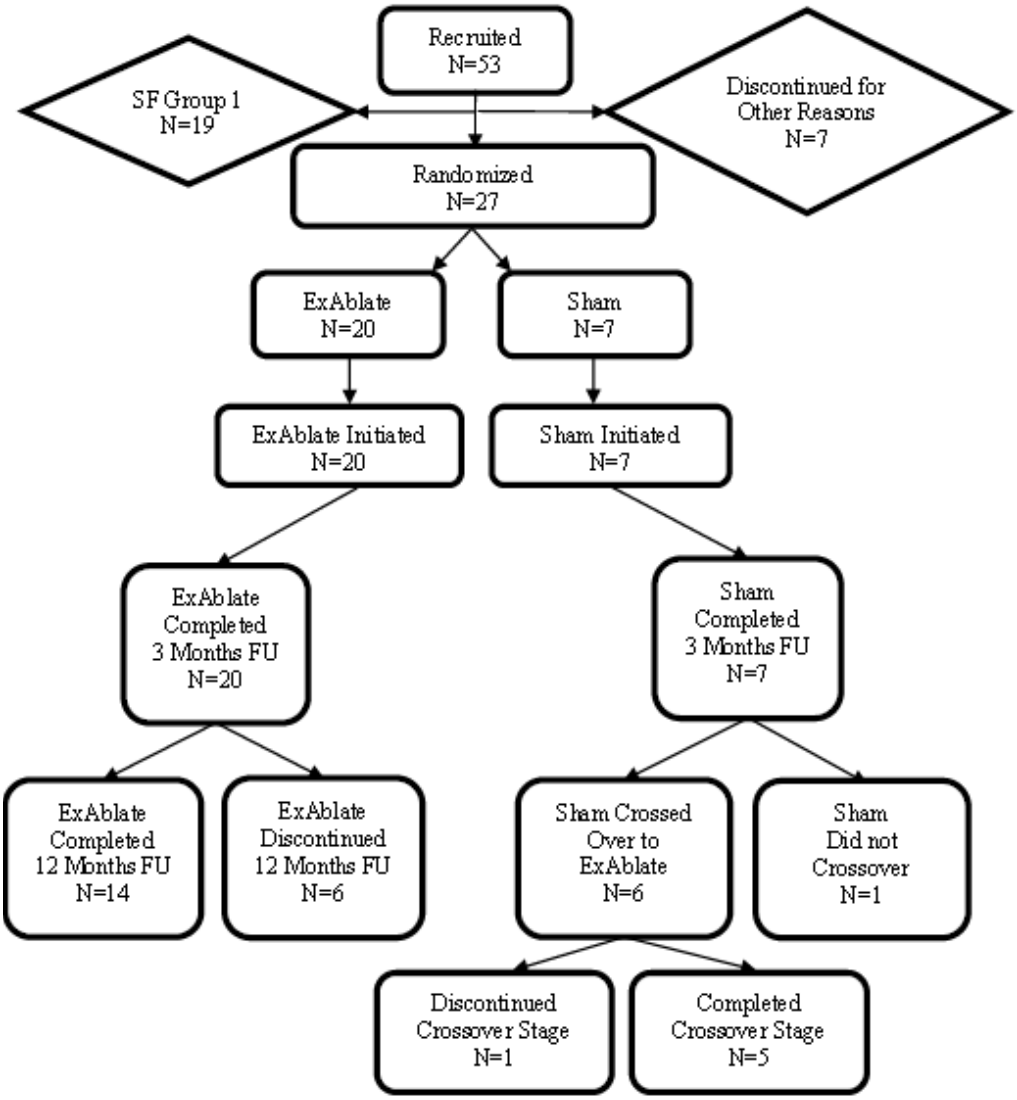


Figure 4. Patient Flowchart.

3.1.7. STUDY DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline and demographic characteristics of the population are presented in **Error! Reference source not found.**. The ExAblate and Sham groups were similar at Screening /Baseline in all respects. The ExAblate group had a mean age of 68 and the Sham group had a mean age of 63. The study sample consisted predominantly of Caucasian males.

Table 5. Baseline and Demographic Information by Treatment Group

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

3.2. STUDY RESULTS

3.2.1. SAFETY RESULTS

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

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

- Half (50 events, 50% frequency) of the adverse events were transient, i.e., most resolved right after the sonication or the same day up to 3 days post-procedure (see **Table 6**).
- Another fifth (21 events, 21% frequency) of events were considered Unrelated to device, thalamotomy, or procedure (see **Table 6**).
- The remaining ExAblate Arm events 29 (29%) were related to the device, thalamotomy or procedure (see **Table 6**)

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

Table 6 Overall Summary of Safety Between Groups				
Severity	**ExAblate**		**Sham**	
	Frequency N=100	**Incidence N=20**	**Frequency N=10**	**Incidence N=7**
Mild	72 (72%)	19 (95%)	3 (30%)	2 (29%)
Moderate Thalamotomy-related SAE Unrelated SAE	20 (20%) 1 (1%) 2 (2%)	14 (70%) 1 (5%) 2 (10%)	6 (60%)	4 (57%)
Severe Thalamotomy-related SAE Unrelated SAE	3 (3%) 1 (1%) 1(1%)	2 (10%) 1 (5%) 1 (5%)	0 (0%) 1 (10%)	0 (0%) 1 (14%)
Total	100 (100%)	20 (100%)	10 (100%)	5 (100%)

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

Table 5: Summary of Safety (Adverse Events) Between Groups by Severity				
Severity of SAE	**ExAblate**		**Sham**	
	Frequency N=100	**Incidence N=20**	**Frequency N=10**	**Incidence N=7**
Thalamotomy-related	2 (2%)	2 (10%)	0 (0)	0 (0%)
Unrelated	3 (3%)	2 (10%)	1 (10%)	1 (14%)
Total SAEs	5 (5%)	4 (20%)	1 (10%)	1 (14%)

Two subjects experienced Serious Adverse Events:

- One subject experienced ataxia/hemiparesis. They were originally reported separately, but later it was determined that the ataxia was an expression of the hemiparesis. The patient required a walker to assist with walking after discharge. The event resolved in approximately 30 days. MR showed cerebral edema and the lesion trailed off into the internal capsule.

- One subject experienced severe hemiparesis resulting from local cerebral edema and trailing of the lesion toward the internal capsule. Immediately post procedure the patient had no difficulties, but the next day he developed hemiparesis.

