

ExAblate® Model 4000 Type 1

Application: Brain Essential Tremor

INFORMATION FOR PRESCRIBERS

System Software Version 6.6

July - 2016

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InSightec
ExAblate® System

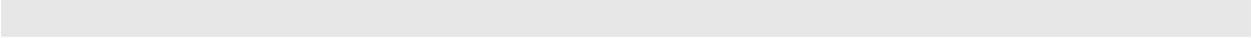
INFORMATION FOR PRESCRIBERS

Caution	FEDERAL LAW RESTRICTS THIS DEVICE TO SALE BY OR ON THE ORDER OF A PHYSICIAN WHO HAS COMPLETED TRAINING IN THE USE OF THE DEVICE.
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Read all instructions, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, prior to use. Failure to follow these instructions could result in serious patient injury.

Training in both magnetic resonance imaging and use of the ExAblate are critical to ensure proper performance and safe use of this device.

Physicians should contact their local InSightec representative prior to initial use of the ExAblate to obtain information about training and receive team training requirements.



1.0 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
Version	1
Application	Brain Essential Tremor
Clinical SW Ver.	6.6
CPC SW Ver.	4.76

The ExAblate system for this indication will also be marketed under

- “Exablate Neuro” with the following logo:

The logo for Exablate Neuro features the word "Exablate" in a light blue, sans-serif font, followed by "Neuro" in a slightly larger, grey, sans-serif font. A vertical blue bar is positioned to the left of the "Exablate" text, and a horizontal green bar is positioned above the "a" in "Exablate".

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 Essential Tremor (ET), 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 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 ET 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 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.

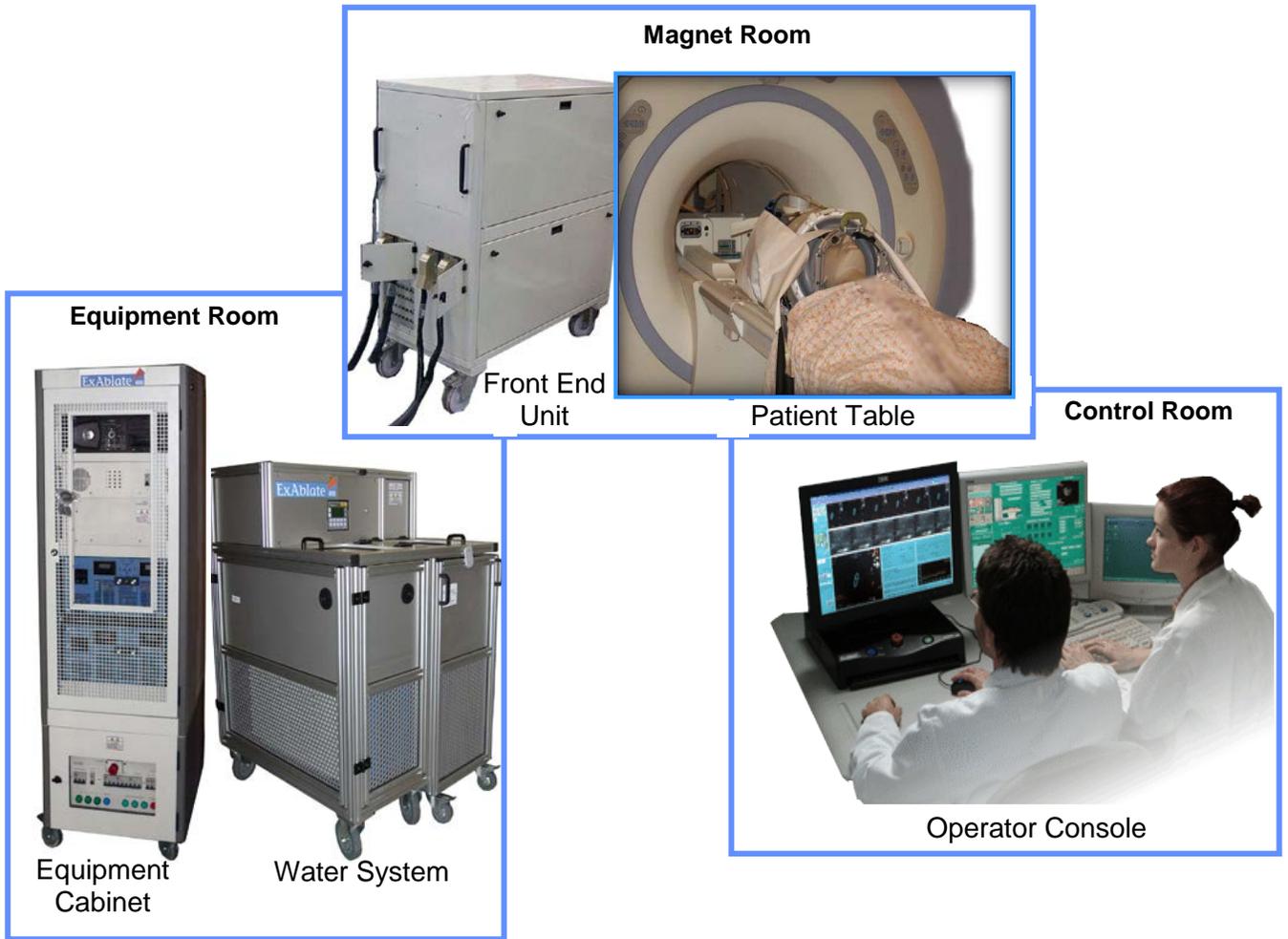
Supporting Equipment:

- 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 acquisition electronics, and power supplies **(Figure 1)**.

- **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



1.1.4 ExAblate Neuro Accessories

The full list of ExAblate Neuro accessories are listed in **Table 1** below.

Table 1: List of Accessories for Use with the ExAblate Neuro		
Name	InSightec P/N	Comments
Long / Short Stereotactic Frame Pins Set [‡]	MPR000444 / MPR000445	For Stereotactic frame fixation.
Stereotactic Frame [‡]	ASM001399	Stereotactic head frame, including adapters to ExAblate 4000 patient interface.
Frame Attachment Strap	MEC001647	Assists with stereotactic frame placement.
Protective Frame Pin Caps	MPR001164	Silicone protective caps used to cover the frame pins, for membrane protection. For single use. Supplied in groups of 5 units.
Silicone Membrane	ASM000355	For coupling of patient head to FUS helmet. Allows multiple uses. For use only with 3.0T MRI ExAblate system.
Helmet Sealant	BUY000180-AA	Tube containing sealant material for water-tight coupling to the transducer. For single-use.
DQA Gel	SET000893	Tissue mimicking phantom gel, used for Daily Quality Assurance (DQA).
Cleaning Kit	SET000870	Bottle filled with Sodium hypochlorite Chloride [*] based solution, and disinfectant wipes (based on ammonium chloride [*]). This is used for cleaning after each treatment. For single-use.
[‡] : Integra Radionics MR-compatible stereotactic head frame with insulated pins and non-metallic posts (K946252 and K944463). [*] : In full compliance with FDA recommendations: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=178.1010		

1.1.5 Software

The ExAblate Neuro clinical software, which is based on Graphical User Interface (GUI), 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 fiducial 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

1.1.6 Manual Graphical User Interface (GUI)

The GUI, shown in **Figure 2**, 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.

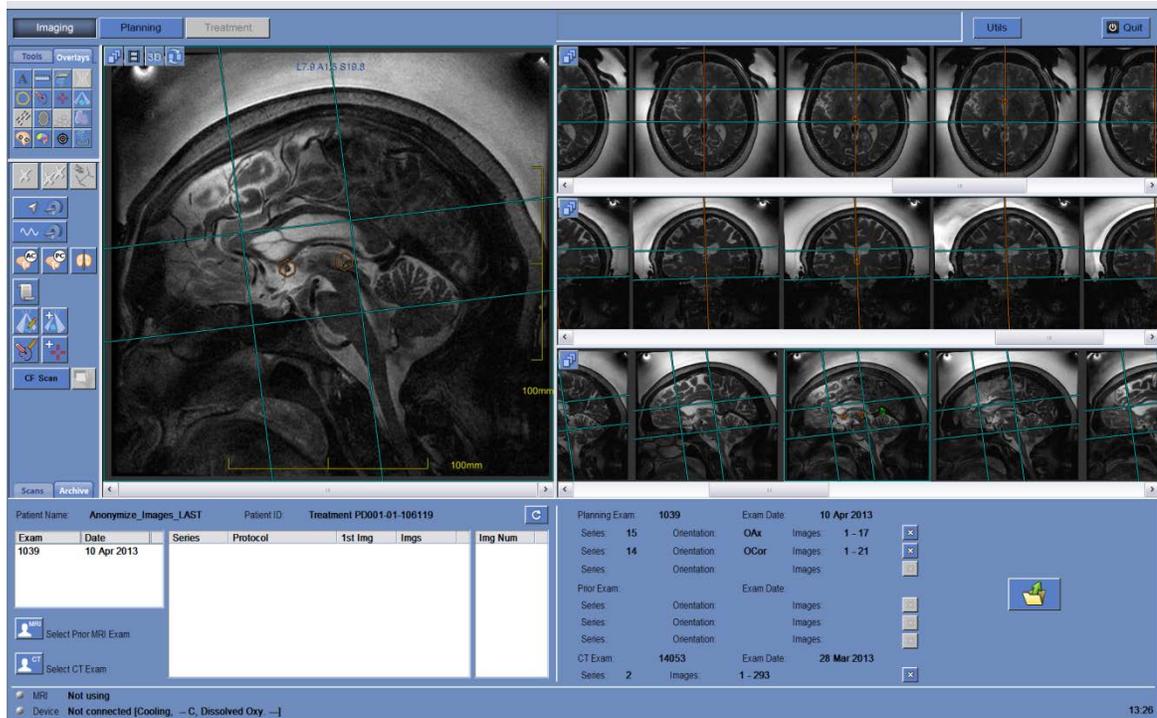


Figure 2: ExAblate Software Graphical User Interface: 1) Graphical user interface uses buttons and icons to identify functions during treatment, 2) the software overlays graphical displays on MR image(s), 3) treatment parameters and treatment progress easily accessible for continuous tailoring and monitoring 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, the skin line must be drawn before the system can create a sonication plan, and 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 - **Figure 2**).

➤ **Cavitation / Reflection monitoring**

During treatment, the software displays the reflection 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

The ExAblate Neuro is intended for use in the unilateral Thalamotomy treatment of idiopathic Essential Tremor patients with medication-refractory tremor. Patients must be at least age 22. The designated area in the brain responsible for the movement disorder symptoms (*ventralis intermedius*) must be identified and accessible for targeted thermal ablation by the ExAblate device.

2.0 PATIENT SELECTION CRITERIA FOR TREATMENT WITH EXABLATE NEURO

2.1 PATIENT SELECTION CRITERIA

1. Men and women age 22 years or older;
2. A confirmed diagnosis of Essential Tremor refractory to medication therapy such as propranolol or primidone;
3. Able to fit into MRI unit;
4. Able to tolerate the procedure with or without some form of sedation (e.g.: conscious sedation);
5. Able to communicate sensations to the physician during the procedure; and
6. 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.
- A CT 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.**

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

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

3.0 SUMMARY OF PIVOTAL CLINICAL STUDY

3.1 STUDY DESIGN

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

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

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

3.1.1 ELIGIBILITY CRITERIA

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

3.1.1.1 Inclusion Criteria

- 1) Men and women age 22 years or older
- 2) Subjects who are able and willing to give consent and able to attend all study visits,
- 3) A diagnosis of ET as confirmed from clinical history and examination by a neurologist or neurosurgeon specialized in movement disorder
- 4) Tremor refractory to adequate trials of at least two medications, one of which should be a first line therapy of either propranolol or primidone. An adequate medication trial is defined as a therapeutic dose of each medication or the development of side effects as the medication dose is titrated.
- 5) Following the 1-month medication stability period, subject must be on stable medication for tremor
 - a) The 1-Month stability period visit will be 1-month post consent date
- 6) Vim nucleus of thalamus can be target by the ExAblate device. The thalamic region must be apparent on MRI such that targeting can be performed by measurement from a line connecting the anterior and posterior commissures of the brain.
- 7) Able to communicate sensations during the ExAblate Neuro treatment

- 8) Postural or intention tremor severity score of greater than or equal to 2 in the dominant hand/arm as measured by the CRST rating scale while stable on medication.
- 9) May have bilateral appendicular tremor
- 10) Significant disability due to essential tremor despite medical treatment (CRST score of 2 or above in any one of the items 16-23 from the Disability subsection of the CRST: [speaking, feeding other than liquids, bringing liquids to mouth, hygiene, dressing, writing, working, and social activities])
- 11) Inclusion and exclusion criteria have been agreed upon by two members of the medical team.
- 12) Subjects on stable antidepressant medications for at least 3 months may be enrolled into this study (i.e., no change in medication drug or dosage for 3 months).

3.1.1.2 Exclusion criteria

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

- 1) Subjects with unstable cardiac status including:
 - a) Unstable angina pectoris on medication
 - b) Subjects with documented myocardial infarction within six months of protocol entry
 - c) Significant congestive heart failure defined with ejection fraction < 40
 - d) Subjects with unstable ventricular arrhythmias
 - e) Subjects with atrial arrhythmias that are not rate-controlled
- 2) Subjects exhibiting any behavior(s) consistent with ethanol or substance abuse as defined by the criteria outlined in the DSM-IV as manifested by one (or more) of the following occurring within a 12 month period:
 - a) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household).
 - b) Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use)
 - c) Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)
 - d) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for

example, arguments with spouse about consequences of intoxication and physical fights).

- 3) Severe hypertension (diastolic BP > 100 on medication)
- 4) Subjects with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc.
- 5) Known intolerance or allergies to the MRI contrast agent (e.g. Gadolinium or Magnevist) including advanced kidney disease
- 6) Patient with severely impaired renal function with estimated glomerular filtration rate <30 mL/min/1.73m² (or per local standards should that be more restrictive) and/or who is on dialysis;
- 7) History of abnormal bleeding and/or coagulopathy
- 8) Receiving anticoagulant (e.g. warfarin) or antiplatelet (e.g. aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk of hemorrhage (e.g. Avastin) within one month of focused ultrasound procedure
- 9) Active or suspected acute or chronic uncontrolled infection
- 10) History of immunocompromise including those who are HIV positive.
- 11) History of intracranial hemorrhage
- 12) Cerebrovascular disease (multiple CVA or CVA within 6 months)
- 13) Subjects with uncontrolled symptoms and signs of increased intracranial pressure (e.g., headache, nausea, vomiting, lethargy, papilledema).
- 14) Individuals who are not able or willing to tolerate the required prolonged stationary supine position during treatment (can be up to 4 hrs of total table time.)
- 15) Are participating or have participated in another clinical trial in the last 30 days
- 16) Significant claustrophobia that cannot be managed with mild medication.
- 17) Subjects unable to communicate with the investigator and staff.
- 18) Presence of any other neurodegenerative disease such as Parkinson-plus syndromes suspected on neurological examination. These include: multisystem atrophy, progressive supranuclear palsy, dementia with Lewy bodies, and Alzheimer's disease.
- 19) Anyone suspected to have the diagnosis of idiopathic Parkinson's disease. Anyone with the presence of parkinsonian features including bradykinesia, rigidity, or postural instability will be excluded. Subjects who exhibit only mild resting tremor but no other symptoms or signs of PD may be included.

- 20) Presence of significant cognitive impairment as determined with a score ≤ 24 on the Mini Mental Status Examination (MMSE)
- 21) Subjects with life-threatening systemic disease that include and not limited to the following will be excluded from the study participation: HIV, Liver Failure, blood dyscrasias, etc.
- 22) Subjects with a history of seizures within the past year
- 23) Subjects with presence or history of psychosis will be excluded. Subjects with significant or active mood disorders including depression will be excluded. For the purpose of this study, we consider a significant mood disorder to include any subject who:
 - a) Scores ≥ 20 on the PHQ-9 questionnaire
 - b) Is currently under the care of a psychiatrist
 - c) Is currently participating in cognitive-behavioral therapy
 - d) Has been hospitalized for the treatment of a psychiatric illness within 12 months
 - e) Has ever received transcranial magnetic stimulation
 - f) Has ever received electroconvulsive therapy
- 24) Subjects with risk factors for intraoperative or postoperative bleeding: platelet count less than 100,000 per cubic millimeter, INR coagulation studies exceeding local institution laboratory standards, or a documented coagulopathy
- 25) Subjects with brain tumors
- 26) Any illness that in the investigator's opinion preclude participation in this study.
- 27) Pregnancy or lactation.
- 28) Legal incapacity or limited legal capacity.
- 29) Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia
- 30) Subjects who have been administered botulinum toxins into the arm, neck, or face for 5 months prior to Baseline.
- 31) Subjects who have an Overall Skull Density Ratio of 0.45 (± 0.05) or less as calculated from the screening CT.

3.1.2 PATIENT TREATMENT

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

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

3.1.3 STUDY FOLLOW UP

Study Follow-up

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

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

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

Table 2 provides the full schedule of evaluations in the study.

Table 2. Summary of Study Schedules and Measurements									
	Screening	Baseline Assessment*	Treatment	1 Day	1 Week	1 Month	3 Month	6 Month	12 Month
Consent	X								
Eligibility Evaluation with labs	X	X							
Medications	X	X	X	X	X	X	X	X	X
30 day meds stabilization		X							
Medical History	X								
Physical Exam	X	X		X	X	X	X	X	X
Neurological status	X		X	X	X	X	X	X	X
CRST (unblinded)	X							X	X
Site Blinded Assessor CRST		X				X	X		
Blinded Tremor Core Lab CRST		X				X	X	X	X
QOL (QUEST)	X	X				X	X	X	X
PHQ-9	X					X	X	X	X
CT	X								
MR		X	X						X
Treatment			X						
Adverse Events			X	X	X	X	X	X	X
Exit Form									X

3.1.4 STUDY ENDPOINTS

Safety Endpoint

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

Primary Effectiveness Endpoint

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

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

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

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

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:

$$CRST_{[Contralateral]} = \frac{PART_A + PART_B}{Max_Score}$$

- **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 of the study are as follows:

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

3.1.5 STUDY STATISTICAL ANALYSIS PLAN AND ANALYSIS POPULATION

3.1.5.1 Study Sample Size

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

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

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

^[1] It should be noted that a score of one represents the worst case scenario, whereas the score of “zero” represents the best case scenario in the Essential Tremor impact on the subject’s life. An improvement in the combined Tremor/Motor Function matrix at follow-up will reflect scores with decreasing values.

0.52 for the 15 subjects in the crossover arm. The probability of observing an event rate of 0.01 is 45% with 60 subjects.

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

3.1.5.2 Study Analysis Population

The following analysis populations were used to evaluate study results:

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

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

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

3.1.6 STUDY SUBJECT ACCOUNTABILITY

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

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

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

A subject accountability table (**Table 3**) and study flowchart (**Figure 3**) are provided below.