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

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

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

The frequency and incidence of all adverse events is presented by treatment group and severity and by body system and coded term in **Table 7**

Table 7. Frequency and Incidence of Adverse Events by Severity and Treatment Arm

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

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Relation to Device	Body System	Preferred Term	ExAblate (N events = 100; # subjects = 20)						Sham (N events = 10; # subjects = 7)					
			Mild		Moderate		Severe		Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
	Nervous	Dysgnosia	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Vestibular Disorder	Dizziness	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Procedure Related Subtotal			5 (5%)	4 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thalamotomy Related	Musculoskeletal	Dysmetria	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (%)	0 (0%)	0 (%)	0 (0%)	0 (%)	0 (0%)	0 (0%)	0 (0%)
		Gait disturbance	2 (1%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Hemiparesis	0 (0%)	0 (0%)	2 (2%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Imbalance	4 (4%)	4 (20%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 7. Frequency and Incidence of Adverse Events by Severity and Treatment Arm

Relation to Device	Body System	Preferred Term	ExAblate (N events = 100; # subjects = 20)						Sham (N events = 10; # subjects = 7)					
			Mild		Moderate		Severe		Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
	Nervous	Dysmetria	1 (1%)	1 (5%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Ataxia	1 (1%)	1 (5%)	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Numbness/tingling	7 (7%)	6 (30%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Neurological	Numbness/tingling	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		Unsteady	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Thalamotomy Related Subtotal			18 (18%)	9 (45%)	3 (3%)	2 (10%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Transient	Cardiovascular	Hypertension	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Syncope	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)

Table 7. Frequency and Incidence of Adverse Events by Severity and Treatment Arm

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

Table 7. Frequency and Incidence of Adverse Events by Severity and Treatment Arm

Relation to Device	Body System	Preferred Term	ExAblate (N events = 100; # subjects = 20)						Sham (N events = 10; # subjects = 7)					
			Mild		Moderate		Severe		Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
		Dysgnosia	2 (2%)	2 (10%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Numbness/tingling	7 (7%)	5 (25%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
	Pain/Discomfort	Headache	5 (5%)	5 (25%)	6 (6%)	6 (30%)	0 (0%)	0 (0%)	2 (%)	2 (29%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Sonication-related scalp pain	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Sonication-related head pain	3 (3%)	2 (10%)	2 (2%)	2 (10%)	1 (11%)	1 (5%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (%)	0 (0%)
	Stereotactic Frame	Pin site pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (%)	0 (0%)

Table 7. Frequency and Incidence of Adverse Events by Severity and Treatment Arm

Relation to Device	Body System	Preferred Term	ExAblate (N events = 100; # subjects = 20)						Sham (N events = 10; # subjects = 7)					
			Mild		Moderate		Severe		Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
	Vestibular Disorder	Dizziness	6 (6%)	6 (30%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
Transient Subtotal			33 (33%)	17(85%)	16 (16%)	11 (55%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	3 (30%)	3 (42%)	0 (%)	0 (0%)
Unrelated	Eye	Pigment change in eye	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Vision change	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
	Gastrointestinal	Cholecystitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Stomach Pain	0 (0%)	0 (0%)	1 (%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
	General	Vocal change	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Table 7. Frequency and Incidence of Adverse Events by Severity and Treatment Arm

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

Table 7. Frequency and Incidence of Adverse Events by Severity and Treatment Arm

Relation to Device	Body System	Preferred Term	ExAblate (N events = 100; # subjects = 20)						Sham (N events = 10; # subjects = 7)					
			Mild		Moderate		Severe		Mild		Moderate		Severe	
			Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)	Freq N (%)	Incidence # (%)
		TIA	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (0%)	0 (0%)
	Stereotactic Frame	Facial edema	3 (3%)	3 (15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Pin site numbness/tingling	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
		Pin site pain	3 (3%)	3 (15%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (%)	0 (0%)
		Stereotactic frame-Bruising	0 (0%)	0 (0%)	1 (1%)	1 (5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (%)	0 (0%)
Unrelated Subtotal			15 (15%)	9 (45%)	4 (3%)	4 (20%)	2 (2%)	2 (10%)	0 (0%)	0 (0%)	2 (20%)	1(14%)	0 (0%)	0 (0%)

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

Table 8.Adverse Events Onset versus Adverse Event Duration by Treatment Group

Duration	ExAblate[1]						Sham					
	100 events in 20 subjects						10 events in 5 subjects					
	Onset < 30 days		Onset 31-90 days		Onset > 90 days		Onset < 30 days		Onset 31-90 days		Onset > 90 days	
<30 days	63 (63%)	19 (95%)	1 (1%)	1 (5%)	1 (1%)	1 (5%)	8 (80%)	4 (57%)	1 (10%)	1 (14%)	0 (0%)	0 (0%)
31-90 days	6 (6%)	4 (20%)	0 (0%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
> 90 days	7 (7%)	4 (20%)	0 (1%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ongoing	14 (14%)	9 (45%)	3 (3%)	2 (10%)	2 (2%)	4 (20%)	0 (0%)	0 (0%)	1 (10%)	1 (14%)	0 (0%)	0 (0%)
TOTAL	90 (90%)	20 (100%)	4 (4%)	3 (15%)	5 (5%)	3 (15%)	8 (80%)	4 (57%)	2 (20%)	1 (14%)	0 (0%)	0 (0%)

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

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

Summary of Safety.

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

Two subjects experienced Thalamotomy-related Serious Adverse Events:

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

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

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

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

3.2 EFFICACY ANALYSIS

3.2.1. PRIMARY EFFICACY CRITERION

An ExAblate versus Sham treatment comparison of the change from baseline in the upper extremity CRST sub-score (Part A and B) was the primary endpoint in the ET pivotal trial (P150038). This comparison in the present TDPD trial was 51.9% versus 12.7% (p=0.030) for the ExAblate and Sham control respectively. The change from baseline results, **Table 9** and **Figure 5,** compared very favorably to improvement observed in the ET pivotal trial. In the ET pivotal trial, the 3 Month improvement from baseline was 53.3% versus the Sham of 1.9%.

Table 9. Descriptive Statistics of Percent Improvement from Baseline at Three Months Post-Treatment in the Treated (Contralateral) Upper Extremity CRST Sub Score by Treatment Group (ITT)

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

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

*p-value reflects testing between groups.