Table 3. Patient Disposition by Treatment Group and Scheduled Visit.								
Category	Baseline		1 Month FU		3 Months FU		6 Months FU	12 Months FU
	ExAblate	Sham	ExAblate	Sham	ExAblate	Sham	ExAblate	ExAblate
Recruited	121							
SF 1 ¹	33							
Discontinued for Reasons Other than SF (not yet randomized)	7							
Randomized ²	61	20						
SF 2 ³	5	0						
Theoretical ⁴	56	20	56	20	56	20	56	56
Death	0	0	0	0	0	0	0	0
Failure ⁵	0	0	0	0	0	0	1	1
Exited –Other Reasons ⁶	0	0	0	0	2	0	4	6
Expected ⁷	56	20	56	20	54	20	51	49
Actual ⁸	56	20	56	20	54	20	48	49
Actual % ⁹	100%	100%	100%	100%	100%	100%	94%	100%
<p>1 - SF 1 – Those subjects Recruited, but not meeting enrollment criteria</p> <p>2 - Randomized equals those Recruited minus SF 1 minus Discontinued for Reasons Other than SF (not yet randomized)</p> <p>3 - SF 2 – Randomized subjects who have not received any sonication and did not meet inclusion/exclusion criteria.</p> <p>4 - Theoretical is equal to the number of subjects Recruited minus SF 1 minus Discontinued for Reasons Other than SF minus SF 2. Therefore, theoretical is equal to the number of subjects eligible to receive treatment in either group</p> <p>5 - Failures include any subjects (ExAblate or Sham) who discontinued the study due to beginning another treatment for their condition</p> <p>6 - Exited the Main Analysis for reasons other than Failure.</p> <p>7 - Expected equals Theoretical minus Exited-Other Reasons minus Failures minus Death</p> <p>8 - Actual is the number of subjects actually returning for the follow-up visit</p> <p>9 - Actual % is the number of Actual subjects divided by Expected</p>								

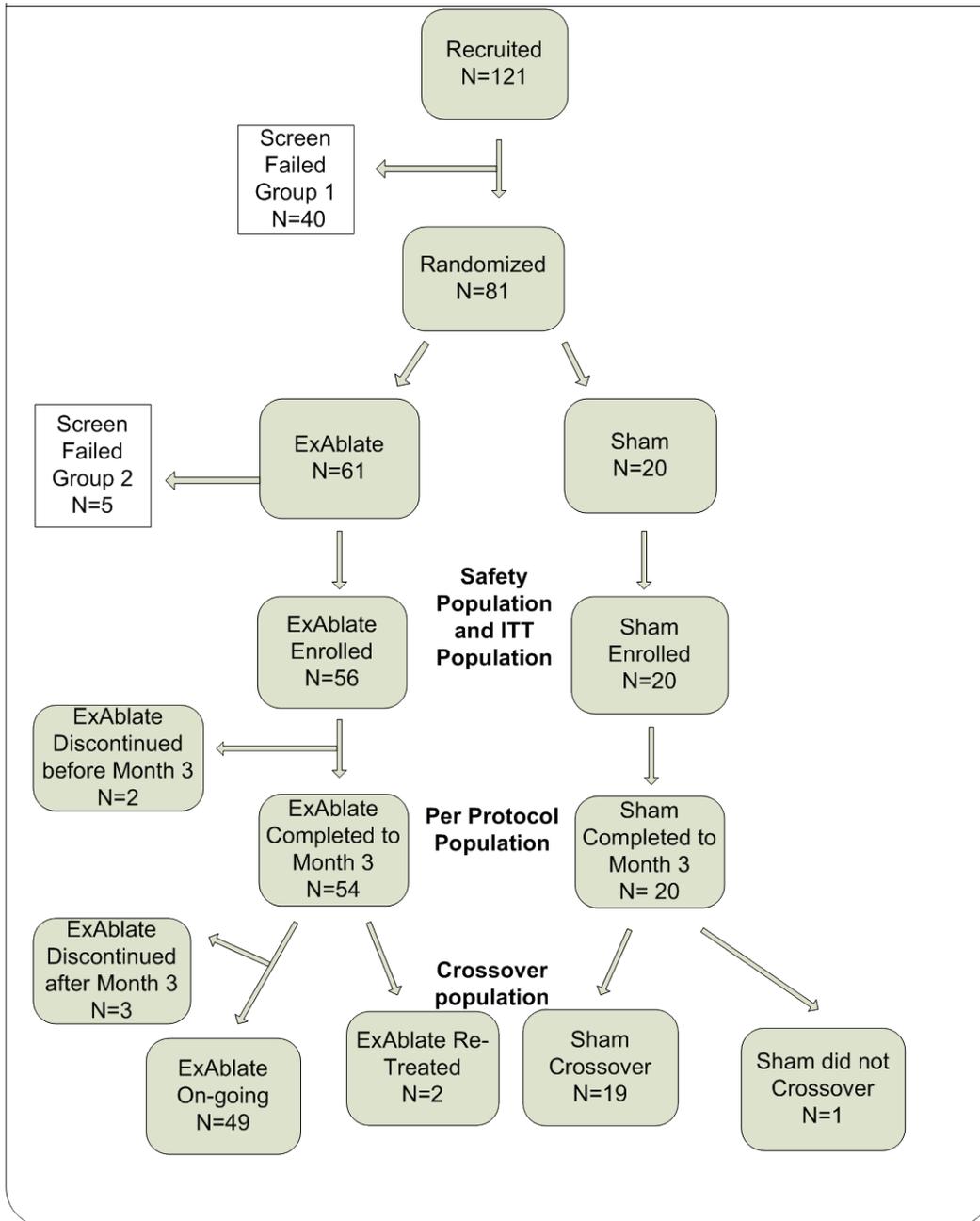


Figure 3: ET002 Study Flow Chart

3.1.7 STUDY DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The demographics of the study population are typical for an Essential Tremor study performed in the United States. The demographics, baseline, and operative characteristics were similar between the two treatment groups, as shown in **Table 4** below.

Table 4. Baseline and Demographic Information by Treatment Group			
Demographic Characteristics		Treatment Group	
		ExAblate N=56	Sham N=20
Age [Years]	Mean	70.8	71.4
BMI [kg/m ²]	Mean	26.9	27.9
Height [cm]	Mean	171.9	173.3
Weight [kg]	Mean	79.6	85.5
Gender	Male	37 (66%)	15 (75%)
	Female	19 (34%)	5 (25%)
Race	Caucasian	41 (73%)	16 (80%)
	African-American	0	0
	Asian	14 (25%)	4 (20%)
	Hispanic	0	0
	Other	1 (2%)	0
Family History of ET	Yes	39 (70%)	16 (80%)
	No	17 (30%)	4 (20%)
Average Years ET History (yrs)	Mean	13.9	14.7
Skull Density Ratio “SDR”	Mean	0.6	0.5
Treated (Contralateral UE CRST Primary Endpoint Subscore)	Mean	0.57	0.51
QUEST Summary of Dimensions Total Score*	Mean	42.55	42.76
Functional Disabilities CRST Part C Total Score	Mean	2.07	2.01
Note: None of the above baseline/demographic characteristics showed statistical differences between treatment groups.			
*Quest is missing at Baseline for one Sham subject, so N = 19.			

3.2 STUDY RESULTS

3.2.1 SAFETY RESULTS

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

12 follow-up visit for the ExAblate group and data through the Month 3 follow-up visit for Sham group.

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

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

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

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

AEs are reported in **Table 5** to **Table 11** below. See **Table 5** for a summary of safety by severity between groups.

Table 5: Summary of Safety (Adverse Events) Between Groups by Severity				
Severity of AE	ExAblate		Sham	
	Frequency N=184	Incidence N=56	Frequency N=26	Incidence N=20
Mild	137 (74.4%)	46 (82%)	18 (70%)	10 (50%)
Moderate	45 (24.4%)	27 (48%)	8 (30%)	6 (30%)
Thalamotomy Related SAE	1 (0.6%)	1 (2%)	0 (0%)	0 (0%)
Severe				
Unrelated SAE	1 (0.6%)	1 (2%)	0 (0%)	0 (0%)
Total	184 (100%)	49 (88%)	26 (100%)	14 (70%)

Two adverse events were reported as serious in the Main Analysis (Table 6). In this study, there were 2 AEs that met the definition of SAE as per FDA regulation. Both occurred in the ExAblate group. Both were reviewed by the DSMB and adjudicated and FDA was notified of the occurrence of these events. The second ExAblate subject experienced an embolic peripheral cortical stroke likely due to left carotid artery disease or a cardiac event. The stroke specialist, the treating physician, and the DSMB concurred that the event was unrelated to ExAblate and not due to the study intervention

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

Serious Adverse Events (SAEs)	ExAblate		Sham	
	Frequency N=184	Incidence N=56	Frequency N=26	Incidence N=20
Thalamotomy Related	1 (0.6%)	1(2%)	0 (0%)	0 (0%)
Unrelated	1 (0.6%)	1(2%)	0 (0%)	0 (0%)
Total SAE's	2 (1.2%)	2 (4%)	0 (0%)	0 (0%)

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

Body System	Preferred Term	ExAblate (N events = 184; # pts = 56)			Sham (N events = 26; # pts = 20)	
		Mild	Moderate	Severe	Mild	Moderate
		N (%)	N (%)	N (%)	N (%)	N (%)
Cardiovascular	Bradycardia	1 (0.5%)	1 (0.5%)	0	0	0
	Hypertension	1 (0.5%)	4 (2%)	0	0	1 (4%)
	Hypotension	0	1 (0.5%)	0	0	0
	TIA	0	0	1 (0.5%)	0	0
ENT	Tinnitus	3 (2%)	0	0	0	0
Eye	Vision problems	1 (0.5%)	0	0	0	0
	Watering Eyes	1 (0.5%)	0	0	0	0
Gastrointestinal	Dysphagia	1 (0.5%)	0	0	0	0
	Increased salivation	1 (0.5%)	0	0	0	0
	Nausea/Vomiting	6 (3%)	7 (4%)	0	2 (8%)	0
General	Fatigue	2 (1%)	0	0	0	0
	Generalized Weakness	0	1 (0.5%)	0	1 (4%)	0
	Impatience	1 (0.5%)	0	0	0	0
	Restlessness	1 (0.5%)	0	0	0	0
Infection	Common Cold	1 (0.5%)	0	0	0	0
	Ear Infection	0	1 (0.5%)	0	0	0
Musculoskeletal	Gait Disturbance	2 (1 %)	2 (1%)	0	0	0
	Dysergia	1 (0.5%)	1 (0.5%)	0	0	0
	Imbalance	7 (4%)	3 (2%)	0	1 (4%)	0
	Muscukoskeletal Weakness	1 (0.5%)	1 (0.5%)	0	0	0

Table 7 Frequency and Incidence of Adverse Events by Treatment Group and Severity.						
Body System	Preferred Term	ExAblate (N events = 184; # pts = 56)			Sham (N events = 26; # pts = 20)	
		Mild	Moderate	Severe	Mild	Moderate
		N (%)	N (%)	N (%)	N (%)	N (%)
	Other Musculo skeletal Pain	0	1 (0.5%)	0	0	0
	Positional Pain	5 (3%)	0	0	1 (4%)	0
	Unsteady	5 (3%)	1 (0.5%)	0	0	0
Nervous	Anxiety	1 (0.5%)	0	0	1 (4%)	1 (4%)
	Ataxia	6 (3%)	1 (0.5%)	0	0	0
	Dizziness	0	1 (0.5%)	0	0	0
	Dysesthesia	1 (0.5%)	0	0	0	0
	Dysgeugia	3 (2%)	0	0	0	0
	Dysnogia	2 (1%)	0	0	0	0
	Dysmetria	2 (1%)	0	0	0	0
	Involuntary Movements-UE	1 (0.5%)	0	0	0	0
	Memory Deterioration	1 (0.5%)	0	0	0	0
	Numbness/Tingling	24 (13%)	3 (2%)	0	2 (8%)	1 (4%)
	Slurred speech	1 (0.5%)	0	0	0	0
	Paresthesia	1 (0.5%)	0	0	0	0
	Somnolence	1 (0.5%)	0	0	0	0
	Pain/Discomfort	Ankle pain	0	1 (0.5%)	0	0
Foot pain		0	1 (0.5%)	0	0	0
Headache		10 (5%)	5 (3%)	0	4 (15%)	1 (4%)
Sonication-related Head pain		7 (4%)	7 (4%)	0	0	0
Respiratory	Hiccups	1 (0.5%)	0	0	0	0
Skin	Bruising	1 (0.5%)	0	0	0	0
	Skin Rash	1 (0.5%)	0	0	0	1 (4%)
Stereotactic Frame	Eyelid Ptosis	2 (1%)	0	0	0	0
	Facial edema	0	1 (0.5%)	0	0	0
	Numbness/Tingling	1 (0.5%)	0	0	1 (4%)	1 (4%)
	Bruising – Stereotactic Frame	1 (0.5%)	0	0	0	0
	Pin Site Edema	1 (0.5%)	0	0	1 (4%)	1 (4%)
	Pin Site Abrasion	2 (1%)	0	0	0	0
	Pin site bleeding	0	0	0	0	1 (4%)
	Pin site pain	7 (4%)	1 (0.5%)	0	4 (15%)	0
Urinary	Catheter Irritation	1 (0.5%)	0	0	0	0
	Urinary Urgency	1 (0.5%)	0	0	0	0
	BHP	0	1 (0.5%)	0	0	0
Vestibular Disorder	Vertigo	2 (1%)	0	0	0	0
	Dizziness	11 (6%)	0	0	0	0
	Paroxysmal Vertigo Episodes	1 (0.5%)	0	0	0	0
Vision	Vision change	1 (0.5%)	0	0	0	0
TOTAL		137 (74%)	46 (25%)	1 (0.5%)	18 (69%)	8 (31%)

As shown in **Table 8** , the majority (89% ExAblate; 96% Sham) of all events begin within 30 days of the procedure and nearly all resolved.

Table 8. Adverse Events Onset versus Adverse Event Duration by Treatment Group						
Onset/ Duration	ExAblate			Sham		
	Onset < 30 days	Onset 31-90 days	Onset > 90 days	Onset < 30 days	Onset 31-90 days	Onset > 90 days
	Freq N=184	Freq N=184	Freq N=184	Freq N=27	Freq N=27	Freq N=27
<30 days	88 (48%)	2 (1%)	4 (2%)	24 (92%)	0	0
31-90 days	14 (8%)	2 (1%)	1 (1%)	2 (8%)	0	0
> 90 days	25 (14%)	2 (1%)	4 (2%)	0	0	0
Ongoing	35 (20%)	2 (1%)	5 (3%)	0	0	0
TOTAL	162 (88%)	8 (4%)	14 (8%)	26 (100%)	0	0

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

Adverse events were categorized by relation into groups. Out of the 184 AEs in the ExAblate group, 53 (29%) events were categorized as Transient (i.e., resolved right after the sonication or same day up to 3 days post-procedure) and 57 (31%) AEs were determined to be Unrelated to the study. **Table 9** summarizes the Transient and Unrelated AEs by body system, coded term, and treatment arm.

Table 9. Frequency of ExAblate Adverse Events Categorized as Transient or Unrelated to ExAblate.						
Relation / Body System / AE Coded Term			ExAblate N=184		Sham N=26	
			N	%	N	%
Transient Events	Gastrointestinal	Nausea/Vomiting	12	7%	2	8%
	Nervous	Anxiety	1	0.5%	2	8%
		Dysgnosia	1	0.5%	0	0%
		Dysgeugia	1	0.5%	0	0%
		Numbness/Tingling	4	2%	2	8%
	Pain/Discomfort	Headache	10	5%	4	15%
		Sonication-Related Head Pain	13	7%	0	0%
	Vestibular Disorder	Dizziness	9	5%	0	0%
Vertigo		2	1%	0	0%	
Transient Subtotal			53	29%	10	39%
Unrelated Events	Cardiovascular	Bradycardia	2	1%	0	0%
		Hypertension	5	3%	2	8%
		Hypotension	1	0.5%	0	0%
		TIA	1	0.5%	0	0%
	Eye	Vision Problem	1	0.5%	0	0%
		Watering Eyes	1	0.5%	0	0%
	Gastrointestinal	Increased Salivation/Drooling	1	0.5%	0	0%
		Nausea/Vomiting	1	0.5%	0	0%
	General	Impatience	1	0.5%	0	0%
		Restlessness	1	0.5%	0	0%
	Infection	Common Cold	1	0.5%	0	0%
		Ear Infection	1	0.5%	0	0%
	Musculoskeletal	Other Musculoskeletal	1	50.5%	0	0%

Table 9. Frequency of ExAblate Adverse Events Categorized as Transient or Unrelated to ExAblate.

Relation / Body System / AE Coded Term		ExAblate N=184		Sham N=26		
		N	%	N	%	
		Pain				
		Positional Pain	5	2.7%	0	0%
		Unsteady	2	1.1%	0	0%
	Nervous	Anxiety	1	0.5%	0	0%
		Dizziness	1	0.5%	0	0%
		Dysgeugia	1	0.5%	0	0%
		Involuntary Movements - UE	1	0.5%	0	0%
		Memory Deterioration	1	0.5%	0	0%
		Somnolence	1	0.5%	0	0%
		Pain/Discomfort	Positional pain	2	1%	1
	Ankle pain		1	0.5%	0	0%
	Foot pain		1	0.5%	0	0%
	Respiratory	Hiccups	1	0.5%	0	0%
	Skin	Bruising	1	0.5%	0	0%
		Skin Rash	1	0.5%	1	4%
	Stereotactic Frame	Bruising - Stereotactic Frame	1	0.5%	0	0%
		Eyelid Ptosis	2	1.1%	0	0%
		Facial edema	1	0.5%	0	0%
		Numbness/Tingling	1	0.5%	2	8%
		Pin Site Abrasion	2	1.1%	0	0%
		Pin site bleeding	0	0.0%	1	4%
		Pin Site Edema	1	0.5%	1	0%
	Urinary	Catheter Irritation	1	0.5%	0	0%
Urinary Urgency		1	0.5%	0	0%	
Urogenital	Benign Prostate Hypertrophy	1	0.5%	0	0%	
Subtotal Unrelated		57	31%	13	50%	
TOTAL		110	60%	23	88.5%	

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

Table 10. Frequency of Adverse Events Categorized as Related to the Procedure/Device/Thalamotomy.						
Relation/Body System, AE Coded Term			ExAblate Arm N=184		Sham Arm N=26	
			N	%	N	%
Procedure-related	ENT	Tinnitus	3	2%	1	0%
	Gastrointestinal	Dysphagia	1	0.5%	0	0%
	General	Fatigue	2	1%	0	0%
		Generalized Weakness	1	0.5%	1	4%
	Muskuloskeletal	Imbalance	0	0%	1	4%
	Nervous	Dysgnosia	1	0.5%	0	0%
		Numbness/ Tingling	1	0.5%	0	0%
	Pain/Discomfort	Headache	5	3%	0	0%
		Sonication-Related Head Pain	1	0.5%	0	0%
	Vestibular Disorder	Dizziness	1	0.5%	0	0%
Thalamotomy related	Muskuloskeletal	Dysergia	2	1%	0	0%
		Gait Disturbance	4	2%	0	0%
		Imbalance	10	5%	0	0%
		Muskuloskeletal Weakness	2	1.1%	0	0%
		Unsteady	4	2.2%	0	0%
	Nervous	Ataxia	7	3.8%	0	0%
		Dysesthesia	1	0.5%	0	0%
		Dysgeugia	1	0.5%	0	0%
		Dysmetria	2	1.1%	0	0%
		Numbness/ Tingling	22	12%	0	0%

Table 10. Frequency of Adverse Events Categorized as Related to the Procedure/Device/Thalamotomy.

Relation/Body System, AE Coded Term			ExAblate Arm N=184		Sham Arm N=26	
			N	%	N	%
		Tingling				
		Paresthesia	1	0.5%	0	0%
		Slurred Speech	1	0.5%	0	0%
TOTAL			74	100%	3	12%

3.2.1.1 Mental Status Assessment - PHQ-9

An additional safety measure that was captured in this study was mental status of patients using the PHQ-9 for depression. Per protocol, subjects with a score of 20 or higher were excluded until their depression was managed. Any subject who scored a 20 or more on follow-up was to be referred out for psychiatric evaluation and treatment. Any treatment beyond medication would be counted as a SAE. The follow-up PHQ-9 scores show no study subject scoring a 20 or higher on the PHQ-9 (Table 11) at any time during the study. This outcome indicates that the ExAblate treatment does not induce depression.

Table 11. Frequency Distribution of PHQ9 Exam Results (Safety)

Visit	Total Score of PHQ9 Tests Above 20							
	ExAblate				Sham			
	Yes		No		Yes		No	
	N	%	N	%	N	%	N	%
Screening	0	0.0	56	100.0	0	0.0	18	100.0
1 Month FU	0	0.0	56	100.0	0	0.0	20	100.0
3 Months FU	0	0.0	54	100.0	0	0.0	20	100.0
6 Months FU	0	0.0	47	100.0	0	0	0	0
12 Months FU	0	0.0	34	100.0	0	0	0	0

3.2.2 EFFECTIVENESS RESULTS

The primary analysis of effectiveness was based on the ITT population, i.e., the 76 evaluable subjects at the Month 3 time point, while some secondary efficacy endpoints continued to Month 12. Key effectiveness outcomes are presented in **Table 12** to **Table 17**.

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

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

3.2.2.1 Primary Endpoint

As shown in **Table 12**, the ExAblate group demonstrated nearly a 50% improvement in the Composite Tremor/Motor Function score compared to baseline, while the Sham group demonstrated virtually no improvement to slight worsening by Month 3. This difference in the percent change between treatment groups was highly significant (46.9% versus -0.1%, $p < 0.001$). Hence, this demonstrates that the Composite Tremor/Motor Function Primary Endpoint was successfully met.

Table 12. Primary Endpoint (Composite Tremor/Motor Score): Mean Score and Percent Change from Baseline at Three Months by Treatment Group (ITT)					
PE	Treatment Group				P-Value*
	ExAblate N = 56		Sham N = 20		
	Mean Score	% Change	Mean Score	% Change	
ITT Mean	0.30	46.9%	0.50	-0.1%	<0.001
Lower 95% CI		40.3%		-9.6%	
Upper 95% CI		53.5%		9.5%	
1. SE1 was calculated as Percent Change $((\text{Baseline} - \text{Visit})/\text{Baseline}) * 100$. 2. Higher SE1 values represent improvement *p-value reflects testing between groups.					

3.2.2.2 Confirmatory Secondary Endpoints Safety Results

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

PE Composite Tremor/Motor Function Score was recorded through Month 12 to assess the treatment response over time. As shown in **Table 13** below the mean difference between baseline and each scheduled visit was highly significant ($p < 0.001$) through the Month 12 visit. This demonstrates that the secondary endpoint involving the change in PE Composite score compared to baseline was successfully met through Month-12.

The data of **Table 13** is also presented in **Figure 4**.

Table 13. Confirmatory Endpoint: Percent Change in the Composite Tremor/Motor Function in ExAblate Arm by Visit (ITT)			
		Treatment Group	
Visit	SE2	ExAblate	P-Value
3 Months FU	Mean (%)	46.9	<0.001
	Lower 95% CI	40.3	
	Upper 95% CI	53.5	
	N	56	
6 Months FU	Mean (%)	43.1	<0.001
	Lower 95% CI	36.4	
	Upper 95% CI	49.9	
	N	56	
12 Months FU	Mean (%)	39.6	<0.001
	Lower 95% CI	34.0	
	Upper 95% CI	45.3	
	N	56	
Notes:			
1. SE2 was calculated as Percent Change ($\{(Baseline - Visit)/Baseline\} * 100$)			
2. Higher SE2 values represent improvement			
**p-value reflects testing vs. baseline			

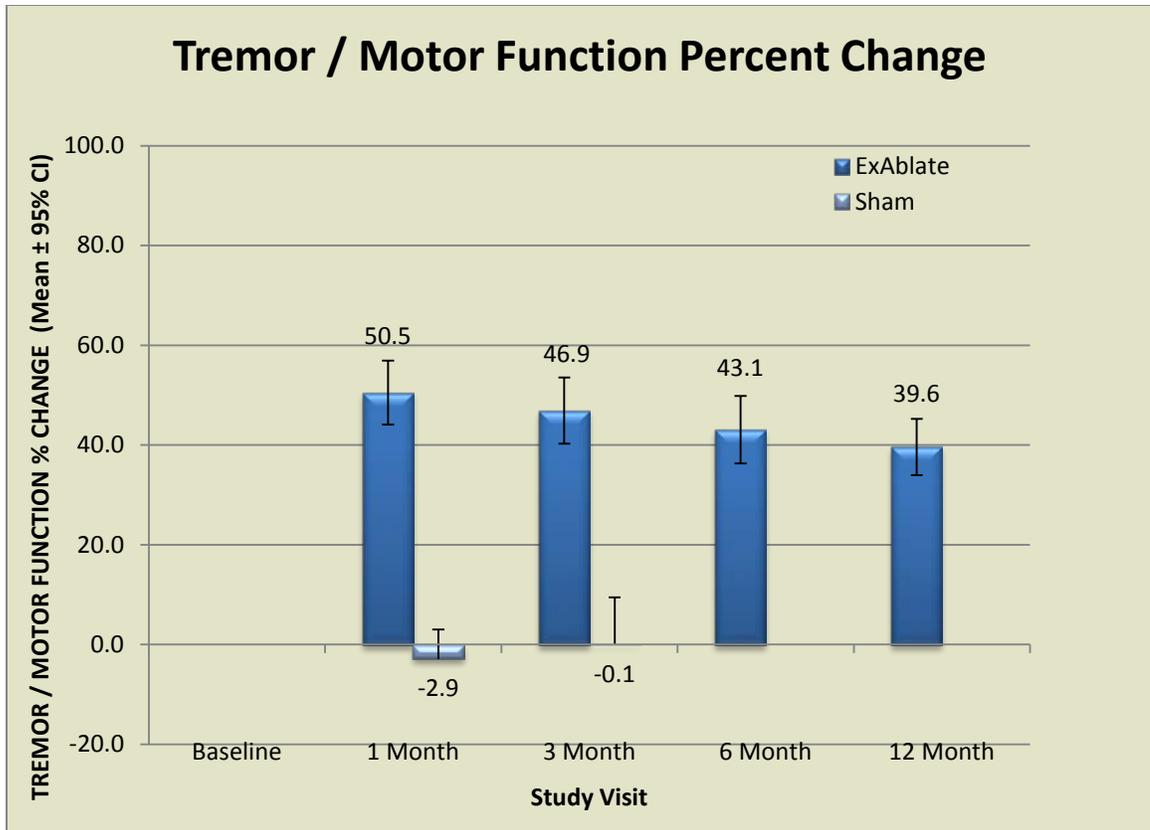


Figure 4: Tremor / Motor Function percent of change as defined by the Primary Endpoint of the study.

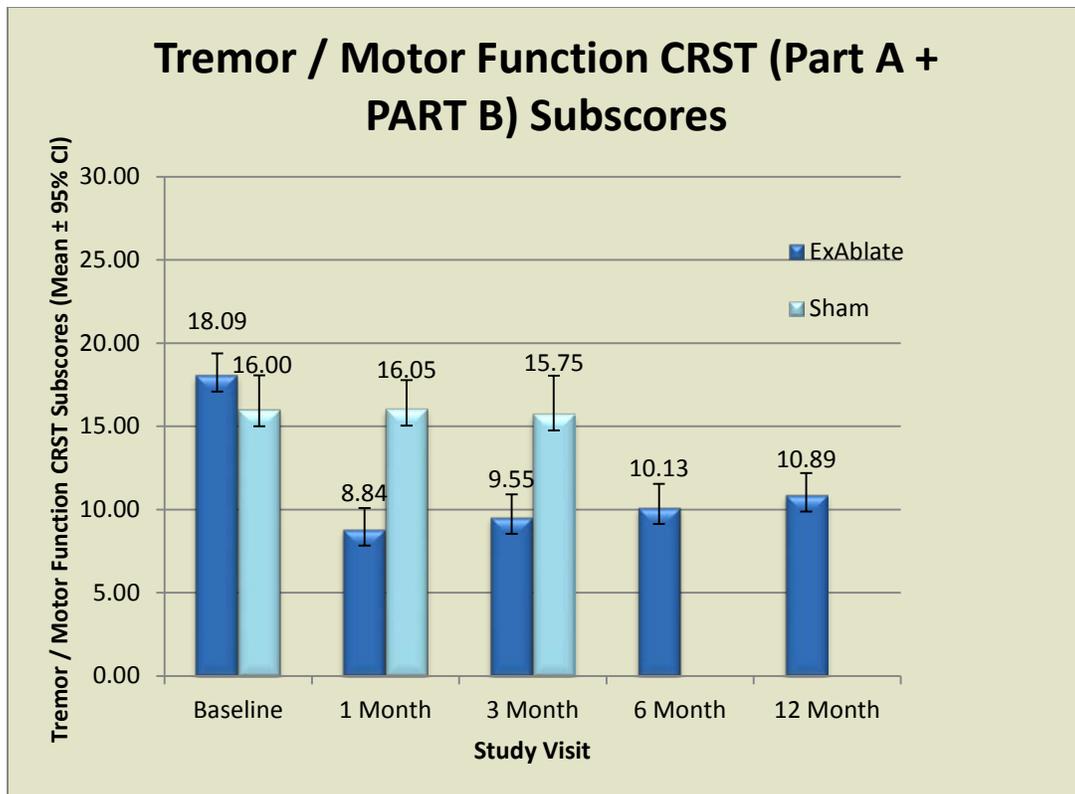


Figure 5: Tremor / Motor Function CRST actual Subscore (Part A + Part B) through Month-12 for both ExAblate and Sham study Arms. The maximum score of the 8-components of the CRST subscore is either 32 or 28 depending on the treated hand.

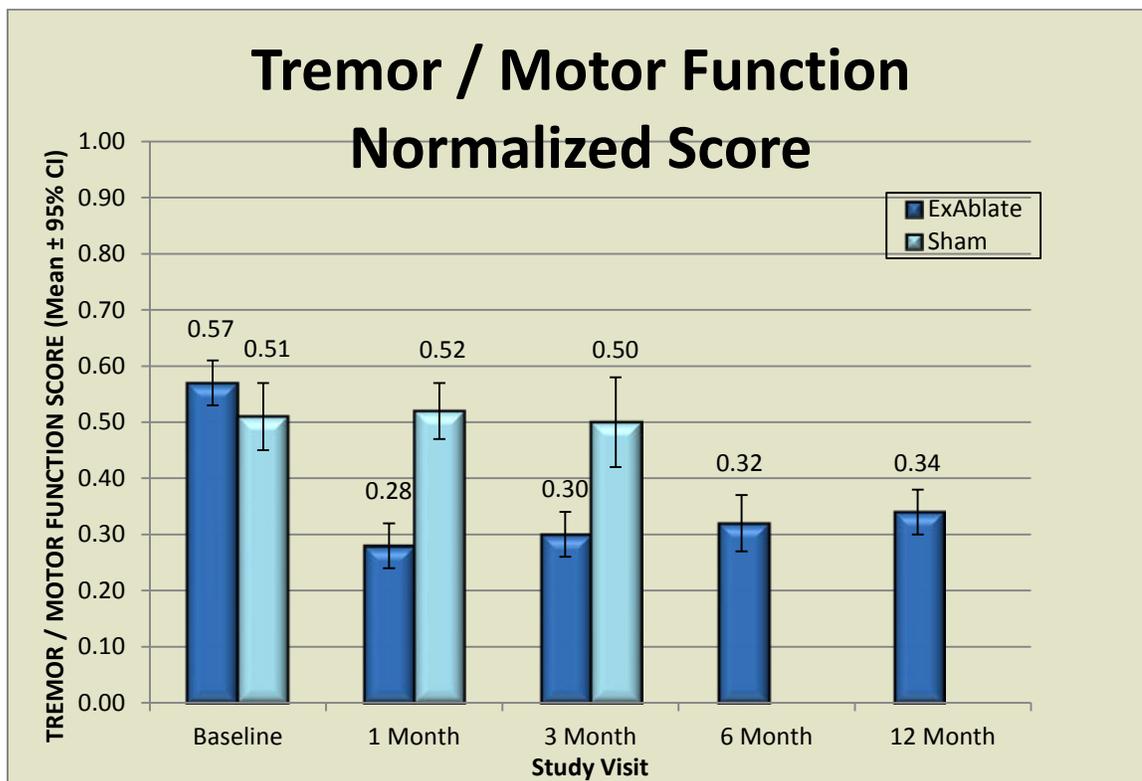


Figure 6: Same data as in Figure 5 where the actual score is normalized by the maximum score of 32 or 28 depending on the treated (contra-lateral) Arm

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

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

The percent change from baseline indicates that “Posture” improvement was 71.6%, 64.3%, 62.5%, and 65.5% at Months 1, 3, 6, and 12 respectively (**Table 14** and **Figure 7**).

Table 14. CRST Part A Upper Extremity, Posture Component Only for Treated Arm by Treatment Group by Visit Through Month 12.

CRST Part A Posture / Visit			Score Values		Change from Baseline		ExAblate % change from baseline ³	Sham % change from baseline ³
			Treated Side		Treated Side			
			ExAblate N=56	Sham N=20	ExAblate (N=56)	Sham (N=20)		
Part A - Posture Only	Baseline	Mean	2.13	1.65				
		Lower 95% CI	1.82	1.08				
		Upper 95% CI	2.43	2.22				
	1 Month FU	Mean	0.50	1.55	1.63	0.10	71.6%	13.0% (n=16)
		Lower 95% CI	0.28	1.11	1.33	-0.35	61.3%	-6.09%
		Upper 95% CI	0.72	1.99	1.92	0.55	81.9%	32.4%
	3 Months FU [±]	Mean	0.64	1.85	1.48	-0.20	64.3%	-4.4% (n=17)
		Lower 95% CI	0.39	1.36	1.16	-0.69	52.1%	-27.0%
		Upper 95% CI	0.90	2.34	1.80	0.29	76.5%	18.2%
	6 Months FU	Mean	0.71		1.41		62.5% (n=52)	
		Lower 95% CI	0.44		1.08		50.8%	
		Upper 95% CI	0.99		1.74		74.2%	
	12 Months FU	Mean	0.68		1.45		65.5%	
		Lower 95% CI	0.42		1.14		54.7%	
Upper 95% CI		0.94		1.76		76.3%		

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

Figure 7 below shows the mean score value in the ExAblate group compared to the Sham group which showed no improvement.

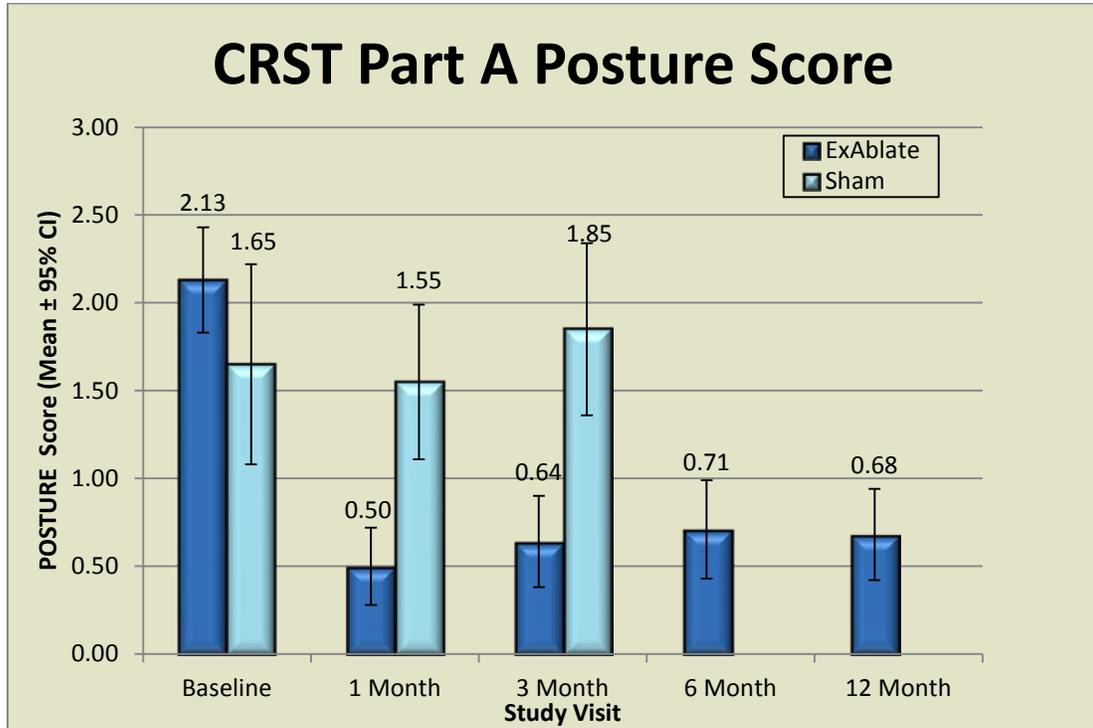


Figure 7. CRST Part A Posture Component Scores over Time and by Treatment Group. ⁺Between groups testing at Month 3 was statistically significant ($p < 0.001$). ⁺⁺Within groups testing for ExAblate as compared to baseline was ($p < 0.001$) at all visits.

3.2.2.2.2 CRST Part C Total Score

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

Part C Composite Functional Disabilities improvements from baseline, obtained at the Month 3 follow-up visit, are compared between treatment groups (**Table 15**). The ExAblate treated group showed significant improvement (63.8%) as compared to the Sham-treated group (1.8%) at Month 3, which was statistically significant ($p < 0.001$).

The Total Part C confirmatory endpoint was successfully met.

As shown in **Table 15**, the improvement in the subject overall Functional Disability (CRST Part-C) when compared to baseline was 64%, 62% and 64% at Months 3, 6 and 12, respectively (p<0.001). This improvement was observed across all Functional Disability components for ExAblate-treated subjects. However, little/no change to slight worsening was observed in the Sham-treated group for all Functional Disabilities

Table 15. Confirmatory Endpoint - CRST Part C Overall Functional Disabilities Score /% Change from Baseline by Treatment Group and by Visit (ITT)						
SE3	ExAblate N=56		Sham N=20		Between groups P Value ⁺	Within groups p-value ExAblate Arm
	Change from Baseline	% Change from Baseline ^f	Change from Baseline	% Change from Baseline ^f		
Month 3	10.38	63.8%	0.45	1.8%	P<0.001	P<0.001
Lower 95% CI	8.81	55.3	-0.50	-6.7%		
Upper 95% CI	11.94	72.4%	1.40	11.1%		
Month 6	10.05	61.8% ⁺⁺				P<0.001
Lower 95% CI	8.42	64.3%				
Upper 95% CI	11.69	81.8%				
Month 12	10.20	64.0% ⁺⁺				P<0.001
Lower 95% CI	8.66	55.2%				
Upper 95% CI	11.74	72.7%				

^f: % change: 100*(Baseline - Follow-up Visit)/Baseline
⁺ Difference between treatment groups was statistically significant (P<0.001) (Wilcoxon signed rank test).
⁺⁺% Change from Baseline to Months 3, 6 and 12 was tested and found to be statistically highly significant (P<0.001) for ExAblate Arm

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

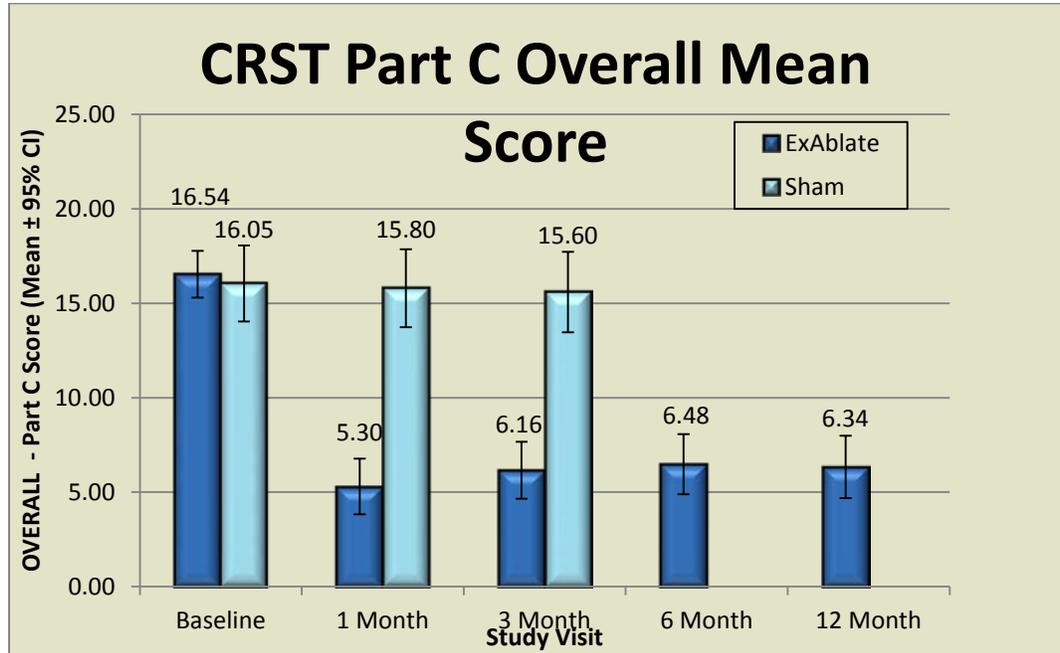


Figure 8: the Overall CRST Part-C scores through Month-12. This Part-C is a composite of 8-components with a maximum total score of 32.

Figure 8 shows the overall CRST Part-C scores through Month-12. This Part-C is a composite of 8-components: Speaking, Drinking, Eating, Hygiene, Dressing, Writing, Working, Social Activities. The graphs for all the individual activities are shown in the figures below across time for both treatment groups (**Figure 9** through **Figure 16**).

Figure 9. CRST Part C Functional Disability – Speaking by Visit and by Treatment Arm

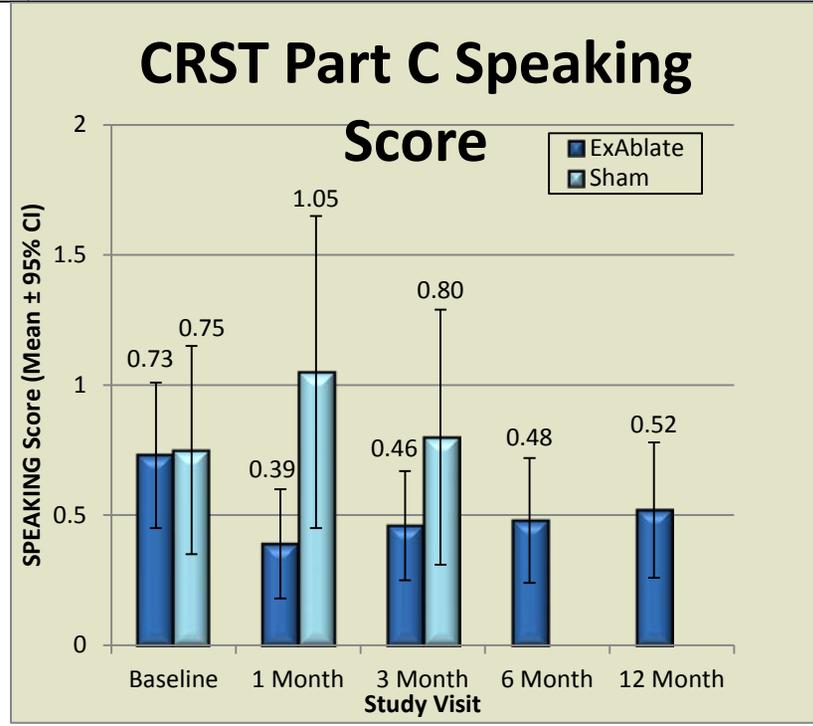


Figure 10. CRST Part C Functional Disability – Eating [Feeding (other than liquids)] by Visit and by Treatment Arm

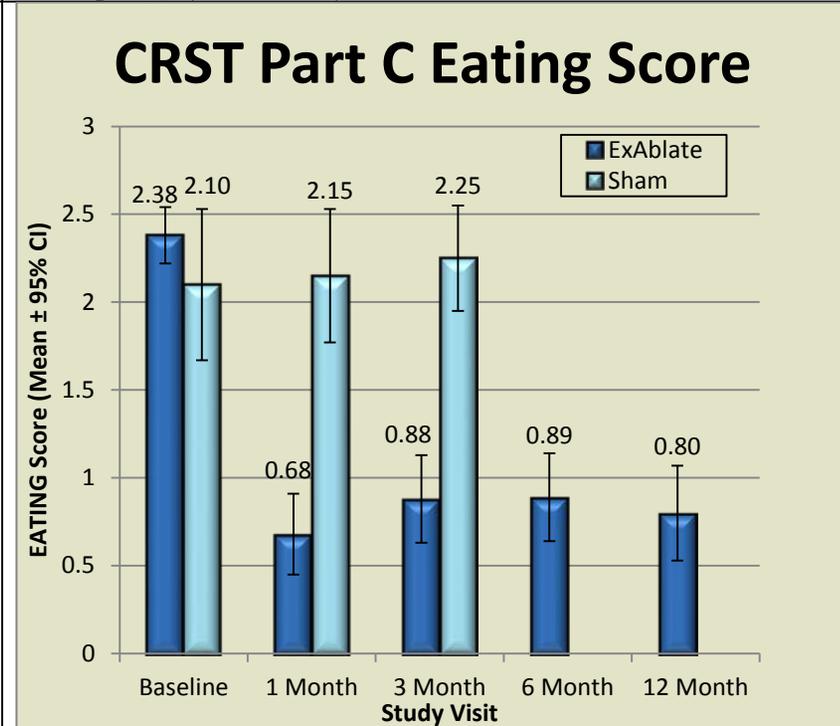


Figure 11. CRST Part C Functional Disability – Drinking [Bringing liquids to mouth] by Visit and by Treatment Arm