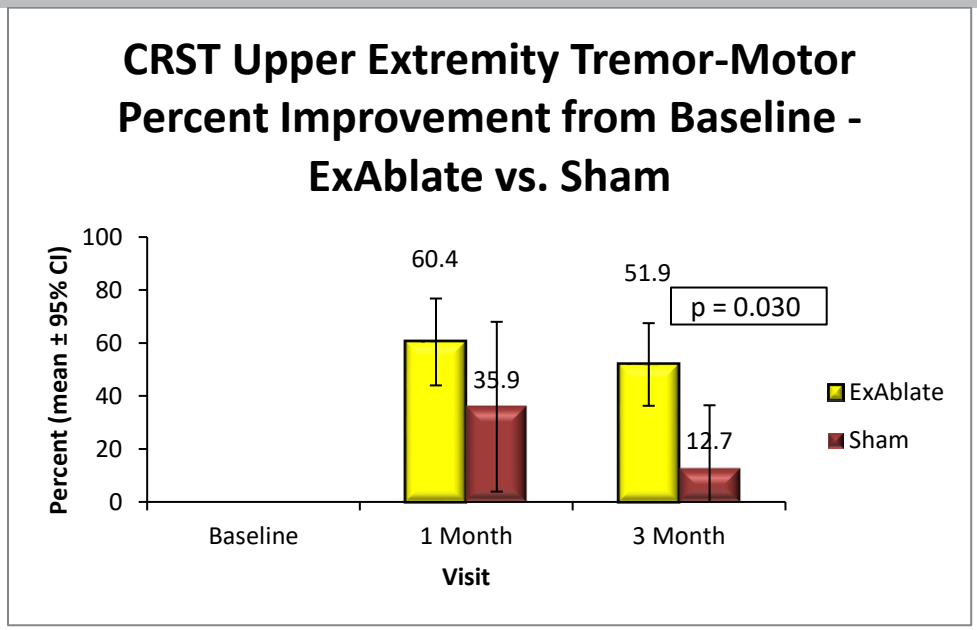

Figure 5 ExAblate versus Sham comparison of improvement from Baseline in the CRST upper extremity scores.

Not only was the upper extremity tremor-motor improvement from baseline significant, but it was similar to the outcomes of the ET pivotal trial. Additionally, the improvement in upper-extremity tremor-motor score persisted through the 12 Month visit (see below **Figure 8, Figure 9, Table 11**).

3.2.2. SECONDARY EFFICACY ENDPOINTS

Analysis was conducted on the ITT Analysis Population, and is shown in **Table 10** and **Figure 6** below. The ExAblate group demonstrated a mean 51.9% improvement from baseline at the 3 Month visit (90 days post ExAblate treatment). For illustration, the p-value for change from baseline at the 3 Month visit was $p < 0.001$ based on the Wilcoxon signed-rank test. For comparison to the 51.9% improvement from baseline, the improvement from baseline for the ExAblate group in the pivotal trial was 53.3%.

Table 10. Descriptive Statistics of Percent Improvement from Baseline at Three Months Post-Treatment in the Treated (Contralateral) Upper Extremity CRST Sub Score (ITT) for the ExAblate group

	Treatment Group N = 20			
Within group comparison between baseline and 3 Months	ExAblate Baseline	ExAblate 3 Months		
	Mean Score	Mean Score	% Change	p-Value*
ITT Mean	19.0	9.6	51.9%	$p < 0.001$

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

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

3. Higher PE values represent improvement

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

*p-value reflects testing between groups.

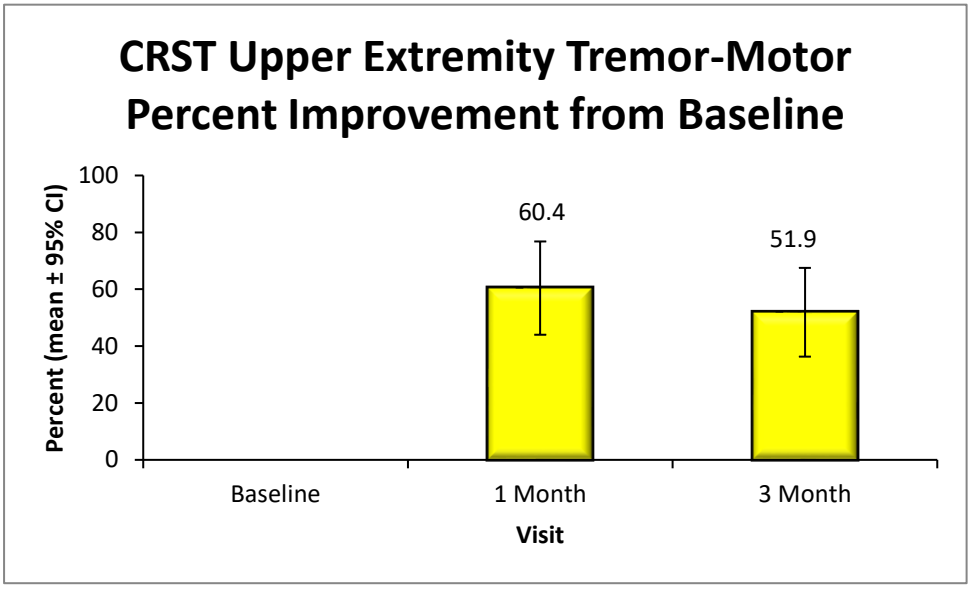

Figure 6. CRST upper extremity tremor-motor improvement from Baseline in the ExAblate group.

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

3.2.3. CRST TREMOR/MOTOR AB

Figure 7 and **Table 11** presents the CRST Part A and Part B summary statistics for the ExAblate-treated and Sham Control groups through the 12 Month follow up visit. The percent change from Baseline is illustrated in **Figure 8**. As noted above, the treated-side tremor improved by 51.9% by the 3 Month visit and 45.9% by the 12 Month visit whereas the Sham control group showed improvement of 12.7% by the 3 Month visit. There was a clear trend of improvement from baseline observed in the ExAblate-treated group not seen in the Sham group. In fact, the improvement from baseline was very similar to that observed in the ET trial; 51.9% versus 53.3% at 3 Months, and 45.9% versus 54.7% at 12 months for the present trial versus ET pivotal trial respectively (see **Figure 8** and **Figure 9** below).

The mean scores in the ExAblate-treated group were 19.0, 8.6, 9.6, and 10.5 at Baseline, 1 Month, 3 Month and 12 Month visits respectively (**Table 11** and **Figure 7**). The mean scores in the Sham Control group were 20.1, 13.6, and 17.4 at Baseline, 1 Month and 3 Month visits respectively.