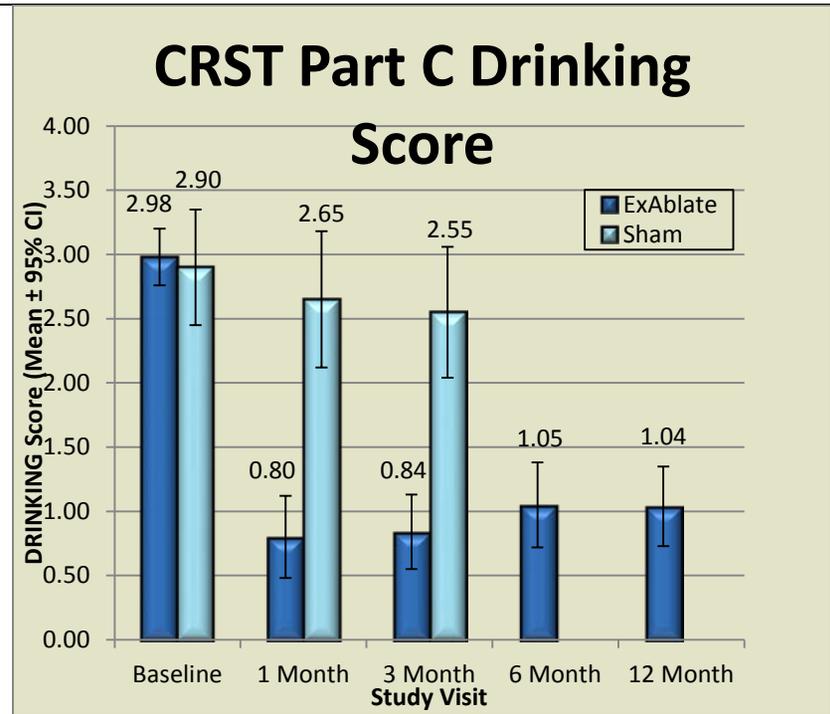


Figure 12. CRST Part C Functional Disability – Hygiene by Visit and by Treatment Arm

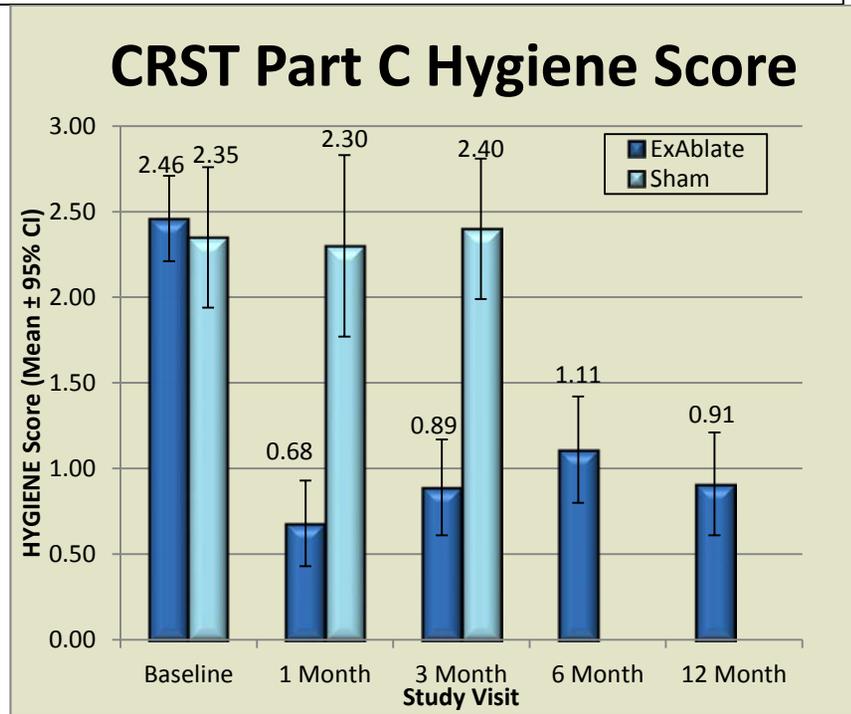


Figure 13. CRST Part C Functional Disability – Dressing by Visit and by Treatment Arm

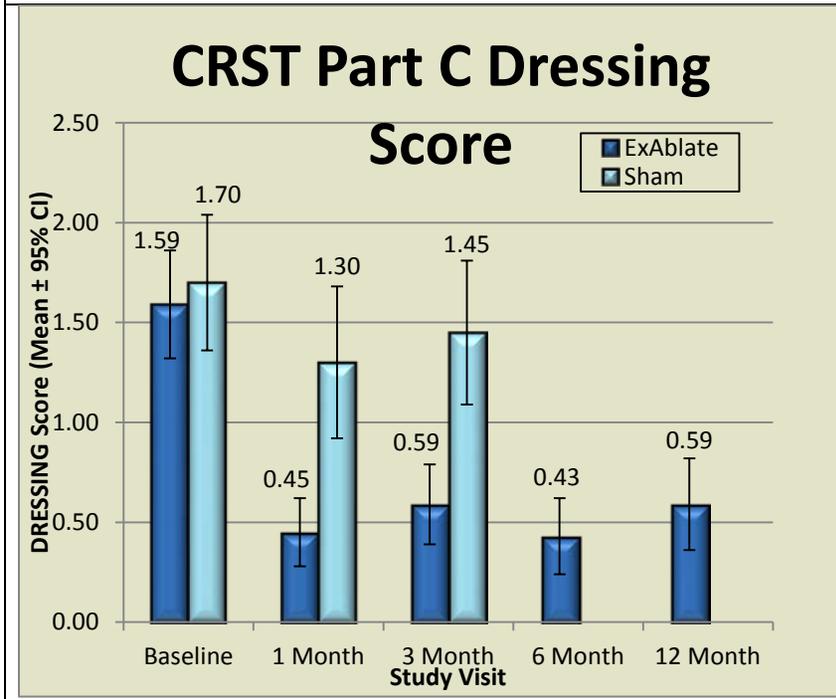


Figure 14. CRST Part C Functional Disability – Writing by Visit and by Treatment Arm

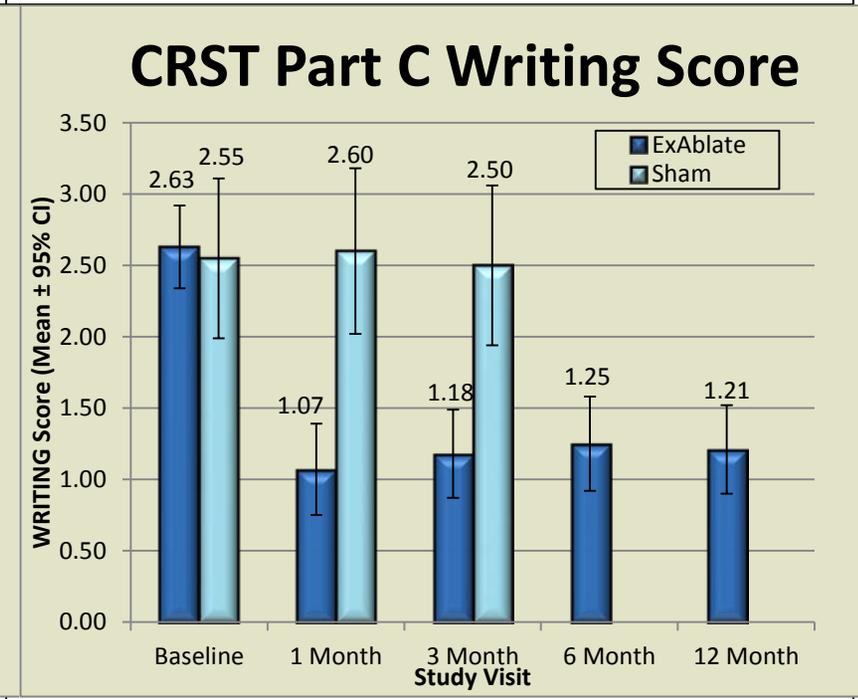


Figure 15. CRST Part C Functional Disability - Working by Visit and by Treatment Arm

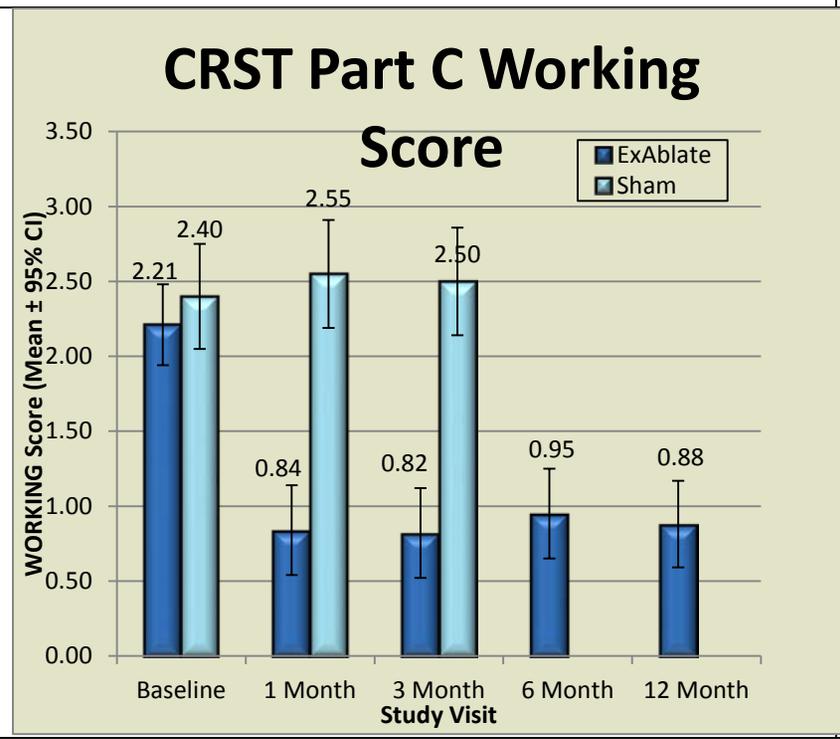
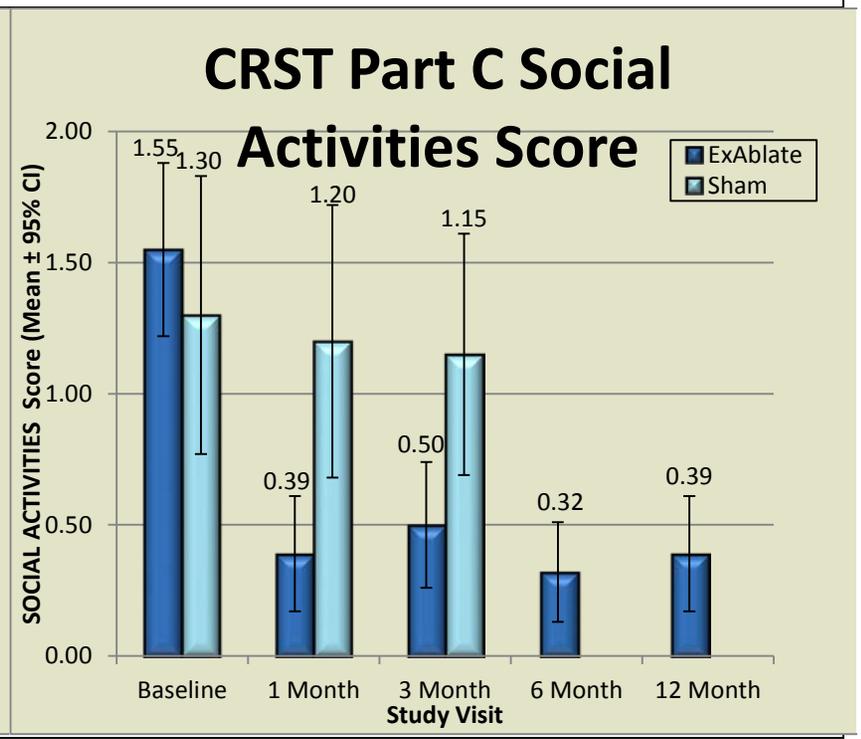


Figure 16. CRST Part C Functional Disability – Social Activities by Visit and by Treatment Arm



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

From the results reported in **Table 16**, it may be determined that the result of the QUEST quality of life at the Month 3 time point mimics that of the PE, with a 43.2% improvement in the mean score of dimensions in the ExAblate group compared to baseline, and almost no change (5%) for the same measure in the Sham group. This difference between treatment groups was, again, highly significant (p<0.001).

Table 16. Confirmatory Secondary Efficacy QUEST Summary of Dimensions Score % Change from Baseline at Month 3 by Treatment Group (ITT)					
	Treatment Group				
SE1	ExAblate N=56		Sham N=19**		P-Value*
ITT Mean	23.11	43.2%	41.37	5.0%	<0.001
..Lower 95% CI	13.33	34.3%	26.04	-14.9%	
Upper 95% CI	26.11	56.3%	54.22	36.2%	
1. SE1 was calculated as Percent Change ((Baseline - Visit)/Baseline)*100. 2. Higher SE1 values represent improvement * p-value testing between groups ** One Sham subject did not complete the QUEST at baseline					

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

3.2.2.2.4 Summary of Main Efficacy

The efficacy analysis shows a powerful, robust result at Month 3 with the ExAblate group experiencing a highly significant improvement in the PE and all secondary confirmatory endpoints, as summarized in **Table 17** and **Figure 17**.

Table 17. Efficacy Analysis Summary

	% of Improvement At Month-3 – ITT			% of Improvement At Month 12 – ITT	
	ExAblate (N=56)	Sham (N=20)	Between Groups p-value	ExAblate (N=56)	P-value Vs Baseline
Primary Endpoint – Composite Tremor/Motor Function	46.9%	- 0.1%	p< 0.001	39.6%	p< 0.001
..Lower 95% CI	40.3%	-9.6%		34.0%	
Upper 95% CI	53.5%	9.5%		45.3%	
CRST, Part A- Tremor “Posture”	64.3%	- 4.4% (n=17)	P<0.001	65.5 %	p< 0.001
..Lower 95% CI	52.1%	-26.9		54.7 %	
Upper 95% CI	76.5%	18.2		76.3 %	
CRST, Part C	63.8%	1.8%	p< 0.001	64.0%	p< 0.001
..Lower 95% CI	55.3%	-6.7%		55.2%	
Upper 95% CI	72.4%	11.1%		72.7%	
QUEST	43.2%	5.0% (n=19)	p< 0.001	47.1%	p< 0.001
..Lower 95% CI	34.3%	-14.9%		36.5%	
Upper 95% CI	56.3%	36.2%		62.1%	

A negative sign “-“ indicates worsening

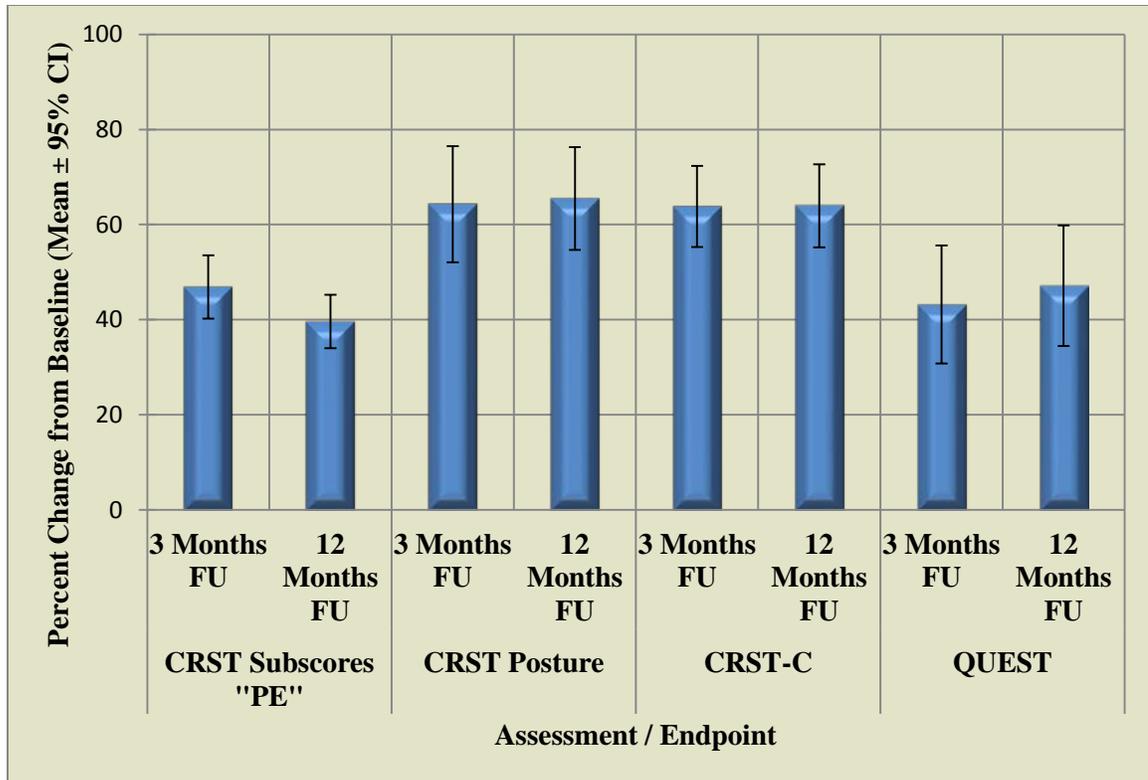


Figure 17: Study Effectiveness Assessment Endpoints; “PE” is the Primary Endpoint

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

3.2.2.2.5 Covariate and Sensitivity Analyses

The Covariate and Sensitivity analyses were performed in this study:

- The data were tested for potentially confounding variables through use of a Covariate analysis. Age, Baseline, CRST score at Baseline, Gender and Center were assessed for all primary and secondary confirmatory analyses. No significant interaction was found on the study results with any of these variables.
- Sensitivity analyses were performed to determine how robust the results were using Best case and Worst case imputation methods. Only 2 subjects in the ExAblate dropped out prior to the study endpoint of Month 3. Using both methods, the result by either method had negligible change on the PE values,

and did not affect the difference between groups which was still high at $p < 0.001$.

3.2.2.2.6 Additional Analyses – CRST Part – B

Figure 18 shows the CRST Part-B total score through Month-12 for both Main ExAblate and Sham Arms. This data shows that while sham shows little to no change in their total score, the ExAblate Arm shows a mean of approximately 5 points change was achieved at all the visits.

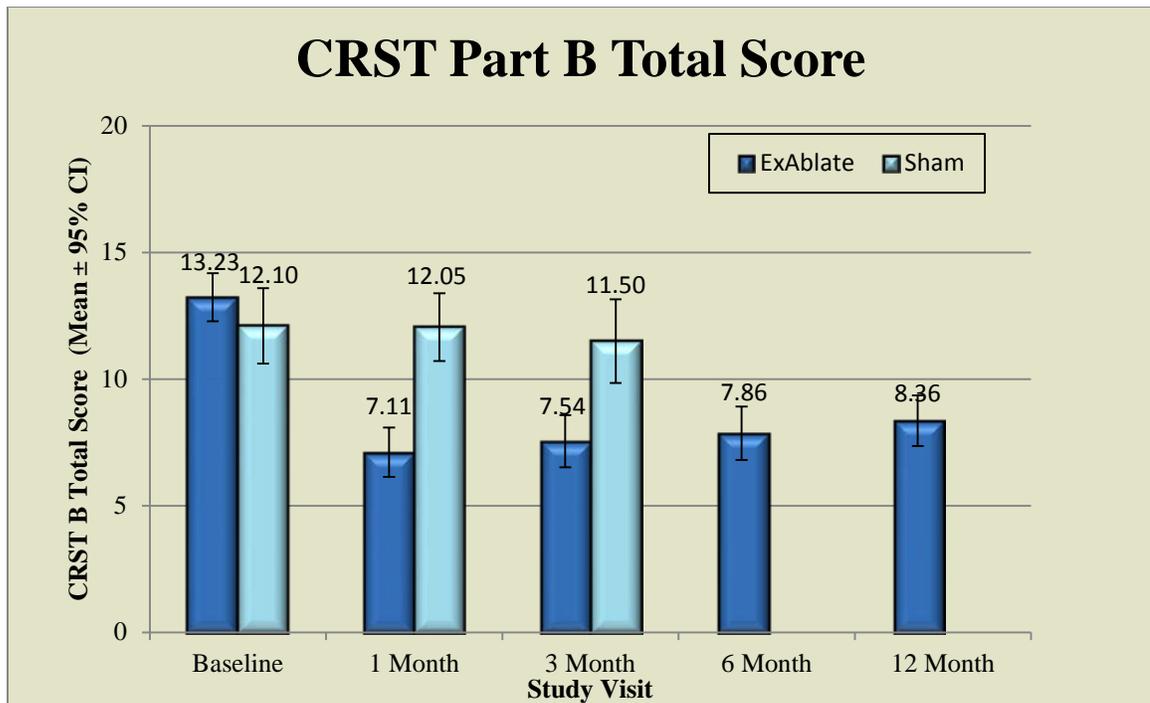


Figure 18. CRST Part-B Total score through Month-12.

3.2.2.3 Confirmatory Secondary Endpoints Safety Results

3.2.2.3.1 Subject Disposition & Accountability

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

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

Subject disposition in the Crossover arm is presented in **Table 18**. As discussed with the Agency, some of these subjects are still in follow-up, but all data available at the time of the PMA submission are presented herein.

Table 18. Subject Disposition for Crossover Subjects						
Category	Baseline	1 Week FU	1 Month FU	3 Months FU	6 Months FU	12 Months FU
Theoretical ¹	21	21	21	21	21	21
Not Due Yet	0	0	0	0	0	12
Death	0	0	0	0	0	0
Failure ²	0	0	0	0	0	0
Expected ³	21	21	21	21	21	9
Actual ⁴	21	21	21	21	21	9
Actual % ⁵	100%	100%	100%	100%	100%	100%
1 - Theoretical is equal to the number of subjects entered Rescue stage of the study 2 - Failures include any subjects who discontinued study due to non-response to treatment 3 - Expected equals Theoretical minus Death minus Failures 4 - Actual is the number of subjects actually returning for the follow-up visit 5 - Actual % is the number of Actual subjects divided by Expected.						

3.2.2.3.2 Subject Disposition & Accountability

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

Table 19 succinctly summarizes the safety profile of the ExAblate 4000 as used in unilateral thalamotomy for the ExAblate Crossover group. A total of 76 AEs in 20 subjects was reported for the ExAblate Crossover group. Most reported AEs (61/76, 80% in 13 subjects) were Mild and Moderate (13/76, 17% in 7 subjects) with one unrelated SAE (1/76, 1% in 1 subjects).

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

Table 19. Overall Summary of Adverse Events by Severity in ExAblate Crossover Arm		
Severity	ExAblate Crossover	
	Frequency N=76	Incidence N=21
Mild	61 (80%)	16 (76%)
Moderate	13 (17%)	7 (33%)
Severe	1 (1.5%)	1 (5%)
TOTAL	76 (100%)	19 (90%)

Table 20 shows the AEs by time occurrence. The majority of AEs occurred within the first 30 days following the procedure and resolved within 30 days (68 events in 21 ExAblate Crossover subjects). In fact, many of them resolved on the same day as treatment or within 1 week of treatment (92/184, 50%). Many AEs were procedure related events (such as those related to the stereotactic frame, the urinary catheter, the IV line, the head shave, claustrophobia within the MR, etc.). A number of events are generally associated with any ablative treatment of the Vim nucleus (thalamotomy- related), such as numbness/tingling of the lip, face, tongue, or index finger/thumb. These events are generally reported as Mild or possibly Moderate.

Table 20. Starting time of occurrence for adverse events in the ExAblate Crossover Arm		
Start window	ExAblate	
	Frequency N=76	Incidence N=21
Within 30 days of procedure	68 (89%)	18 (86%)
31-90 days post-procedure	3 (4%)	2(10%)
>90 days post-procedure	5 (7%)	3 (14%)
Total	76 (100%)	19 (90%)

Most of the events that occurred within the first 30 days of the procedure were events that would occur in relation to the procedure itself, such as headache, nausea/vomiting, numbness/tingling, pin site events, pain and discomfort. Many of these AEs resolved within days of the procedure. The frequency and incidence of AEs that occurred during the Crossover study are presented in **Table 21** by severity.

Table 21. Frequency and Incidence of Adverse Events for ExAblate Crossover by Severity ExAblate

Body System	Preferred Term	Mild	Moderate	Severe
		Frequency N (%)	Frequency N (%)	Frequency N (%)
Cardiovascular	Hypertension	1 (1%)	1 (1%)	
	Preventricular Contractions	1 (1%)		
	Sick Sinus Syndrome			1 (1%)
Gastrointestinal	Dry mouth	1 (1%)		
	Dysgeusia	2 (3%)		
	Nausea/Vomiting	3 (4%)	1 (1%)	
General	Fatigue	1 (1%)	1 (1%)	
	Musculoskeletal Weakness	1 (1%)	1 (1%)	
Infections	Flu	1 (1%)		
Musculoskeletal	Musculoskeletal Weakness	2 (3%)		
	Dysmetria	2 (3%)		
	Imbalance	2 (3%)	1 (1%)	
	Unsteady	1 (1%)	1 (1%)	
Nervous	Ataxia	2 (3%)	2 (3%)	
	Cognitive Disturbance	1 (1%)		
	Dizziness	1 (1%)		
	Dysarthria	2 (3%)	1 (1%)	
	Grogginess	1 (1%)		
	Dysmnnesia	1 (1%)		
	Hand Tremor (untreated side)	1 (1%)		
	Numbness/Tingling	10 (13%)		
	Paresthesia	2 (3%)		
	Slow Movements	1 (1%)		
Pain/Discomfort	Headache	5 (7%)	2 (3%)	1 (1%)
	Sonication-related head pain	4 (5%)	2 (3%)	
Stereotactic Head	Pin Site Bleeding	1 (1%)		

Table 21. Frequency and Incidence of Adverse Events for ExAblate Crossover by Severity ExAblate				
Body System	Preferred Term	Mild	Moderate	Severe
		Frequency N (%)	Frequency N (%)	Frequency N (%)
Frame	Pin Site Edema	1 (1%)		
	Pin Site Pain	4 (5%)		
	Ptosis	1 (1%)		
Vestibular Disorder	Dizziness	3 (4%)		
	Vertigo	1 (1%)		
TOTAL		60	14	2

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

The device/procedure unrelated events include events such as the IV, catheter, and frame-related events that occur and are directly attributable to them, as well as any miscellaneous events that occur such as colds, ear infections, miscellaneous musculoskeletal events and positional events.

Table 22 summarizes the transient and unrelated AEs, which account for 43 of 76 AEs. Events with the highest frequency included headache (7), sonication-related headache (6), and nausea/vomiting (4) and were transient.

Table 22. Transient Adverse Events or Adverse Events That are Unrelated to Device/ Procedure or Thalamotomy in the ExAblate Crossover Arm.				
Relation / Body System / AE Coded Term			ExAblate Crossover	
			N	%
Transient	Gastrointestinal	Nausea/Vomiting	4	5%
	Nervous	Cognitive Disturbance	1	1%
		Dizziness	1	1%
		Numbness/Tingling	2	3%
		Parasthesia	1	1%
	Pain/Discomfort	Headache	7	9%
		Sonication-Related Head Pain	6	8%
	Vestibular Disorder	Dizziness	3	4%
		Vertigo	1	1%
	Subtotal Transient			26
Unrelated Events			17	22%
Total Transient and Unrelated			43	57%

Thirty-three of 76 AEs were related to ExAblate safety profile and were determined to be either procedure/device related or thalamotomy related (**Table 23**). These events lasted longer than 72 hours. The most frequent events include numbness/tingling (8) and ataxia (4).

Table 23. Frequency of Adverse Events Related to the Procedure or Device or Thalamotomy in the ExAblate Crossover Arm.

Relation / Body System / AE Coded Term			ExAblate Crossover	
			N	%
Procedure-Related	General	Fatigue	2	3%
		Musculoskeletal Weakness	2	3%
	Musculoskeletal	Imbalance	2	3%
		Musculoskeletal Weakness	2	3%
		Unsteady	2	3%
	Nervous	Grogginess	1	1%
	Pain/Discomfort	Headache	1	1%
	Vestibular Disorder	Dizziness	1	1%
Thalamotomy-Related	Gastrointestinal	Dysgeusia	1	1%
	Musculoskeletal	Dysmetria	2	3%
		Imbalance	1	1%
	Nervous	Ataxia	4	5%
		Dysarthria	2	3%
		Numbness/Tingling	8	11%
		Parasthesia	1	1%
Slow Movements		1	1%	
Total			33	43%

Sixteen AEs with onset within 30 days post-procedure, reported by 9 ExAblate subjects, were still on-going at the Month 12 follow-up visit (See **Table 24**). All of these events are either Mild or Moderate.

Table 24. Ongoing Adverse Events from the First 30 Days in ExAblate Crossover Arm.			
Body system	Preferred term	Frequency N=	Incidence N=21
Gastrointestinal	Dysgeusia	2	2 (10%)
General	Fatigue	2	2 (10%)
Musculoskeletal	Dysmetria	1	1 (5%)
	Imbalance	2	2 (10%)
	Musculoskeletal weakness	1	1 (5%)
Nervous	Dysarthria	1	1 (5%)
	Numbness/tingling	5	3 (14%)
	Slow movements	1	1 (5%)
Stereotactic Frame	Pin Site Pain	1	1 (5%)
TOTAL		16	9 (43%)

Serious Adverse Event

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

PHQ-9

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

3.2.2.3.3 Primary Efficacy Endpoint Subject Disposition & Accountability

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

Using the same formula for PE calculation (Composite Tremor/Motor Function Percent Change from Baseline), the ExAblate Crossover group at Month 3 CRST was calculated as compared to baseline at the Crossover study screening (**Table 25**). An analysis of statistical significance as compared to baseline was performed. The ExAblate Crossover group experienced a 53.1% improvement at Month 3 in the Composite Tremor/Motor Function Score ($p < 0.001$) (**Table 25**). This is highly significant showing a treatment response which is slightly better than that of the Main analysis.

Table 25. Crossover Arm - Primary Endpoint (Composite Tremor/Motor Function % Improvement): Three Months Post-Treatment Analyses			
	Treatment Group		
PE _{crossover}	ExAblate Crossover N =21		P-Value*
	Mean Score	% Change	
Mean	0.24	53.1%	<0.001
Lower 95% CI	0.18	43.4%	
Upper 95% CI	0.30	62.8%	
1. PE was calculated as Percent Change ((Baseline - Visit)/Baseline)*100. 2. Higher SPE values represent improvement			

The percent change of improvement of the Composite Tremor/Motor Function score for the ExAblate Crossover group is similar to that experienced by the ExAblate group in the blinded portion of the study (46.9% ExAblate, p<0.01), thus the treatment effect is of a similar magnitude, or slightly better, as in the blinded portion of the study (see **Figure 22**).

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

This second confirmatory endpoint is based on CRST, primary endpoint calculation, the Composite Tremor/Motor Function Score at Month 3, 6, and 12. **Table 26** and **Figure 19** show all available data shown through Month 12 for the ExAblate Crossover group. While not all the subjects have completed the Month-12 follow up visits, the p-value at Month-12 shows high significance (p=0.004).

As shown in **Figure 19**, the percent change from baseline in the CRST Composite Tremor/Motor Function was 50% or greater at each follow-up visit.

Table 26. Crossover Analysis - Confirmatory Efficacy: Composite Tremor Motor Function Score (PE) in ExAblate Crossover Arm as Compared to Baseline by Visit

	ExAblate Crossover N = 21		P-Value*
	Calculated Score Change	% Change	
Month 3	0.24	53.1%	<0.001
Lower 95% CI	0.18	43.4%	
Upper 95% CI	0.30	62.8%	
Month 6	0.26	50.7%	<0.001
Lower 95% CI	0.20	41.8	
Upper 95% CI	0.31	59.6	
Mean 12 (N=16)	0.26	47.0%	<0.001
Lower 95% CI	0.17	30.6	
Upper 95% CI	0.34	63.3	

Notes:

1. SE2 was calculated as Percent Change $\{(\text{Baseline} - \text{Visit})/\text{Baseline}\} * 100$
2. Higher SE2 values represent improvement
3. Month 12 visits are still on-going for patient follow-up.

**p-value reflects testing Vs baseline

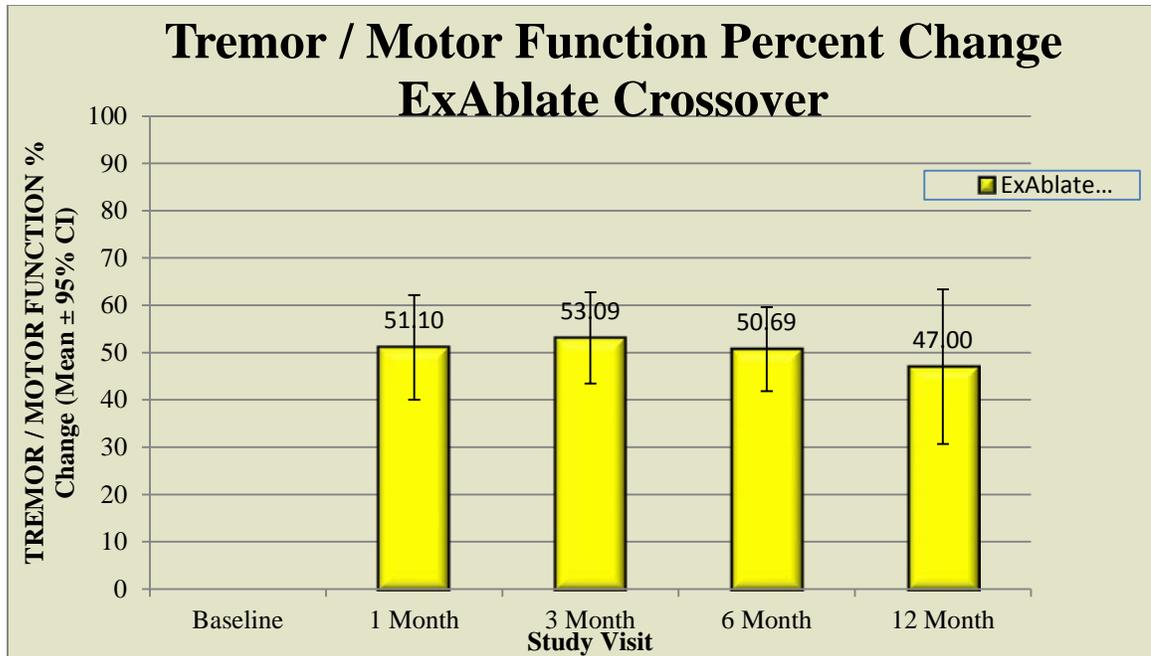


Figure 19. Primary Endpoint (Composite Tremor/Motor Function Score) for the Crossover Arm. The difference from Baseline is highly significant ($p < 0.001$ at Months 3 and 6; $p < 0.001$ at Month 12 with partial data, $n=16$). The result here is similar to that observed in the blinded portion of the study for the ExAblate group.

Similar to the Main “blinded” populations (ExAblate Main Arm and Sham Arm), the total CRST subscores (Part-A + Part B) are presented in **Figure 20**, whereas their corresponding normalized subscores are present in **Figure 21**.

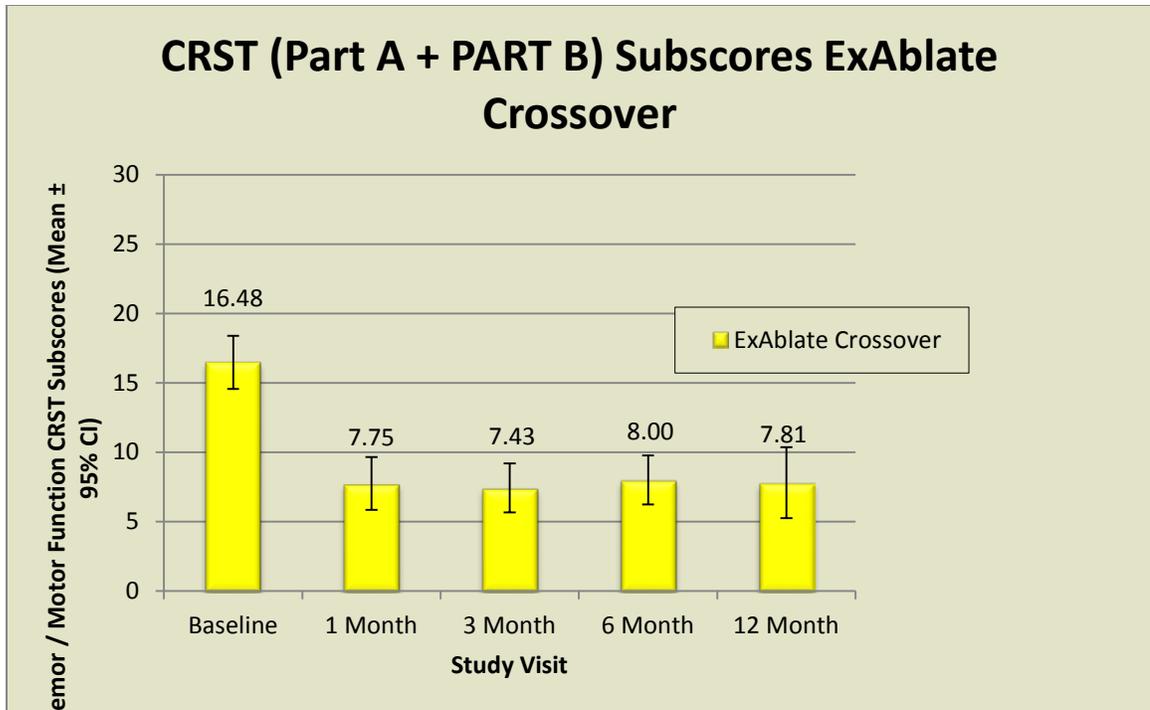


Figure 20: Tremor / Motor Function CRST actual Subscores (Part A + Part B) through Month-12 for the Crossover Arm. Note Month-12 Crossover N=16.

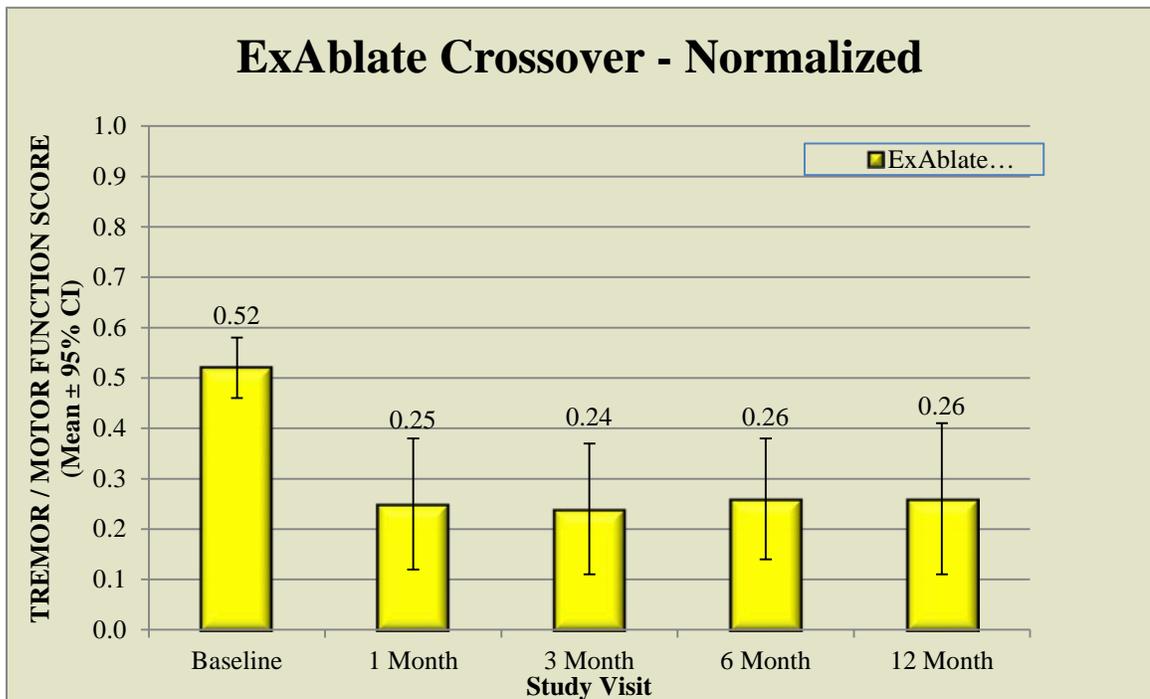


Figure 21: Same data as in Figure 20 where the actual score is normalized by the maximum score of 32 or 28 depending on the treated (contra-lateral) Arm. Note Month-12 Crossover N=16.

The percent of improvement of CRST Composite Tremor/Motor Function Score for the ExAblate Crossover group is similar, or slightly improved, compared to the ExAblate group in the Main Analysis (47% ExAblate, $p < 0.001$) across all visits (**Figure 22**).

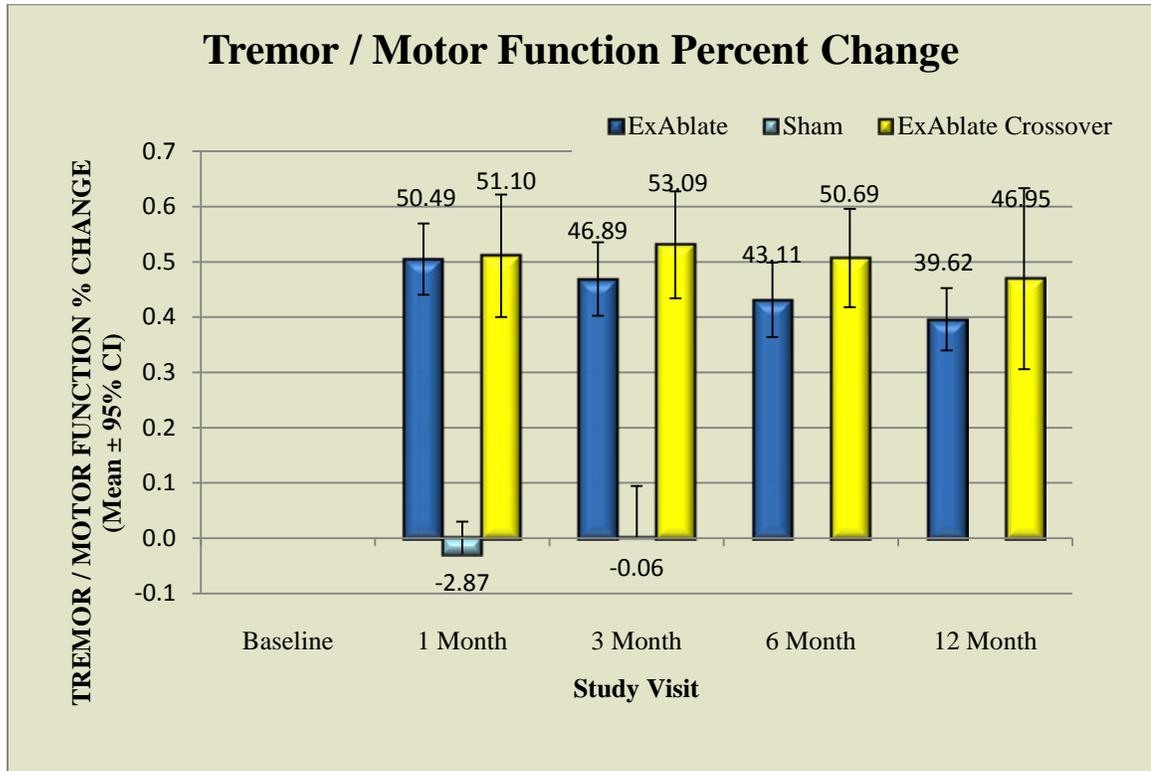


Figure 22. Primary Endpoint (Composite Tremor/Motor Function Score) for the 3 Study Arms: Main, Sham, and Crossover Arms.