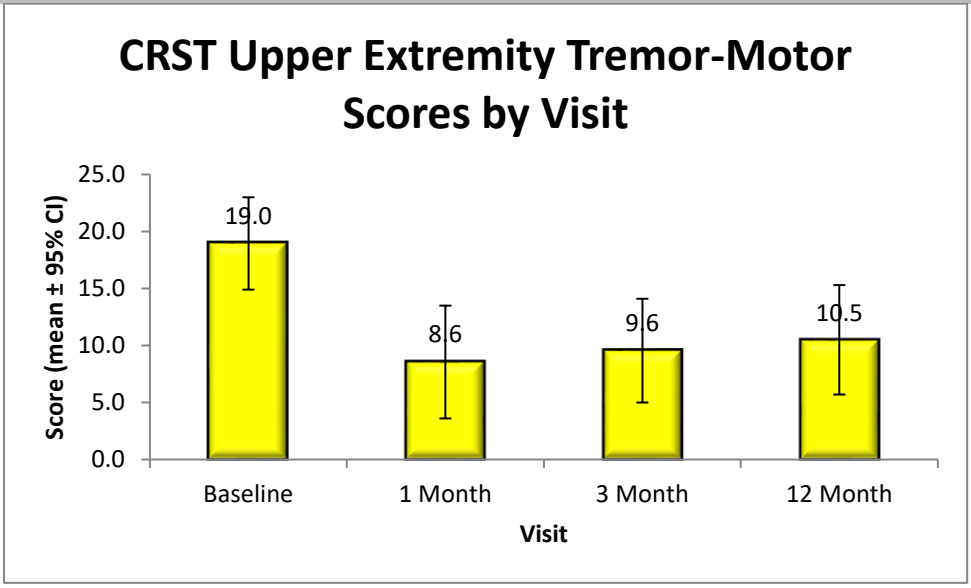

Figure 7 CRST upper extremity tremor-motor scores by visit

Table 11. CRST Tremor-Motor Scores for Treated Arm by Treatment Group by Visit Through Month 12					
Visit / CRST, Part A and B – Tremor-Motor Scores		Observed scores		Percent Change from Baseline	
		Treated Side		Treated Side	
		ExAblate	Sham	ExAblate	Sham
Baseline	Mean	19.0	20.1	NA	NA
	Std	8.7	7.4	NA	NA
	Median	17.0	23.0	NA	NA
	N	20	7	NA	NA
1 Month FU	Mean	8.6	13.6	60.4	35.9
	Std	10.6	6.4	34.9	34.7
	Median	4.0	15.0	66.1	34.8
	N	20	7	20	7
3 Month FU	Mean	9.6	17.4	51.9	12.7
	Std	9.7	7.8	33.4	25.7
	Median	4.5	17.0	62.2	22.2
	N	20	7	20	7
12 Month FU	Mean	10.5	NA	45.9	NA
	Std	10.2	NA	48.6	NA
	Median	6.0	NA	62.4	NA
	N	20	NA	20	NA

Table 11. CRST Tremor-Motor Scores for Treated Arm by Treatment Group by Visit Through Month 12				
Visit / CRST, Part A and B – Tremor-Motor Scores	Observed scores		Percent Change from Baseline	
	Treated Side		Treated Side	
	ExAblate	Sham	ExAblate	Sham
Notes: 1. Change from Baseline was calculated as Percent Change ({Baseline-Visit)/Baseline}*100). 2. Higher Change from Baseline values represent improvement (lower scores are better than higher scores).				

Figure 8 shows the tremor-motor Change from Baseline for the TDPD trial and **Figure 9** showed the observed scores in the TDPD trial to the scores from the ET trial. At the 3 Month visit the percent improvement was 51.9% compared to 53.3% in the ET pivotal trial. The tremor- motor scores at the 3 Month visits were 9.6 compared to 9.5 for the ET trial and at the 12 Month visits were 10.5 compared to 9.9 for the ET trial.

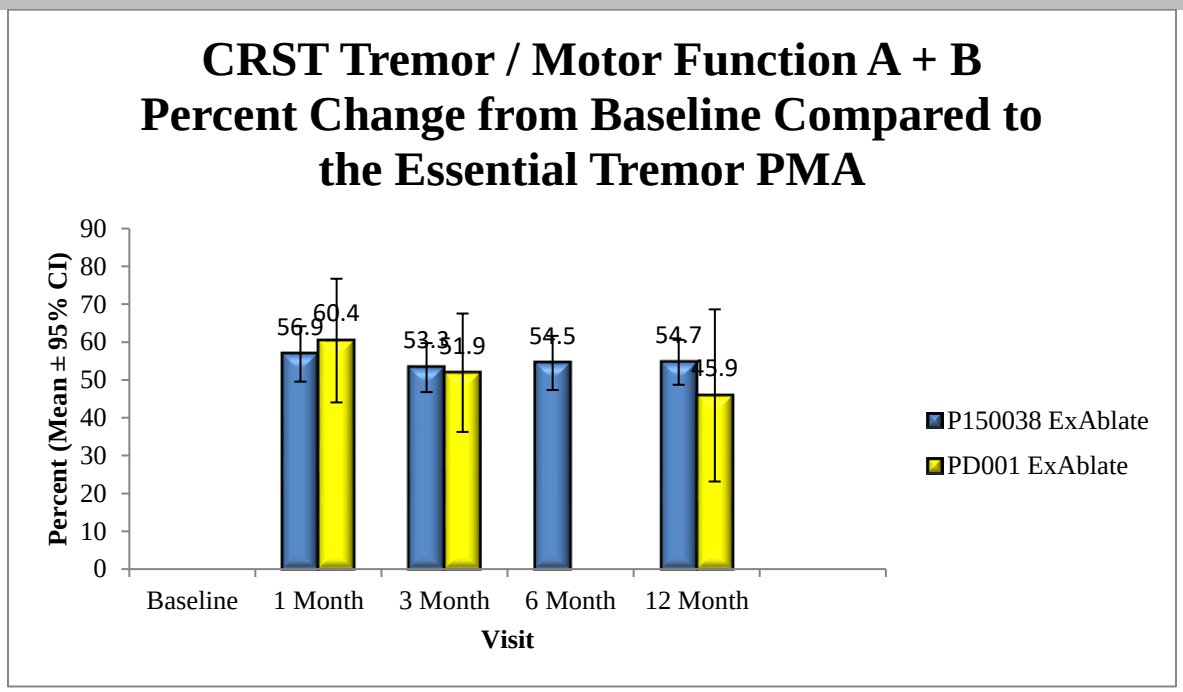

Figure 8. CRST tremor motor function A+ B change from baseline

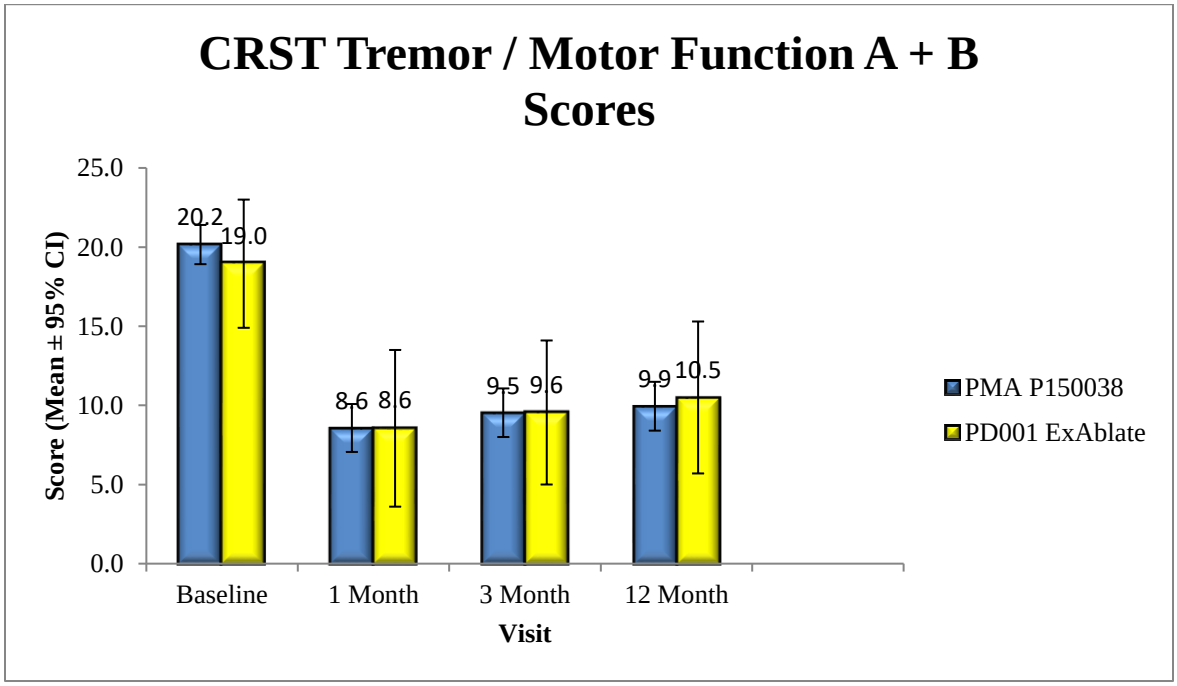

Figure 9. CRST tremor/motor function A + B

3.2.4 CRST PART A POSTURE AND REST

The Part A Posture component (score of 0-4) is an important single indicator of tremor for ET subjects. For this reason, the Part A was evaluated as a lone measure in the ET Pivotal cohort. For Parkinson's Disease, resting tremor is the cardinal symptom. For the purposes of this measure, we have included the Rest component (score of 0-4) for the TDPD along with the Posture component score for comparison of effect. **Table 12** and **Figure 10** shows the actual Postural and Rest component score values in the TDPD cohort.

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

In the ExAblate TDPD Study, the posture scores improved markedly from baseline and compared to the Sham group **Table 12**. The percent improvement in the ExAblate group was 51.7% and was 7.1% in the Sham control group.

Table 12. 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 12. 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).

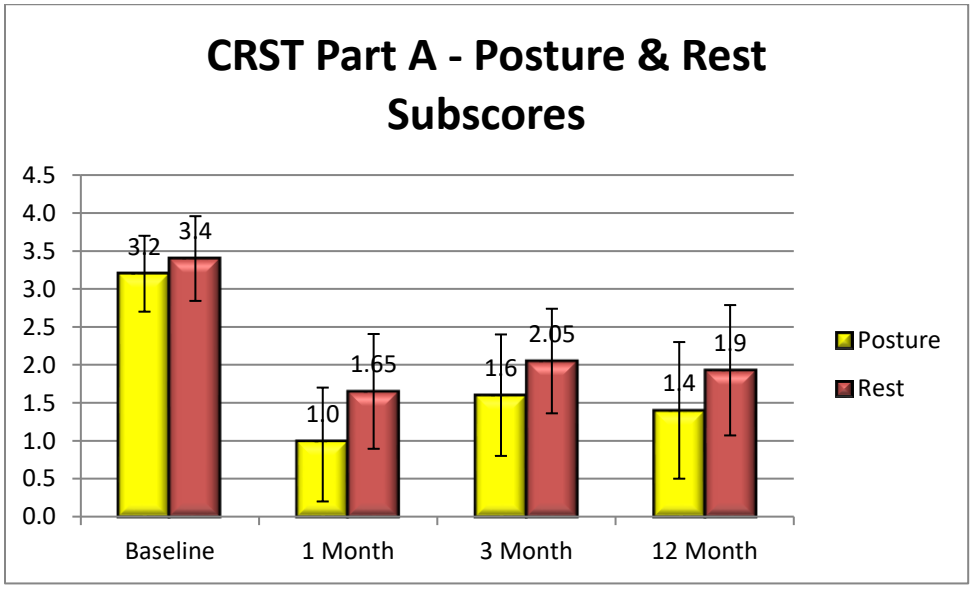

Figure 10. CRST Part A - Posture and Rest components for the ExAblate TDPD Cohort

Figure 11 illustrates the trend over time post-treatment for the ExAblate TDPD Cohort.. The data showed the same trend as that observed for the ExAblate ET Pivotal.