The total CRST subscores (Part-A + Part B) of the 3-study Arms are presented in **Figure 23** below.

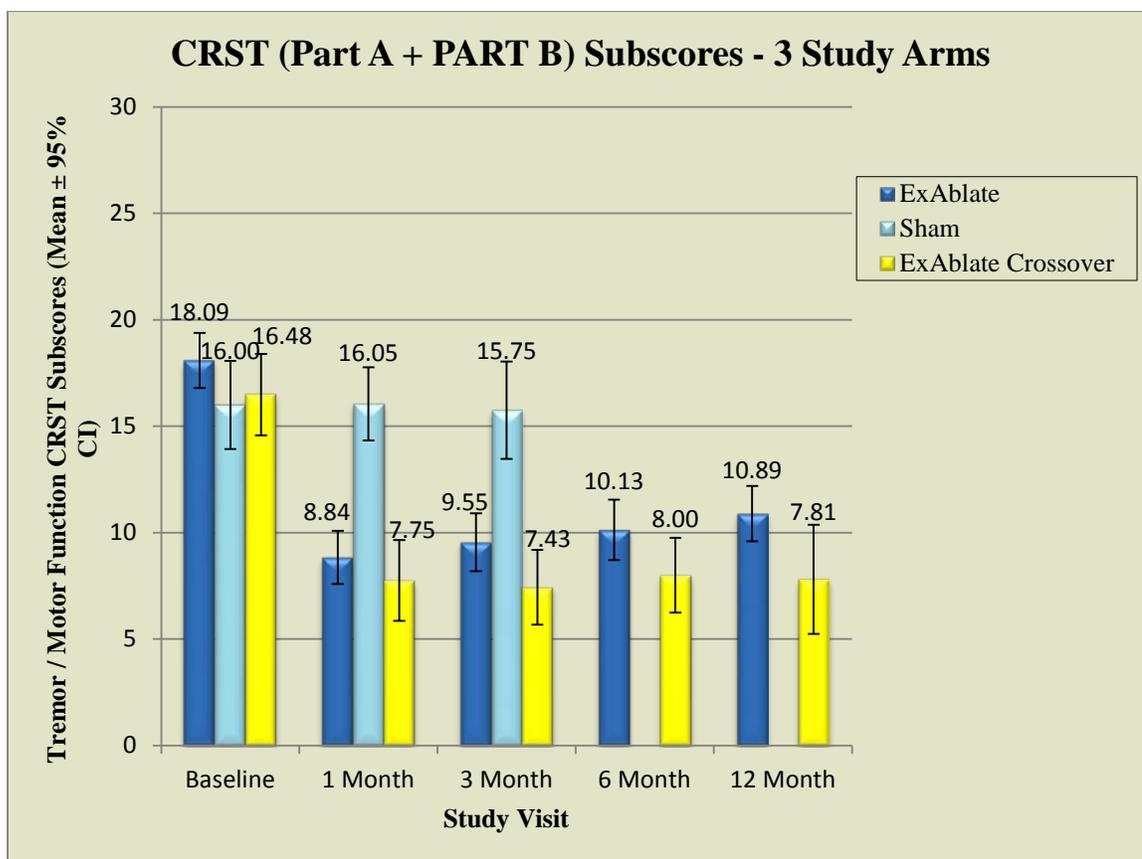


Figure 23: Tremor / Motor Function CRST actual Subscore (Part A + Part B) through Month-12 for ExAblate Main Arm, Sham and Crossover Arms. Note Month-12 Crossover N=7.

3.2.2.3.5 CRST, Part A Posture Component

As was done for the Main Analysis and as a means for comparison to literature, using the single component of CRST, Posture pulled from the Composite Tremor/Motor Function Score, the mean CRST-Part A Posture score was calculated and is presented in **Table 27**.

As can be seen in **Table 27** below, an improvement in contralateral or treated arm tremor (CRST-Part A, Posture) of 56.4% at Month 3, 56.8% at Month 6, and 46.4% at Month 12 (at Month 12, N = 16) with a highly significant p-values of <0.001 at Month-3 and 6, and of 0.004 at Month-12.

Table 27. CRST Part A Posture for Treated Arm by Treatment Group by Visit Through Month 3

		CRST Posture Calculated Scores ¹	Change from Baseline ²	Percent Change from Baseline
		Treated Side	Treated Side	Treated Side
		ExAblate Crossover	ExAblate Crossover	ExAblate Crossover
Baseline	Mean	1.71		
	Lower 95% CI	1.17		
	Upper 95% CI	2.26		
	N	21		
1 Month FU	Mean	0.45	1.15	54.2%
	Lower 95% CI	0.06	0.66	32.0%
	Upper 95% CI	0.84	1.64	76.4%
	N	20	20	20
3 Months FU	Mean	0.43	1.29	56.4%
	Lower 95% CI	0.12.	0.78	36.6%
	Upper 95% CI	0.74	1.79	76.1%
	N	21	21	21
Month 6	Mean	0.43	1.29	56.8%
	Lower 95% CI	0.12.	0.81	36.3%
	Upper 95% CI	0.74	1.77	77.2%
	N	21	21	21
Month 12	Mean	0.56	0.94	46.4%
	Lower 95% CI	0.09	0.28	22.3%
	Upper 95% CI	1.04	1.60	70.5%
	N	16	16	16

Notes:

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

Similar to the primary endpoint, the “Posture” CRST outcome for the ExAblate Crossover group is favorable and similar to what was seen in the Main Analysis ExAblate group (**Figure 24** below).

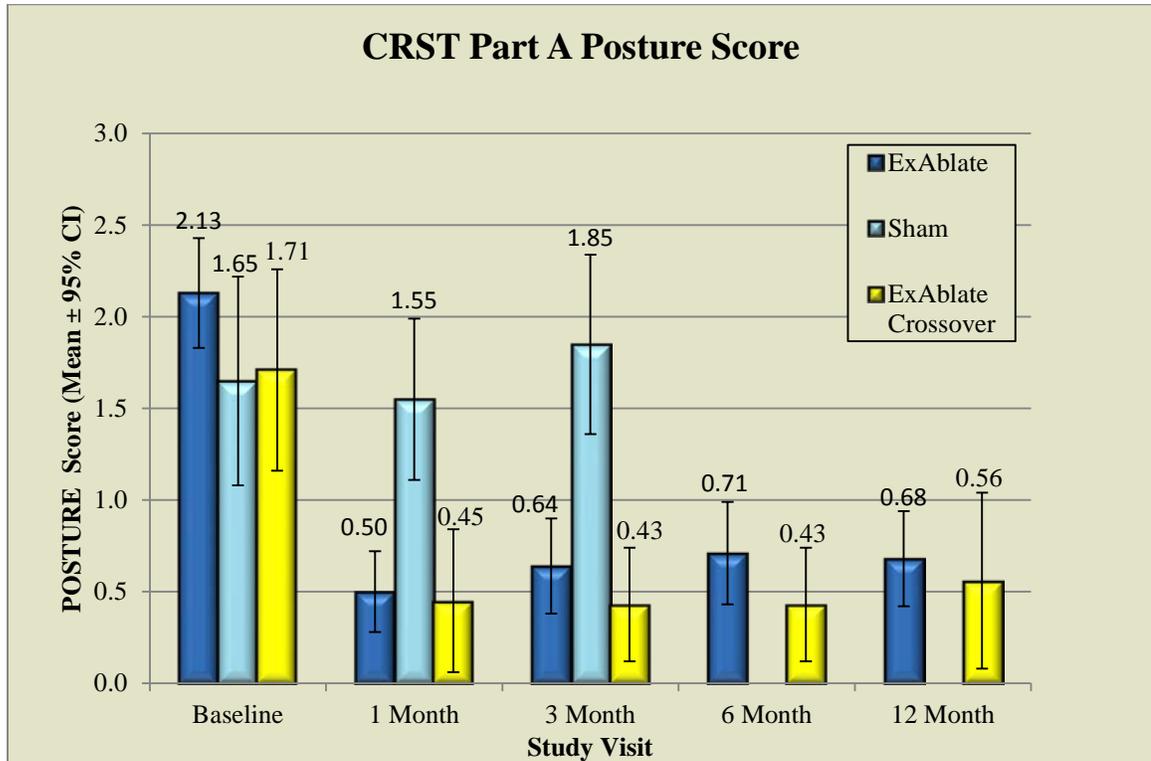


Figure 24. Primary Endpoint (Composite Tremor/Motor Function Score) for the 3 Study Arms: Main, Sham, and Crossover Arms.

3.2.2.3.6 CRST Overall Part C Comparison to Baseline

The Overall Part C percent change from baseline scores are presented below in **Table 28**. The analysis presents all available data. At all scheduled visits, a high percentage of improvement in the functional activities of daily living was observed: 74.6% at Month 3, 72.1% at Month 6, and 68.9 (for data collected up to February 22, 2016) at Month 12. This level of improved functionality was highly significant ($p < 0.001$).

Table 28. Crossover Stage, Confirmatory Secondary Efficacy: CRST Total Part-C Functional Disabilities Total Score - Percent Improvement from Baseline by Visit

Visit /SE ₃ Crossover	Mean Score	% Change from Baseline	P-Value
3 Months FU Mean N=21	4.29	74.6%	<0.001
Lower 95% CI	1.00	66.2%	
Upper 95% CI	7.00	82.9%	
6 Months FU Mean N=21	4.62	72.1%	<0.001
Lower 95% CI	2.00	62.4%	
Upper 95% CI	6.00	81.8%	
12 Months FU Mean N=18	5.17	68.9	<0.001
Lower 95% CI	0.00	55.0	
Upper 95% CI	9.00	82.9	
1. % Change from Baseline for CRST Total part C score was calculated as Percent Change ($\{(Baseline - Visit)/Baseline\} * 100$) 2. Higher % Change from Baseline for CRST Total part C score values represent improvement			

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

3.2.2.3.7 QUEST Endpoint Analyses compared to Baseline

QUEST - Quality of Life, overall score was calculated for the ExAblate Crossover group in the same way as it was done for the Main Analysis population. The percent improvement in QUEST Summary of Dimensions at Month 3 for the ExAblate Crossover group was 59.2 % (p<0.001) (**Table 29** below).

Table 29. Crossover QUEST Analysis - Improvement from Baseline at 3 Months Post-Treatment			
	Treatment Group		
SEI _{crossover}	ExAblate Crossover		P-Value*
Mean	19.20	59.2%	<0.001
Lower 95% CI	3.54	38.16	
Upper 95% CI	30.28	94.94	
2. QUEST Summary of Dimensions was calculated as Percent Change ((Baseline - Visit)/Baseline)*100. 3. Higher QUEST Summary of Dimension values represent improvement * p-value testing compared to Baseline			

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

3.2.2.3.8 *Additional Analyses – CRST Part-B Total Score*

Figure 25 shows the CRST Part-B total score through Month-12 for all three study Arms: Main ExAblate, Sham, and Crossover Arms. This data shows that while sham shows little to no change in their total score, the ExAblate main Arm shows a mean of approximately 5 points change was achieved at all the visits. Further improvement is shown by the Crossover Arm where approximately a mean of 6-points is achieved at all visits.

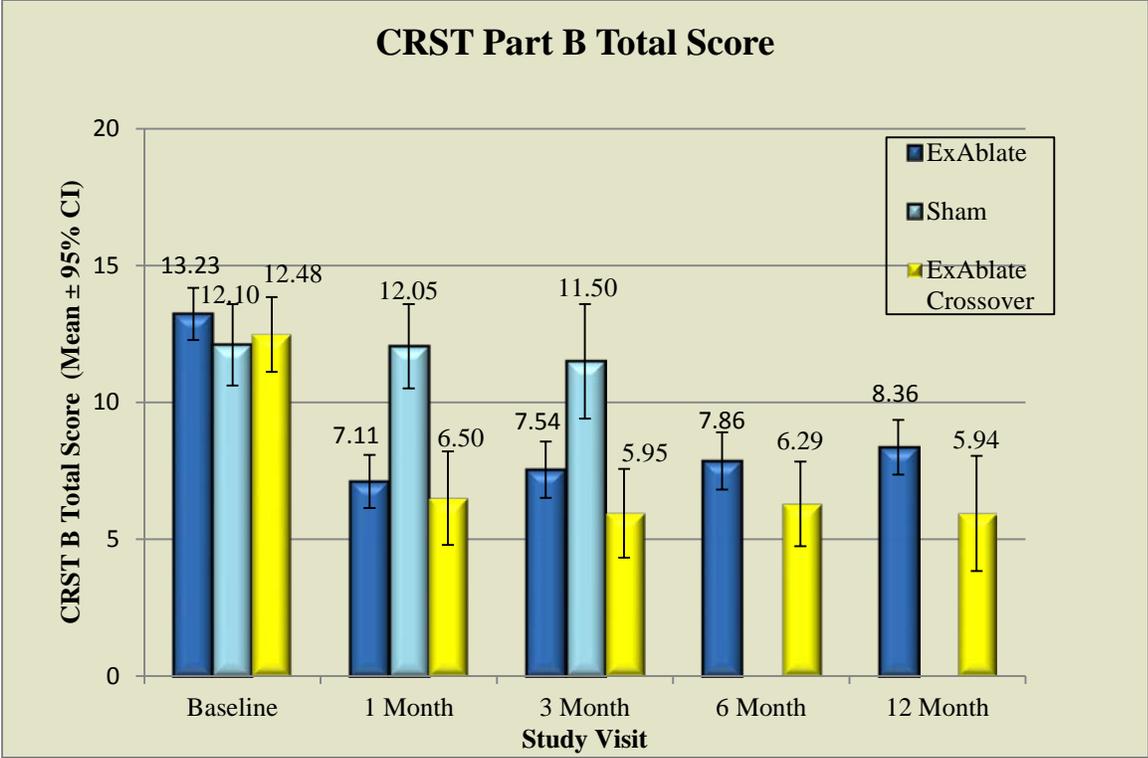


Figure 25: CRST Part B total Score through Month-12 for all 3-Study Arms: ExAblate, Sham, and Crossover Arms.

3.3 CONCLUSIONS DRAWN FROM THE STUDIES

3.3.1 *Study Safety Conclusions*

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

There were 53 AEs that were transient (resolved within 72 hours) and another 57 that were unrelated to ExAblate. Of the remaining 74 AEs, the events with the highest frequency were numbness/tingling (22; 12%), imbalance (10; 5%), unsteady (4; 2%), and gait disturbance (4, 2%). These events are usually coincident with thalamotomy as reported in the literature. Events that were related to the use of the stereotactic frame pins included the following: bruising (1 Mild event in ExAblate group); numbness/tingling (1 Mild event in ExAblate group; 1 Mild event and 1 Moderate event in Sham group); facial edema (1 Moderate event in ExAblate group); eyelid ptosis (2 Mild event in ExAblate group); pin site edema (1 Mild event in ExAblate group; 1 Mild event and 1 Moderate event in Sham group), pin site abrasion (2 Mild events in ExAblate group), pin site bleeding (1 Moderate event in Sham group), and pin site pain (7 Mild events and 1 Moderate event in ExAblate group; 4 Mild events in Sham group). Events categorized as procedure-related (e.g., fatigue, weakness, headache, and sonication-related head pain) lasting longer than 3 days. Of the 210 AEs, 99.5% were categorized as Mild or Moderate and many resolved within 3 months.

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

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

One Moderate event was deemed to become serious at Month 3 when the subject reported that the numbness/tingling in their hand impaired their ability to hold a pencil/write at work.

The safety profile of the ExAblate Crossover group mirrored that of the ExAblate group in the Main Analysis. The transient and unrelated events occurred at a similar frequency, as well as the procedure and thalamotomy events and the on-going events. In the ExAblate Crossover group, 76 AEs were reported. There was 1 serious AE that occurred in the ExAblate Crossover group. The subject was diagnosed with sick sinus syndrome 8

months after the ExAblate procedure and underwent a medical procedure to have a pacemaker implanted. This AE was not related to the ExAblate procedure.

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

3.3.2 Study Efficacy Conclusions

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

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

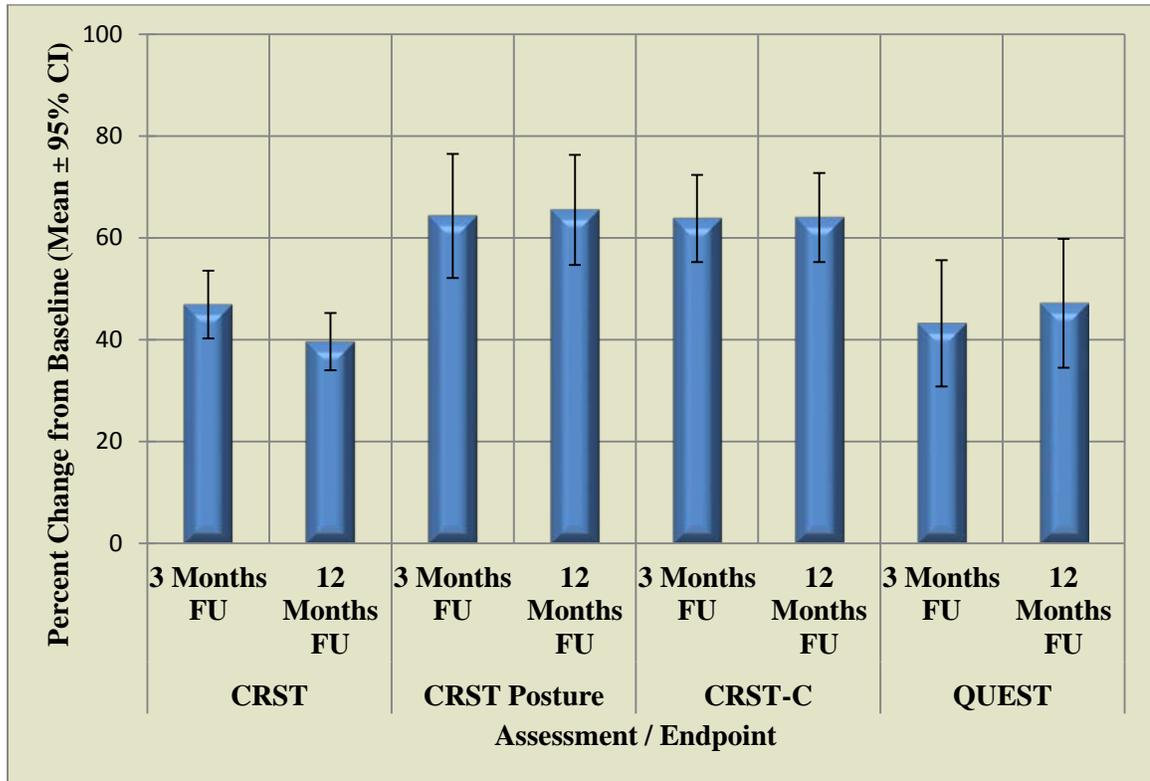


Figure 26: Summary of Study Effectiveness Assessment Endpoints.

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

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

3.3.3 *Study Overall Conclusions*

The data from the pivotal clinical study support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

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

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

4.0 SAMPLE PATIENT LETTER

ExAblate Neuro MR Guided Focused Ultrasound for Essential Tremor

What Patients Should Know?

You have been scheduled for an ExAblate Neuro treatment for your Essential 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 ESSENTIAL TREMOR for approximately 12 hours prior to the procedure.

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 you 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 an 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 comfortable 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, another 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 24-48 hours once your treating physician deems you are ready to go home. Your doctor will be

discussing the whole procedure with you including what the after procedure protocol. Please plan that you may be spending 24-48 hours at the hospital, as you might require staying for further observation.

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 _____.

INSIGHT-TEC

ExAblate Model 4000 Type - 1

Operator's Manual

System SW Version 6.6

Original Instructions

Caution: Federal law restricts this device to sale by or on the order of a physician

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REVISION INFORMATION

This is the **Revision 2.0** release of the ExAblate Model 4000 Type – 1 Operator's Manual for System Version 6.6, applicable for 3-Tesla MR systems.

Each page of this manual has a chapter revision level and date at the bottom. This indicates the release level & date for the individual chapters. Note that when the manual is updated, not all of the chapters are necessarily updated, so some chapters may have a revision level earlier than the release revision level for the manual (the revision level designation for the manual is that which appears on the top of the second page of this manual). The following table provides a complete list of the revision information, by chapter, for this release of the operator's manual.

The cover page, copyright page, this page and the table of contents pages are all **Revision 1.0** with the corresponding chapters of the manual.