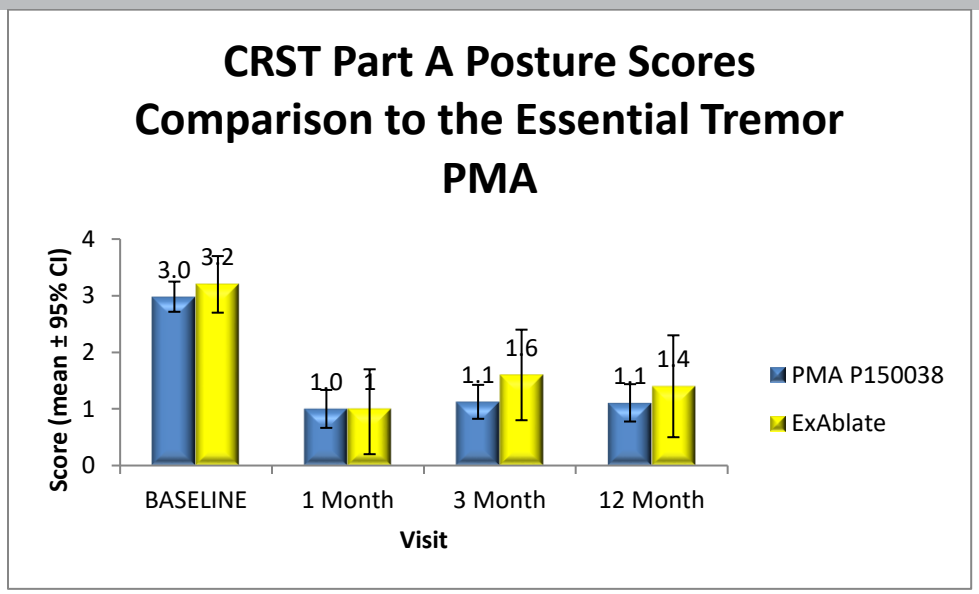

Figure 11. CRST part A Posture for the ExAblate TDPD Cohort compared to the ExAblate ET Pivotal Cohort.

3.2.4 CRST PART C: FUNCTIONAL DISABILITIES

Functional disabilities improvements are presented in **Table 13** below. The ExAblate treated group showed marked improvement (52.9%) improvement as compared to the Sham-treated group (13.4%), the same trend as demonstrated in the CRST Tremor-Motor outcomes. The p-value comparing between the ExAblate and Sham Control groups was p = 0.057 even with the small sample size. Additionally, considering a unilateral treatment affecting only one side of their body, there was a measurable effect in these measures which assess both arms/hands.

Table 13. Descriptive Statistics of Percent Improvement from Baseline at Three Months Post-Treatment in Functional Disabilities Total Score, as Measured by CRST Part-C by Treatment Group

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

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

Second, the functional disability improvement at 12-Months is shown in **Table 14** and **Figure 12.** Results for the 12 Month visit indicate that the improvements achieved at 3 Months were maintained through longer term follow-up. As shown in **Table 14**, at 12 Months improvement compared to baseline was 46%. Finally, the trend over time in the ExAblate-treated group was the same as that observed in the ET trial (**Figure 13**, P150038).

Table 14. CRST Part C Total Score for Treated Arm by Treatment Group by Visit Through Month 12

Visit / CRST, Part C Total Score		Observed scores		Percent Change from Baseline	
		ExAblate	Sham	ExAblate	Sham
Baseline	Mean	14.1	16.7	NA	NA
	Std	5.7	3.9	NA	NA
	Median	13.0	17.0	NA	NA
	N	20	7	NA	NA
1 Month FU	Mean	5.7	15.6	58.3	6.3
	Std	7.5	3.3	49.3	7.4
	Median	2.0	16.0	82.8	9.5

Table 14. CRST Part C Total Score for Treated Arm by Treatment Group by Visit Through Month 12

Visit / CRST, Part C Total Score		Observed scores		Percent Change from Baseline	
		ExAblate	Sham	ExAblate	Sham
	N	20	7	20	7
3 Month FU	Mean	6.4	14.6	52.9	13.4
	Std	6.6	4.2	44.2	18.2
	Median	3.5	16.0	72.1	14.3
	N	20	7	20	7
6 Month FU	Mean	6.4	NA	52.9	NA
	Std	6.6	NA	44.2	NA
	Median	3.5	NA	72.1	NA
	N	20	NA	20	NA
12 Month FU	Mean	6.9	NA	46.3	NA
	Std	7.2	NA	64.0	NA
	Median	3.5	NA	72.6	NA
	N	20	NA	20	NA

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

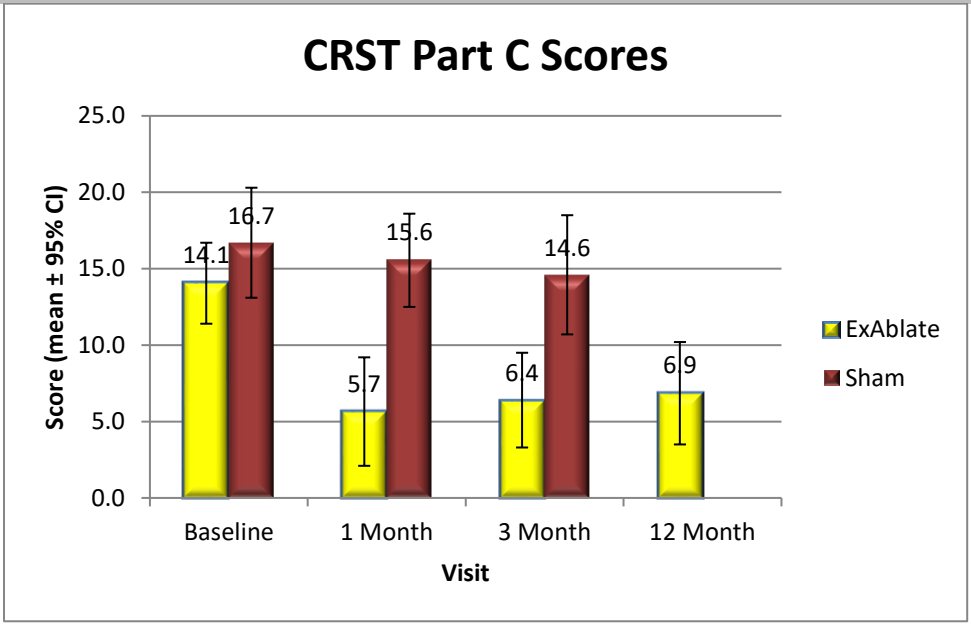

Figure 12. CRST Part C Scores show the treatment effect of ExAblate thalamotomy was maintained over time.

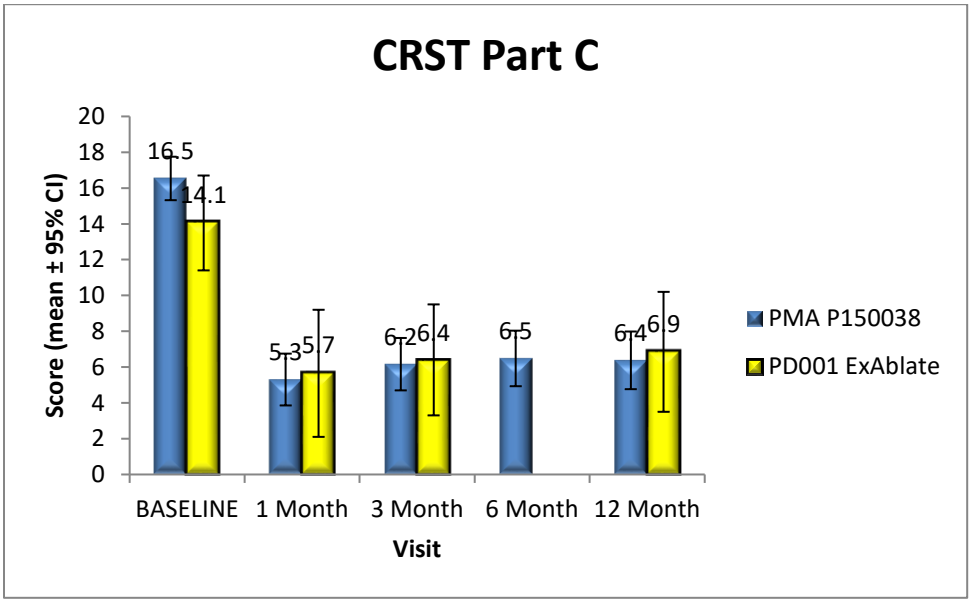

Figure 13. CRST Part C shows the TDPD trial produced similar treatment effects as observed in the ET pivotal trial.

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

3.2.5 QUALITY OF LIFE IN ESSENTIAL TREMOR QUESTIONNAIRE - QUEST

QUEST is a Quality of Life measure specially designed for ET patients that indicates how much ET impacts their life across 5 dimensions: Communication, Work and Finances, Hobbies and Leisure, Physical, and Psychosocial. The Summary of Dimensions score (the average of all 5 dimensions) represents the impact of ET on the subject's overall quality of life, i.e., the subject disability. The results of this analysis mimic that of the primary endpoint at 3 months with a 40% improvement in the ExAblate group as compared to Baseline, **Table 15**. This was comparable to the 43% improvement demonstrated in the pivotal trial.

Table 15. QUEST by Treatment Group by Visit Through Month 12

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

Notes:

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

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

3.2.5 SUMMARY OF EFFICACY RESULTS

ExAblate *Vim* thalamotomy for TDPD subjects resulted in significant improvement in treated side upper extremity tremor that was maintained through the 12-month study visit. Primary effectiveness was evaluated using validated scores: on medication, Upper Limb tremor-motor subscore from Parts A & B of the CRST. In the TDPD cohort study, the percent change from baseline for the ExAblate-treated group was 51.6% compared to 12.7% for the Sham Control, a difference which resulted in a Wilcoxon rank-sum value of $p = 0.030$. We also evaluated the rest tremor components of the CRST and the UDysRS for Parkinson's patients. It is also especially noteworthy that the 51.6% improvement in the ExAblate treated TDPD cohortwas essentially the same (46.9%) as that observed in the ET PMA trial (P150038). The upper extremity tremor score of 19.0 at baseline significantly improved to 9.6 at the 3 Month visit resulting in a Wilcoxon rank-sum value of $p < 0.001$. This response is quite robust, especially considering the small sample size used in this trial. The effect is also durable. The mean score at the 12 Month visit was 10.5 compared to the 9.6 at the 3 Month visit.

The improvement was quite robust given the sample size. Additionally, this improvement supported improvements in functional outcome and quality of life measures (non-statistically significant improvements in QUEST). **Figure 14** presents an overview of study outcomes compared to the ET PMA trial. Finally, improvements in upper extremity tremor of TDPD cohort patients (**Figure 8**, **Figure 9**) was similar to that reported in the PMA for essential tremor (P150038).

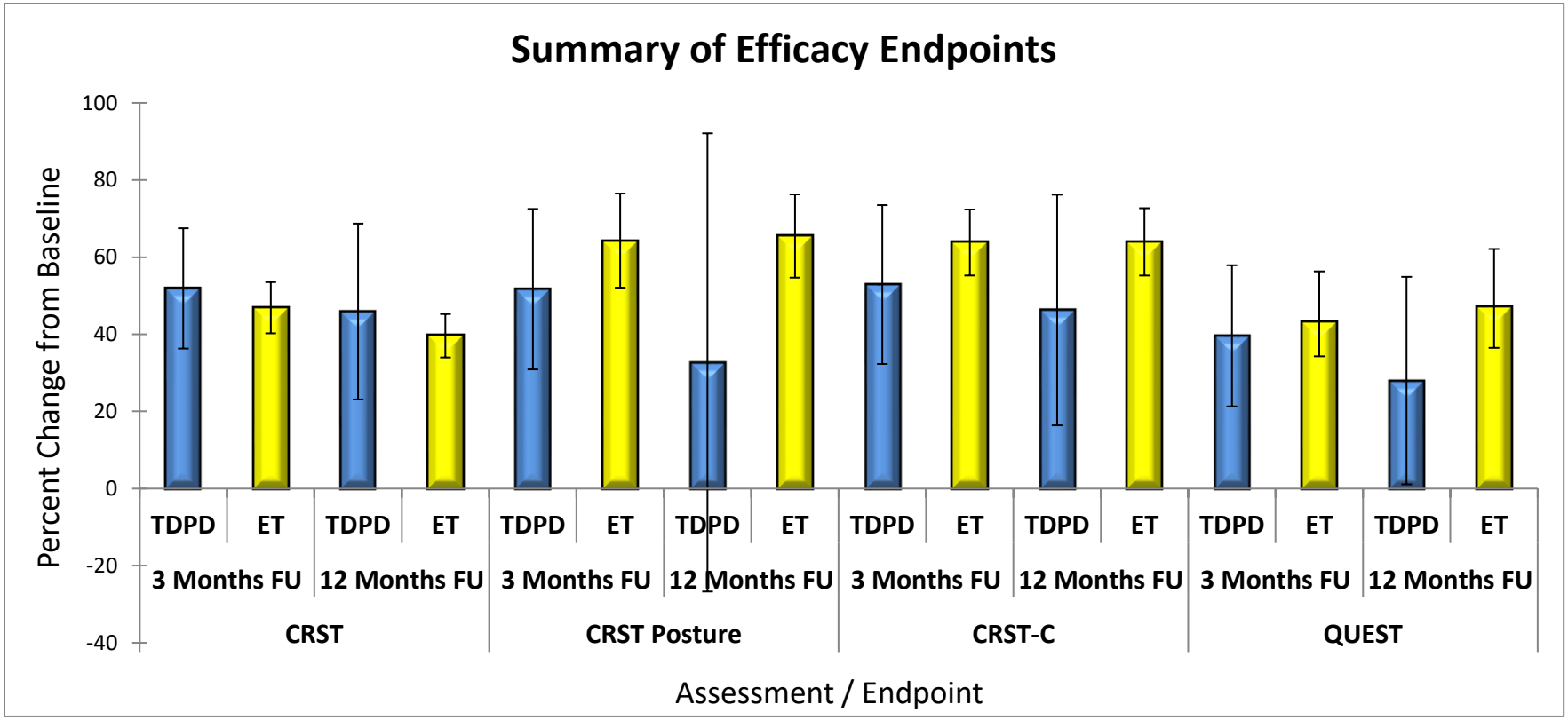

Figure 14. Efficacy TDPD outcomes compared to the ET PMA outcomes.