Chapter #	Chapter Name	Chapter Revision Level, Date	# of Pages in Chapter *
Chapter 1	System Overview	2.0, 08/15	9 (1-1 → 1-9)
Chapter 2	Safety	2.0, 08/15	13 (2-1 → 2-13)
Chapter 3	Getting Started	2.0, 08/15	10 (3-1 → 3-10)
Chapter 4	System Start-Up	2.0, 08/15	3 (4-1 → 4-3)
Chapter 5	Treatment Tools	2.0, 08/15	9 (5-1 → 5-9)
Chapter 6	Imaging Stage	2.0, 08/15	23 (6-1 → 6-23)
Chapter 7	Planning Stage	2.0, 08/15	11 (7-1 → 7-11)
Chapter 8	Treatment Stage	2.0, 08/15	35 (8-1 → 8-35)
Chapter 9	Replay Stage	2.0, 08/15	2 (9-1 → 9-2)
Chapter 10	Utilities	2.0, 08/15	7 (10-1 → 10-7)
Chapter 11	Data Management	2.0, 08/15	6 (11-1 → 11-6)
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Chapter 1

System Overview

1.1. INTRODUCTION

InSightec's **ExAblate Model 4000 Type 1 (“ExAblate Neuro”)** delivers focused ultrasound energy into the brain tissue through an intact skull in a non-invasive manner. In a matter of seconds, the tissue at the focal spot of the ultrasound beam is heated to the point of irreversible thermal coagulation, while nearby tissue remains unaffected. Over time, the body gradually absorbs the ablated tissue.

The **ExAblate Neuro**'s focused ultrasound system operates inside a **Magnetic Resonance Imaging** (MRI) scanner, used to provide images of the patient’s anatomy, and prepare an appropriate treatment plan. The MRI also measures temperature changes inside the body during **Focused Ultrasound** (FUS) treatment. The system acquires MR images and runs dedicated sequences to display temperature maps. The temperature maps are used to calculate the extent of thermal ablation and to help ensure safety and efficacy.

Warning



This document is specifically intended for use with the ExAblate Neuro during clinical treatments and investigations. All patient treatment and therapy procedures must be performed in accordance with the United States Food and Drugs Administration (“FDA”) regulatory clearance(s) and approval(s).

1.2. SCOPE OF THIS MANUAL

This operator's manual covers the following systems:

1. ExAblate system, guided by a 3-Tesla MR scanner
2. System description
 - *Trade name* *ExAblate*
 - *Model* *4000*
 - *Cradle Type* *1.0*
 - *Software version* *6.6*
3. System Characteristics:

Transducer: 1024 elements annular sectored phase array

Transducer aperture (diameter): 300mm

Transducer radius of curvature: 150mm

Focal distance: 135-165mm (achieved by electronic focusing)

Frequencies: 620Mhz –720Mhz

Energy range: 30KJ

<i>Specification</i>	<i>Nominal Mode</i>
<i>Energy density in target (trans-skull, Typical)</i>	<i>800W/cm²</i>
<i>Ultrasound output</i>	<i>~1500W</i>
<i>Effective strength (on Xd Surface, Typical)</i>	<i>~1W/cm²</i>
<i>Max output pulse width</i>	<i>~60sec</i>
<i>Sonication duration</i>	<i>25-60sec</i>
<i>Duty cycle</i>	<i>1</i>
<i>Cooling time</i>	<i>20~400sec</i>

Effective radiating area (ERA): 1400cm²

Focal region size: ~1.5 x 1.5 x 3 mm

Focal control: electronic

Tissue destruction mechanism: thermal coagulation necrosis

Planning: treatment planned in multiple MR Images i.e. Coronal, Axial and Sagittal planes

Imaging during treatment: PRF MR Images at ~3.5seconds interval

Temperature measurement: Proton Resonance Frequency (PRF) MR thermometry

Reflection monitoring: None (data collection only)

Cavitation monitoring: passive cavitation detection, real time display, Sonication automatically halted if cavitation is detected.

Treatment outcome monitoring method: Using the real time thermometry the operator gets real time feedback on treatment outcome, as temperature is correlated to tissue viability

Independent assessment using standard MR imaging sequences is done during and after treatment, to assess ablation size and location.

▪ ***System Electrical Specification***

Rated power voltages: 208V/380V/400V/480V

Number of phases: 3 phases

Rated power frequency: 50/60Hz

Rated power input: ~30Kva

Protection against electric shock: Applied Part Type B

1.3. INTENDED USE / INDICATION FOR USE

The ExAblate Neuro is intended for use in the treatment of unilateral Thalamotomy idiopathic Essential Tremor patients with medication-refractory tremor. Patients must be at least age 22. The designated area in the brain responsible for the movement disorder symptoms (ventralis intermedius) must be identified and accessible for targeted thermal ablation by the ExAblate device.

1.4. 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
- 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.

1.5. SYSTEM COMPONENTS

The ExAblate Neuro system consists of the following integrated components:

- Operating console
- Patient table
- Front end unit
- Equipment cabinet
- Water system

1.5.1. Operating Console

The ExAblate Neuro console allows the operator to control and monitor both the system and the treatment. It is positioned alongside the **GE MRI** workstation in the control room.

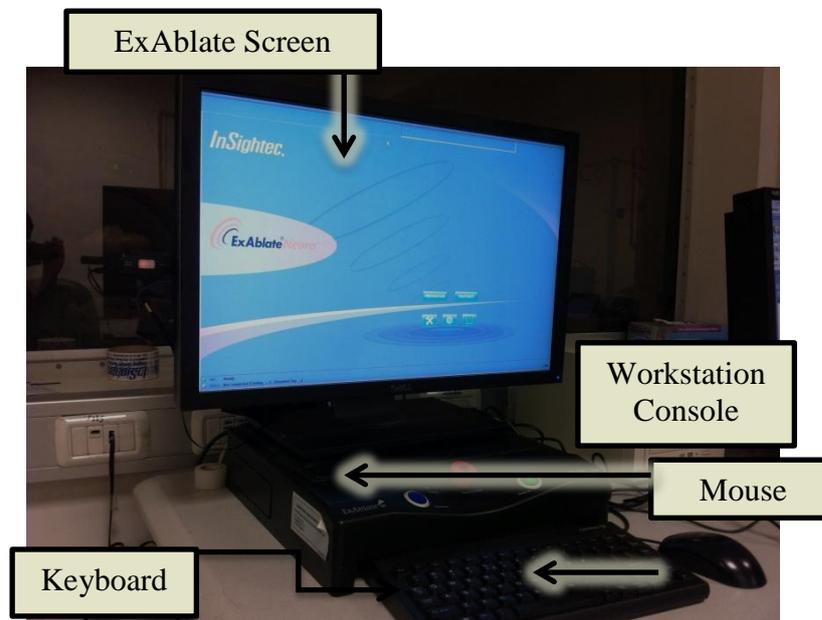


Figure 1-1: ExAblate Neuro Operating Console

1.5.2. Patient Table

Treatments are conducted with the patient lying on the patient table inside the MR scanner (see Figure 1-2).

The patient table incorporates the focused ultrasound transducer along with the mechanical positioning unit that moves and locks the transducer in place. The patient table also includes the patient interface accessories to keep the patient's head immobilized during treatment (see Figure 1-3).

Prior to the treatment, the patient table is docked to the MR Scanner. The patient table is also connected to the front end unit and to the water system.

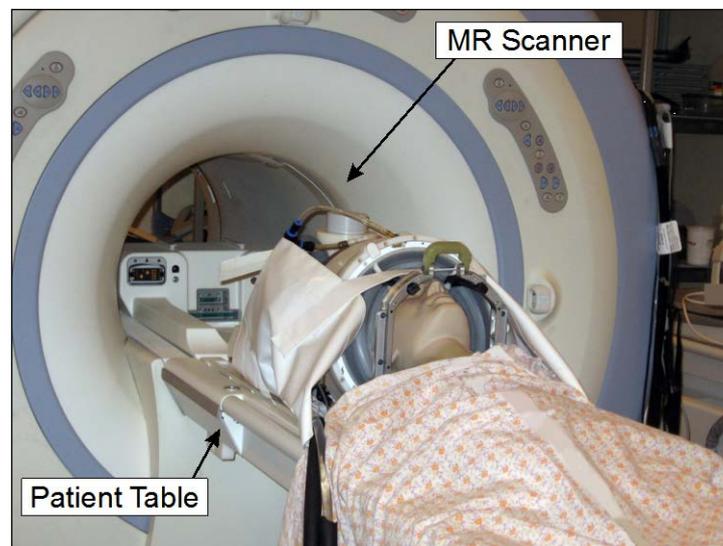


Figure 1-2: The Patient Table

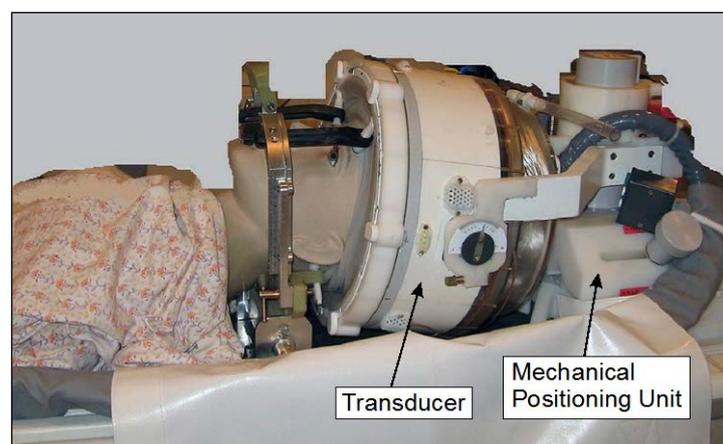


Figure 1-3: The Transducer and the Mechanical Positioning Unit

1.5.3. Front End Unit

The Front End Unit incorporates the electronic systems that drive the ultrasonic transducer. The Front End unit is located in the magnet room and is connected to the equipment cabinet. The unit can be moved in the room but should not be disconnected from its cables. Only authorized InSightec service personnel are qualified to disconnect this unit or move it out of the magnet room (see Figure 1-4).

Two cables coming out of this unit are connected to the treatment table. In cases where the table is stored away from the Front End Unit, these cables may be disconnected by the site personnel after being trained to do so.



Figure 1-4: ExAblate Neuro Front End Unit

1.5.4. Equipment Cabinet

The equipment cabinet incorporates the electrical components of the ExAblate Neuro system and the main power switch. This unit is usually located in the MRI equipment room. Do not interact with the equipment cabinet. Only authorized InSightec service personnel are qualified to move or disconnect this unit (see Figure 1-5).



Figure 1-5: ExAblate Neuro Equipment Cabinet

1.5.5. Water System

The water system offers a semi-closed water circulation loop, designed to provide for several requirements for the trans-cranial treatment (see Figure 1-6):

- Filling and draining the transducer water interface during treatment preparations
 - Circulating the water during treatment to keep interface water cooled and degassed
 - Support the cleaning procedure in between treatments
1. The water system is usually located in the MRI equipment room. Please review *System Cleaning and Disinfection Procedure* for further information. Cleaning procedure requires use of “SET000870 - ExAblate Cleaning kit “



Figure 1-6: ExAblate Neuro Water System

Chapter 2

Safety

2.1. ExAblate Safety Considerations

ExAblate Neuro was designed and manufactured to ensure maximum safety of operation. Maintain the system in strict compliance with the safety precautions, warnings, and operating instructions in this manual. The ExAblate Neuro should be installed, maintained, and serviced by **InSightec** personnel, or other qualified personnel approved in writing by InSightec.

The ExAblate Neuro, in whole or in part, should not be modified in any way without the prior written approval of InSightec.

The owner should ascertain that only fully qualified, properly trained and certified personnel according to InSightec training program, are authorized to operate this equipment.

It is important to keep this manual near the system. It should be studied and reviewed periodically by all authorized operators. However, InSightec makes no representation that the act of reading this operator's manual renders any user qualified to test, calibrate, or operate the system.

Unauthorized personnel should not be allowed access to the system.

If the system does not operate properly, or fails to respond as expected to the controls as described in this manual, tend to the safety of the patient first, and then attend to the system.

As required by IEC60601-1 third edition to define:

- System applied part list: FUS cradle & Treatment helmet.
- System accessory part list: Stereotactic frame ASM001399

System expected usable lifetime is 10 years. Upon lifetime elapsing please consult InSightec for steps to take

2.1.1. Use of ExAblate system within MRI Environment



The ExAblate 4000 Table is MR Safe

2.1.2. Use of MR Equipment

Personnel operating the MR equipment must have a thorough understanding of the proper operation of the system.

Do not operate the MR equipment before reading the appropriate user manuals and gaining a clear understanding of the operation of the system. If any part of the MR system's manual is not clear, contact the MR equipment's technical and/or clinical service personnel for clarification.

For the safety of the patients, operating personnel and technical personnel, all operating instructions and particularly the safety instructions therein must be strictly adhered to.

2.1.3. System service

- The ExAblate system should be installed, maintained, and serviced by InSightec personnel, or other qualified personnel **certified** by InSightec.
- Periodic maintenance should be performed according to InSightec service standards by InSightec or by **InSightec certified** personnel.

Warning



If a System is NOT serviced on a regular basis based on InSightec service schedule, this system must not be used for clinical use on patients.

2.2. DOCUMENT CONVENTIONS

Notes, **Cautions** and **Warnings** are used throughout this manual to highlight important points of information that affect the health and safety of the patient and operator, as well as information intended to preserve system integrity. Examples of these messages appear below:

Note

Notes provide information to aid in obtaining optimum equipment performance.

Caution



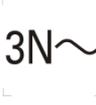
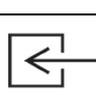
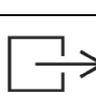
Cautions indicate instructions, or cautionary notes which, if not followed, may result in damage to the equipment or to the quality of treatment.

Warning



Warnings indicate precautions and instructions which, if not followed, may result in personal injury or even death.

2.3. SYMBOLS USED IN THE SYSTEM

Symbol	Title	Description of graphical symbol
	Alternating current	To indicate on the rating plate that the equipment is suitable for alternating current only; to identify relevant terminals.
	Three-phase alternating current	To indicate on the rating plate that the equipment is suitable for three phase alternating current only; to identify relevant terminals.
	Three-phase alternating current with neutral conductor	To indicate on the rating plate that the equipment is suitable for three phase alternating current with neutral conductor only; to identify relevant terminals.
	Protective earth (ground)	To identify any terminal, which is intended for connection to an external conductor for protection against electric shock in case of a fault, or the terminal of a protective earth (ground) electrode.
	Temperature; thermometer	To signify temperature or function associated with temperature (e.g., temperature indication, temperature monitoring points). Units of measurement (e.g., °C) can be added to symbol.
	Caution risk of danger or Attention	To signify caution.
	Caution risk of electric shock or Attention Dangerous Voltage	
	Date of manufacture	
	Type B applied part	To identify a type B applied part complying with IEC 60601-1 third edition.
	Body weight	To identify the control or indicator to enter or call up the body weight of a person.
	Input; entrance	To indicate an entrance (e.g. hydraulic pump).
	Output; exit	To indicate an exit (e.g. hydraulic pump).

2.4. SAFETY INSTRUCTIONS

Warning



Before using the ExAblate Neuro system:
Read and understand each of the following safety warnings
Refer to the safety information supplied with the MRI System

Warning



The ExAblate 4000 is type B applied part.
It is properly grounded by design and by the installation process.
It is important for the safety of the patient and operator to maintain proper system grounding. Connect the system as instructed, and do not disconnect any of the system installation connection

2.4.1. MR Coils

This document covers ExAblate Neuro systems that can be used with MR Body coil and/or with Tc MRgFUS head coil according to the MR system configuration. Read the respective operating guides to ensure correct use.

2.4.2. Patient Positioning

After the patient is lying comfortably on the patient table, insulate the patient from the MR scanner with appropriate thermal-resistant pads to prevent potential RF burns. Place the pads along the patient's sides to insulate the patient from the scanner walls. Patients in danger of touching the scanner ceiling require thermal-resistant pads for the back and buttocks.

Verify that an open space of more than 0.5" (1.25 cm) exists between all system components and patient to the sides and top of the scanner. The maximum allowed patient weight is 285 lbs (130 kg).

Warning



Pay strict attention to the top part of the transducer and ensure proper clearance from the top of the magnet bore.

Ensure that the patient's gown does not hinder the movement of the table mechanism as it goes in and out of the scanner.

Ensure that patient's body is strapped to the patient table to avoid an accidental fall of the patient and/or any objects from the patient table.

Warning

Pay strict attention that no air has entered the transducer interface and that it is completely filled with water in preparation and continuously during the treatment. Incorrect coupling may cause reduced focal zone temperatures, defocusing and misalignment of the focal spot and/or severe damage to system components.

2.4.3. Patient Protection

For MRI safety, refer to the **Safety** section of the MR system operator's manual.

Ensure that the patient does not have any metallic implants, including but not limited to pacemakers and neuron-stimulators.

Metal objects are forbidden in the magnet room. Verify that there are no rings, clips, loose change, or any other metal object on the patient.

Warning

Refer to safety guidelines issued by the MRI safety procedures and restrictions that may apply to the specific site.

Do not leave a patient unattended in the magnet room.

The **Stop-Sonation** button must be given to all patients. Pressing the button immediately interrupts treatment. Three stop-sonication buttons are available on the system:

- One is on the operator's console
- One is given to the patient
- One is controlled by the staff member in the treatment room

Instruct the patient to stop the sonication when feeling pain or heat.

Give the patient hearing protection.

The patient is not always in view of the console operator. Be sure that medical personnel are in the magnet room during the procedure.

Verify that the patient's fingers and clothing (hospital gowns) are not in danger of being caught in the equipment during positioning or cradle motion.

During treatment, frequently ask the patient if he/she is in any pain or discomfort.

To increase patient comfort and reduce the risk of patient hypothermia, body warmth should be maintained by accessories or systems provided by the site.

The use of any medication and/or imaging contrast should be applied after considering possible effects on ultrasound energy absorption or thermal imaging. The ExAblate system creates heat in the target, which may cause thermal ablation based on temperature rise levels and duration. Such ablation (referred to as thermal dose) will be created by temperature of 43°C for 240 minutes, by 54°C for 3 seconds, or by 57°C for 1 second. Carefully examine the thermal images and the thermal dose contours after each sonication to avoid possible damage to unintended tissues.

Cavitation refers to formation and collapse of bubbles (created from dissolved gas), which fill cavities that are created in low pressure regions. As a result, bio-effects may occur due to these bubbles and are dependent on the extent and type of cavitation. The ExAblate has a built in cavitation detector and a mechanism to automatically stop or adjust the power levels in order to avoid cavitation, which may cause unintended tissue damage (see chapter 8.3.7).

Notice

The ExAblate system components are not made with natural rubber latex

2.4.4. Patient Emergencies

Each ExAblate Neuro site must develop appropriate patient emergency procedures.

All personnel who operate the system must study and practice patient emergency procedures.

If there is any sign of danger to the patient, proceed as follows:

1. Press the **Emergency Stop** button mounted on the wall in the operator's control room or the one in the magnet room to shut down the MR and the ExAblate Neuro systems.
2. If necessary, notify emergency personnel.
3. Squeeze the cradle release handle and pull the cradle onto the patient table. If the cradle does not release, use moderate force to pull out the cradle.
4. If it becomes necessary to remove the table from the room, detach the quick-coupler cables and hoses and remove the patient table from the magnet room. The patient table is not very maneuverable. To avoid this limitation perform one of the following options:

- Keep a non-magnetic gurney in the magnet room, or
 - Keep a regular gurney outside of the magnet room.
5. Release the patient from the transducer interface as expediently as possible.
 6. Attend to the patient, following established hospital emergency protocols.
 - **Note:** The water system is drained and filled by the remote control. In case of complete power loss, or other malfunction of the automated water system, Emergency drain kit (SET00174) can be used to drain water from the transducer. Draining water from transducer takes up to 10 minutes. Please review **Emergency Drain kit - Use instructions PUB40023** for further information.
 - In case of Emergency, patient can be released from transducer without draining the water, in less than a minute. This will result in water spillage (up to 10 Liters) and risk of slippery floor.

Warning

Life-support, resuscitation or any other equipment based on ferromagnetic components is not allowed in the magnet room.

2.4.5. System Stability

The ExAblate system complies with COUNCIL DIRECTIVE 93/42/EEC Article 3 and 2006/42/EC Machinery standard regarding stability requirements.

The system table and cradle move in/out of the MR bore on wheels equipped with stoppers. The table can be manually raised or lowered as required by pressing the foot pedal, to a maximum range of 225mm. To ensure the patient's secure and safe positioning on the table, proceed as follows:

1. Always ensure that the patient, while on the table, is safely harnessed with the cross-tying safety belts.
2. Only remove the patient from the table when the table is in final lowering position and its wheels are at STOP position.

The system operator is obliged to meet instructions and take the stability safety precautions in a timely and complying manner as to keep moving parts from collisions, falls, slipping and tripping.

2.5. WATER SYSTEM PRECAUTIONS

The water system is used to keep the skull cool during treatment. The water temperature is monitored by the system and is displayed on the workstation screen.