3.2.6 CROSSOVER GROUP

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

3.3 OVERALL STUDY CONCLUSIONS

The safety profile continues to be favorable and similar to previous experience with ExAblate Thalamotomy for upper extremity tremor in the ET trial (P150038). In the ExAblate-treated TDPD cohort 95% of all adverse events were Mild or Moderate in severity. Five percent of events were reported as severe and no events were life threatening. This was similar to the TDPD Sham control group where 90% of adverse events were Mild or Moderate. For comparison, in the PMA ET trial 99.5% of adverse events were reported as Mild/Moderate.

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

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

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

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

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

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

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

CHAPTER 4: SAMPLE PATIENT LETTER

Exablate Neuro MR Guided Focused Ultrasound for Tremor-Dominant Parkinson's Disease with medication-refractory tremor

What Patients Should Know?

You have been scheduled for an Exablate Neuro Thalamotomy for yourTD PD Tremor. Your treatment appointment has been scheduled for _____ AM / PM.

If your appointment is in the morning, please do not eat or drink anything after midnight the night before the procedure. If your appointment is after noon, do not eat or drink anything after 6:00 AM. Please discuss your medications, including those you are taking for your tremor, with your doctor so they can tell you what to do about medications for the day of the procedure. Please note FOR THE TREATMENT you may not be TAKING YOUR MEDICATIONS FOR TDPD TREMOR for approximately 12 hours prior to the procedure. Please discuss with our treating physician.

The INSIGHTEC Exablate Neuro system that will be used by your doctor is an MRgFUS system. The Exablate Neuro uses information from magnetic resonance ("MR") images of your head and what you are feeling during the procedure to monitor the safety and success of the treatment. You will remain awake and conscious during the procedure in order to provide feedback to the treating physician during the course of the procedure.

As a patient undergoing this treatment, your role in this process is very important. The following information is for you to read prior to starting the treatment. Should you need further information, do not hesitate to ask your treating physician any questions you may have.

On the day of your treatment, medicine will be given through a small tube in your arm vein (I.V.) so that medications can be given to your during the procedure. You may have a urinary catheter to help keep your bladder empty during the treatment. You may need to wear compression stockings during the procedure. If you are female and not menopausal, you may also have a pregnancy test to rule out pregnancy. Wires will be attached to your body to monitor your heart rate, oxygen level, and blood pressure during the procedure.

Because we need good contact between the ultrasound and the brain, we will shave your head on the morning of the appointment. Please do not apply any creams or oil(s) to your head before the treatment appointment.

A stereotactic headframe will be placed around your head to immobilize your head during the procedure. The frame is a metal ring that is anchored into your skull bone so your head will not move around when you lie down on the table. The placement of the pins involves a injection of anesthesia in the location of the pins. A silicone membrane will be placed on your head. This is used to seal the space where cold water will circulate between your scalp and the helmet of the Exablate device. The

circulating cold water will ensure adequate contact (acoustic coupling environment) between your head and the ultrasound transducer.

You will lie down on the table and will be positioned to ensure you feel combatable to lie still for several hours. You may experience a sore neck or discomfort from lying supine in the same position for a period of time during the treatment, but you should make all the efforts not to move during the planning or actual treatment.

Then, the doctor will take a sequence of several MR scans to plan the treatment. This process usually takes about an hour. The doctor will use the MR images to plan your treatment and control where the ultrasound waves are aimed.

During the procedure your vital signs (e.g. pulse, the level of oxygen your blood is carrying etc.) will be measured. You must lie still and not move during this time. You may speak at any time during the treatment and your doctor will be able to hear what you say.

A baseline physiological assessment will be taken prior to the actual treatment. You may be asked to draw spirals, lines and test your handwriting on a clipboard, position or move your hands in certain patterns to allow the team to observe your tremor.

During the treatment, a number of short ultrasound pulses (sonications - about 10-30 second energy pulse followed by a few minutes waiting period) will be aimed into the targeted area. This heating causes the brain tissue on the intended target to absorb the energy and heats up. With the proper amount of heat, the nerve cells will be killed (ablated) with the goal to eliminate your tremor. The energy/heat will be low and will escalate with successive sonications during the treatment. With each sonication more MR images will be taken to see where the heating is taking place. Your doctor will review these pictures throughout the procedure to confirm that the treatment is continuing as it should.

From time to time, you will be asked how you are feeling. A physiological assessment will be done to evaluate any relief in tremor and/or side effects. You should tell the team if you begin to experience any unusual feelings during or post sonications. The kind of feelings that you might experience caused by the treatment itself or the administered medications have been described by previous patients as: warmth, numbness, facial hand or fingertip tingling, changes in speech, nausea during or post sonications, transient pressure or intense heat on your scalp, transient dizziness or vertigo etc. Some of those sensations are an expected part of this treatment and yet you should inform your doctor(s) about any appearance of unusual feeling which may be addressed with medication or adjustment of the treatment.

When you are positioned on the table, an Emergency Stop button will be given to you to hold during the treatment. If you press this button it will immediately stop the treatment and alert your doctor. You will be asked why you used the button and the team will try to alleviate your problem. If at any time you experience a problem, you should press the Stop Button and inform your doctor about the

kind of feeling that you experienced. There are several system parameters that your doctor can change to continue the treatment.

Once the treatment is finished, and other set of MR images will be taken. After that is done, you will be taken out of the MR and the stereotactic headframe, sealing membrane, I.V. and catheter (if was used) will be removed, and you will be taken to a room while the medication from the treatment wears off. You may be observed for approximately a couple of hours once your treating physician deems you are ready to go home. Your doctor will be discussing the whole procedure with you including what happens after the procedure. If you need longer post-procedure recovery time, you may be spending 24-48 hours at the hospital.

We hope that this will help explain your treatment, and what you can expect. Please do not hesitate to ask if you have any further questions.

If you have any questions or concerns that are not answered here, you may contact your doctor at _____.