During treatment the operator must be aware of the following:

- Attend to any system alert to a malfunction in the water system
- Confirm that the circulation has restarted in between sonications and that the water temperature is adequate

An improper seal between the patient's head and the Patient Interface Membrane could result in a water leak in the MR bore. During water filling or draining (see Chapter 3) you need to confirm the following:

- The air ventilation tap is open
- The operator must be next to the patient
- Monitor any water leaks from the transducer
- Watch for any excessive pressure in the Patient Interface Membrane

Prior to moving the cradle into the MR bore, always confirm:

- Place the water protection drape over the transducer to avoid water spillage directly on to the MR bore
- Confirm the water drain below the transducer is empty and dry
- Confirm that the air ventilation pore has been locked

There are 2 elements on the left side of the operating console (see Figure 2-1):

- The blue button is the **Circulation Controller**
- The green LED is the **Water System Indicator**

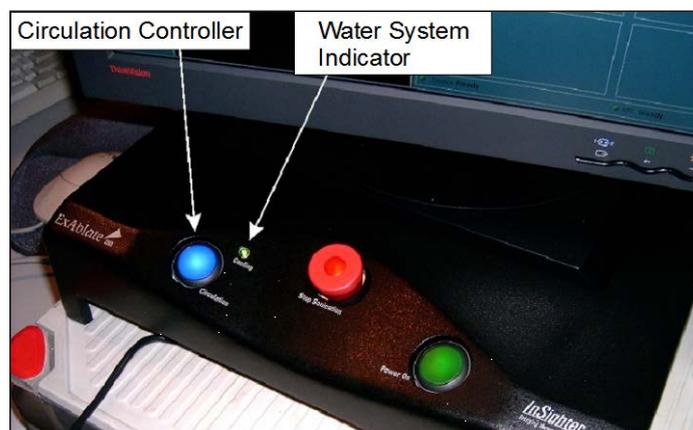


Figure 2-1: Circulation Controller & Water System Indicator

2.5.1. Circulation Controller

The blue **Circulation Controller** on the operator console illuminates continuously when the water circulation in the transducer's interface is active. When the temperature in the water interface is higher than the desired set point, the illumination will flash.

Warning



The water in the transducer's interface may start getting warm as a result of a prolonged sonication sequence. Monitor the water temperature on the workstation's screen.

Note

The blue **Circulation Controller** is also used to pause the circulation. Press it once to pause water circulation (controller illumination will stop), press it again to resume water circulation (controller will illuminate).

2.5.2. Water System Indicator

The green **Water System Indicator** is illuminated when the water system is operating properly.

The system will automatically cease circulation in case there is a chance of water leakage or excessive pressure in the transducer. This will cause the green **Water System Indicator** to blink and activate a warning buzzer. The error status will also be displayed on the workstation's screen.

If this occurs, you must first take the patient cradle out of the bore to confirm:

- No water leaks are visible
- Water level in the transducer interface is nominal
- Water pressure is nominal
- No air is present in the transducer interface
- Water hoses are not tangled or obstructed
- Air ventilation pore is closed

If there is not a noticeable problem, or it has been resolved, fill or drain the water as needed and press the blue **Circulation Controller** once to reset the water system by pressing the blue **Circulation Controller** again.

If the problem persists, contact InSightec service personnel for troubleshooting.

2.6. OPERATOR PRECAUTIONS

The ExAblate Neuro console is designed to protect the patient and the operator from accidental exposure to ultrasound energy.

Review and follow all operator instructions included with the console.

The patient, operator, and nurse must each be able to freely activate a stop-sonication button at any time during the procedure. Pressing the stop-sonication button immediately stops the sonication. Releasing the button enables the treatment to resume.

The ExAblate Neuro console controls the connection between the ultrasound transducer and the rest of the system. The system power should be turned off before leaving the console to prevent undesired activation of the transducer.

The transducer surface is very delicate, therefore clean only with alcohol and soft cloth and avoid any contact of sharp objects. When not in use, cover the transducer with the dedicated cover to avoid damage.

The **Sonication Power-On** light in the magnet room indicates that the transducer is applying ultrasound energy. This light must be in clear view of the nurse and the console operator. Never move the patient or place your hand near the transducer while the sonication power-on light is illuminated.

It is hereby stated that no patients or operators are exposed to any hazardous material.

No modification of this equipment by non-authorized personnel is allowed

2.7. ELECTROMAGNETIC COMPATIBILITY (EMC) PRECAUTIONS

Caution



1. The ExAblate system should not be used adjacent to or stacked with other equipment and, if adjacent or stacked use is necessary, the system should be observed to verify normal operation in the configuration in which it will be used
2. The ExAblate system needs special precautions regarding electromagnetic compatibility (EMC) and needs to be installed and put into service according to the EMC information provided in Appendix C
3. Be aware that portable and mobile RF communications equipment can affect the ExAblate system

A Statement on ExAblate System Essential Performance:

The essential performances of ExAblate Neuro are

1. Safety Monitoring
 - a. Monitors and Verifies the sonication is executed as planned
 - b. Verifies that the monitoring is running continuously.
 - c. If failure of any of the above does NOT stop the sonication, the system is NOT safe.
2. Spectrum monitoring:
 - a. Monitors the spectral signal that exists during the Sonication
 - b. Continuously verifies that the spectrum signal is below the pre-defined threshold.
 - c. If failure of any of the above does NOT stop the sonication, the system is NOT safe.

These 2 functions are not allowed to fail.

2.8. SYSTEM ENVIRONMENTAL CONDITIONS

Operating Conditions:

Temperature range: +10°C to 40 °C

Relative humidity: 30% to 75%

Atmospheric pressure: 700 hPa to 1060hPa

Altitude: -30m (-100ft) to +3000m (+9800ft)

Storage & Transportation Conditions

Temperature range: +0°C to 60°C

Relative humidity: 10% to 90%

Atmospheric pressure: 700 hPa to 1060hPa

Chapter 3

Getting Started

3.1. SYSTEM POWER ON

Warning



The water system will reach its optimal operating conditions after approximately one hour. Take this into consideration, and turn on the system as early as possible before the treatment, to avoid downtime when the patient arrives.

Start up the system in the following sequence:

1. Confirm that the MR console was rebooted at the beginning of the day. If not, reboot it.
2. Undock the imaging table and dock the ExAblate Neuro Treatment table to the MR scanner.
3. Attach the two quick-coupler cables, each uniquely labeled, to the patient table (see Figure 3-1):

Caution



Make sure that the quick coupler connectors are connected each to its intended labeled position. The connectors must be gently aligned into place before locking.

- Open the quick-coupler's cover door (located on the side of the patient table)
 - Align the cable with the connector, and slide it gently inside
 - Lock the quick-coupler's connector
4. Attach the Water System Cable to the patient table (see Figure 3-1):
 - Open the water system connector cover door (located on the side of the patient table, towards the front)
 - Align the cable with the connector, and slide it inside

Warning



Ensure that the cables are securely attached to the patient table before turning on the main power switch. Do not disconnect the cables once the main power is on except in an emergency.

Warning

Visually inspect the ExAblate system:

- Verify the integrity of the transducer and the table
- Confirm that the connectors are properly fastened
- Confirm that the table is properly docked.

Failure to do so may result in improper system functioning.

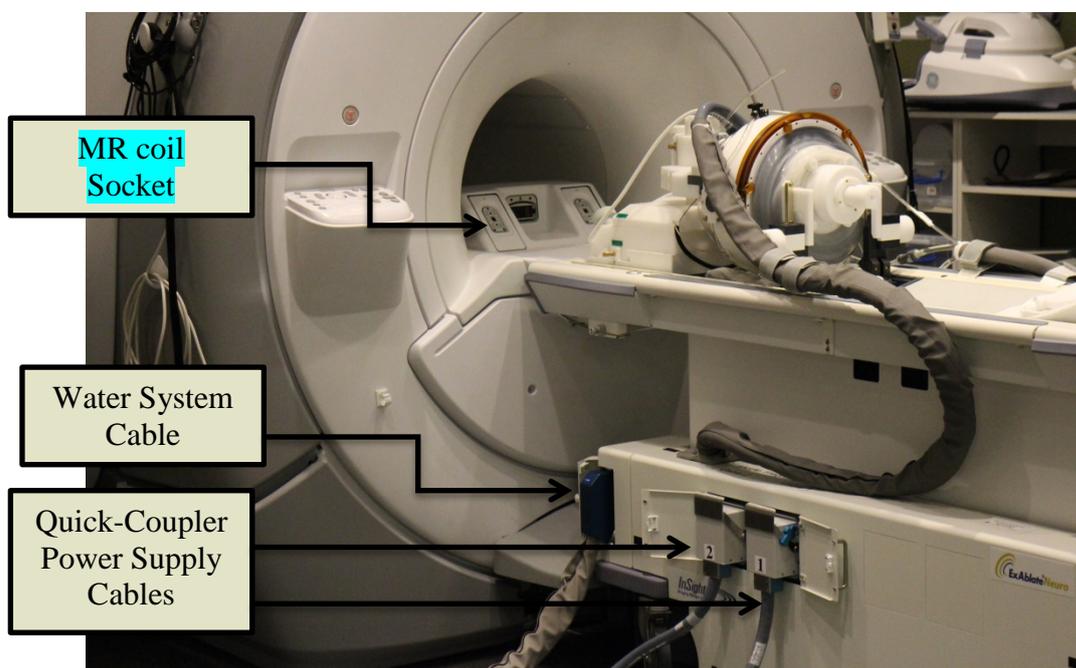


Figure 3-1: System table Cables Connections

5. Connect the Tracking Coil to the MR Coil Socket (see Figure 3-1).
6. Remove all external media drives and or CD's from the console computer.
7. Turn on the system by pressing the **Power On** switch located on the operator's console; the **Begin Logon** notice appears.
8. Press **Ctrl+Alt+Del** to access the logon information dialog box. Type the user name and then enter your password (Windows[®] logon parameters are case sensitive). Click **OK** to continue.
9. The ExAblate Neuro disclaimer popup window opens; click **OK** to continue.

10. Perform Cleaning / Disinfection procedure – See Cleaning and Disinfection procedure for more details.
11. Start water Degassing according to the following procedure, and then proceed with step 10 on page 3-3.



Figure 3-3: Water System Control Panel

- Fill the water system's reservoir with 5.25 gal. (20 liters) of clean water and attach the water connectors.



- On the Startup screen, press  and enter the Utilities screen.



- Press  and choose “Set preparation stage”.
- Degassing process will start, and indication on system's status will appear on the bottom of the screen in the Device's status as [Degassing, Temperature, Dissolved Oxy.]

12. Confirm that the device and MR status are **Ready**, and the green **Water System Indicator** on the operator console is illuminated.

Caution



If the green **Cooling Indicator** starts blinking, there is a malfunction in the system. Review Chapter 2 – **Water System Precautions** – for more details.

3.2. PATIENT POSITIONING AND RELEASE

3.2.1. Patient Positioning

For patient positioning, the following accessories are required:

- Patient interface membrane (ASM000355) – elastic membrane which seals the transducer and enables acoustic interface between the transducer and the patient’s head (Figure 3-4). The cleaning procedure and storage instructions can be found in ***Brain Cleaning and Disinfection Procedure*** .
- Stereotactic frame (ASM001399) – Head frame which allows fixation of patient’s head to the bed (Figure 3-4). The frame is attached with Head ring Screws (MPR000444). A frame attachment strap is used to assist in frame placement (MEC001647). To protect the elastic membrane, Protective frame pin caps are used (MPR001164). Recommended use operating guidelines, cleaning, sterilizing and maintenance procedures can be found in the manufacturer’s site (<http://www.integralife.com/>) under the product name of: ***Radionics® CRW Precision™ Arc: Stereotactic System, and on supplied manual PUB400012***
- Transducer sealing gel (BUY000180) – seals the transducer to prevent water leakages. Information about operating guidelines (MSDS) can be found in the manufacturer’s site (<http://www.dowcorning.com/>) under the product name of: **MOLYKOTE®111 Compound**.

Prior to the treatment, position the patient as follows:

1. Slide the **Patient Interface Membrane** over the patient’s head and place it as low as possible on top of the **Stereo-Tactic Frame** (see Figure 3-4).

Warning



- Stereotactic frame and its accessories should be handled according to frame manufacturer instructions (<http://www.integralife.com/>)
- All Non-InSightec ExAblate parts or material may need to be managed according to local procedures, regulations and all applicable laws.

2. Confirm the tightness of the membrane to avoid discomfort or harm to the patient. If required, the membrane may be enlarged to fit.

Warning



Make sure transducer is positioned as far back from the base plate attachment as possible.

3. Instruct patient to lie down and guide the stereo tactic frame into the **Base Plate Attachment**; lock it in place (see Figure 3-5).

4. Make sure the transducer's front-ring seal (O-ring) is secured tightly in place.
5. Move the transducer to the treatment position.
6. Couple the **Patient Interface Membrane** with the transducer. Confirm all the **latches** are fastened in place and that the patient does not feel any pain or discomfort.
7. Strap the patient to the treatment table.
8. Fill the transducer with water:
 - Open the **Transducer Ventilation Tap**
 - Press and hold down the **Fill** button on the **Water System Remote Control** panel (see Figure 3-4)
 - Watch for any water leaks, and hold the **Fill** button until the transducer is full
 - Close the **Transducer Ventilation Tap**

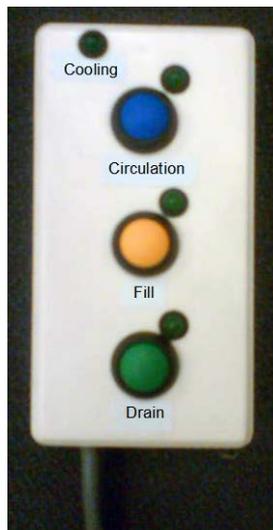


Figure 3-4: The Water System Remote Control

3.2.2. Patient Release

At the end of the treatment, release the patient as follows:

1. Take the cradle out of the MR bore back to home position.
2. Open the **Water Protection Drape**.
3. Drain the water from the transducer:
 - Open the **Transducer Ventilation Tap** (see Figure 3-5)
 - Press and hold down the **Drain** button in the **Water System Remote Control** (see Figure 3-3) until the transducer is completely empty

4. Unfasten the **latches** and disconnect the **Patient Interface Membrane** from the transducer (see Figure 3-5).
5. Move transducer as far away from the patient as possible.
6. Release **Stereo-Tactic Frame** from the **Base Plate Attachment**.
7. Instruct and guide the patient to sit up.
8. Remove the **Patient Interface Membrane** from the patient's head.

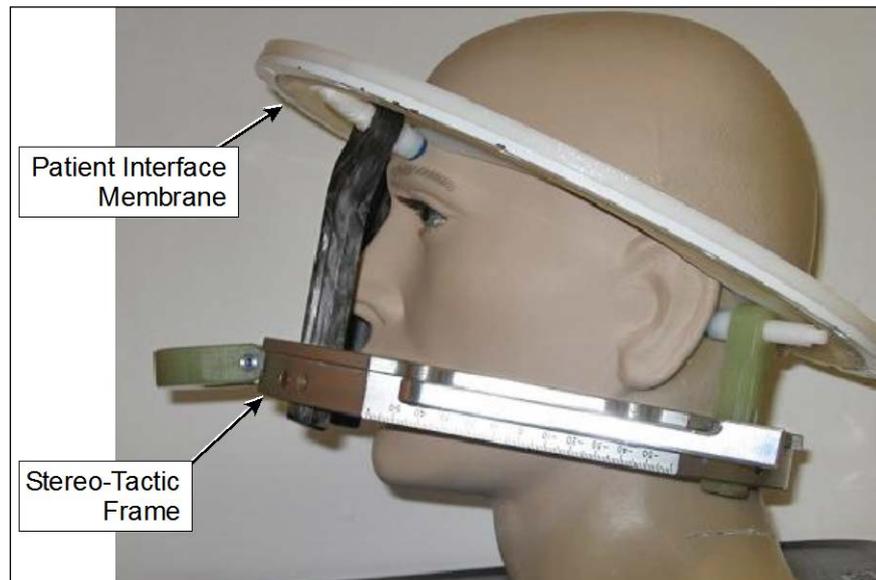


Figure 3-2: The Stereo-Tactic Frame and the Patient Interface Membrane

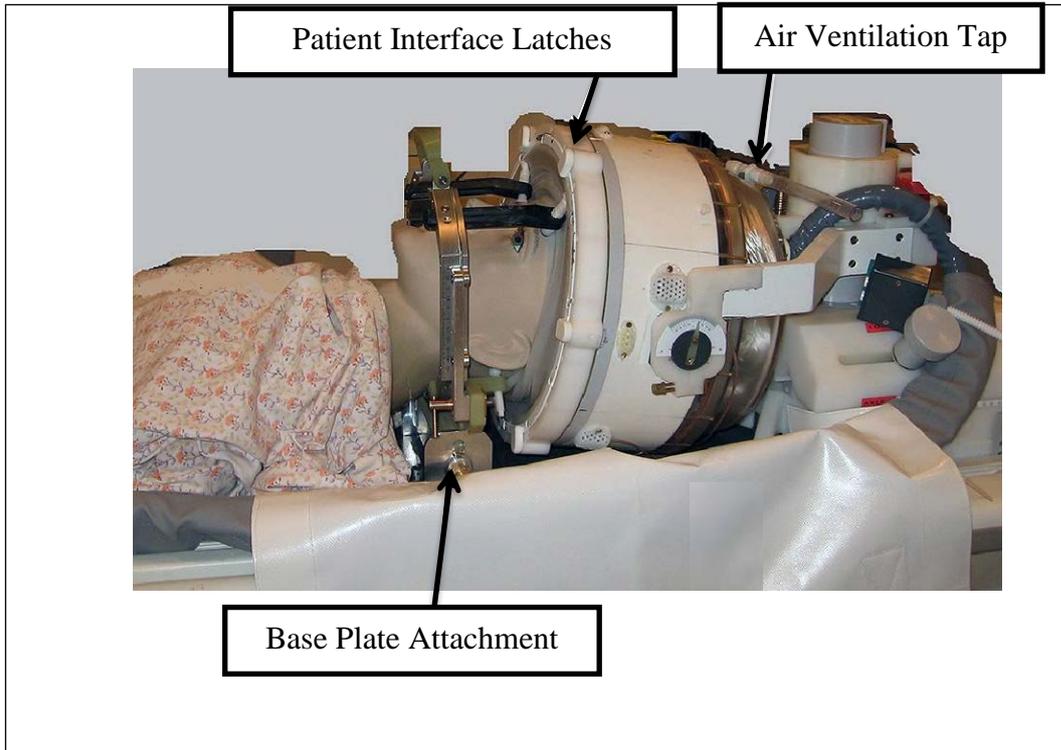


Figure 3-3: The Transducer - Patient Interface

3.3. SHUTDOWN

To shut the system down, proceed as follows:

1. Click  on the **System** toolbar to return to the **Startup** screen.
2. Click ; the system responds with the **Shutdown Confirmation** message.
3. Click **Yes** to continue; the automatic shutdown procedure is initiated. This takes a few minutes.
4. Disconnect the coupler cables from the table **only** when the console has automatically powered down, and the power-on light has extinguished:
 - Unlock the quick-coupler lever and gently slide the quick-coupler cable outside.
 - Pull the white handle towards you and slide the quick-coupler hose cable outside.
5. Undock the patient table.
6. To prevent damage to the transducer, at the end of the working day, verify Transducer is empty and dry, and attach the transducer cover.

Caution



Do not leave the transducer filled with water unattended or for more than 20 hours

7. When not in use, cover the patient table with the protective table cover.

3.4. DAILY QUALITY ASSURANCE (DQA) TEST PROCEDURE

The DQA procedure should be conducted at the start of each day, prior to each treatment, to verify proper operation of the ExAblate Neuro system.

The instructions below provide a general outline of the DQA procedure.

The accessories needed for the DQA procedure are:

- Phantom gel (ASM400327) – solid, water based, crossed linked gel mimicking brain tissue. This gel is disposable.

- Gel holder (ASM0002252) – holds the gel and seals the transducer during DQA procedure.

3.4.1. DQA Set Up Procedure

Note

Use the *ExAblate Neuro DQA checklist* for a detailed description of the DQA procedure. Follow it and ensure proper system functioning. Verify results according to PUB40022 DQA checklist

Prior to starting the DQA please confirm:

1. Reboot the MR System if it has not been rebooted that day.
2. Power on the system (see Section 3.1).
3. Visually check the integrity of the transducer:
 - For loose fittings or cracks
 - Check for any loose or damaged connectors or water lines on the patient table
4. Ensure that the patient table is completely set up and ready for the patient.
5. Move transducer to DQA position according to DQA labels.
6. Fill the transducer with water.
7. Landmark according to the **Landmark labels** that were placed upon the cradle and table. Make sure both labels are accurately aligned before performing the landmark (see Figure 3-6).
8. Be sure the cables are free to travel with the patient table.
9. Send the ExAblate cradle to the center of the MR bore (may use the *Advanced to scan* button on the MR). MR cradle location indicator should show “0mm” on screen while the second label which was placed upon the cradle should be aligned with the one upon the table (same one as in step 7).
10. Open new exam on the MR console and run Localizer scan
11. Enter the ExAblate workstation and choose the Brain DQA protocol from the **Treatment protocol** dialog box (see Section 6.5).
12. Scan images on all 3 orientations from the predefined protocol saved on the MR and upload them to the ExAblate workstation (see Section 6.5).

13. Perform a short treatment and follow the order of planned spots. Check that the system operates properly, the spot is within 3 mm of the target location and that the dose threshold level is achieved.
14. Verify that the system halts the specific sonication which intentionally creates cavitation.

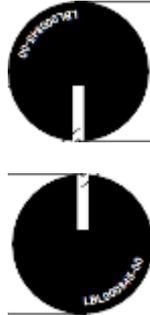


Figure 3-7: Two aligned Landmark labels

Caution



If any of the above inspections or tests fails to meet the expected values, discontinue use of the system until it has been thoroughly inspected by authorized InSightec service personnel.

Note

ExAblate Neuro treatments create many new series on the MR scanner. It is advisable that during DQA, sufficient disk space be available on the MR workstation.

3.4.2. Storage and Maintenance of DQA Phantom Gel

The DQA phantom gel is solid, water based, crossed linked gel.

The gel is delivered in a sealed nylon / aluminum bag. After the use, the DQA phantom gel can be discarded according to local regulations.

To Prepare DQA gel for use:

1. Open bag and retrieve the gel
2. Insert gel to dedicated slot in gel holder.

Chapter 4

System Start-Up

4.1. START-UP SCREEN

Turn on the power to the system and log on (see Chapter 3); the **Start-Up** screen appears:

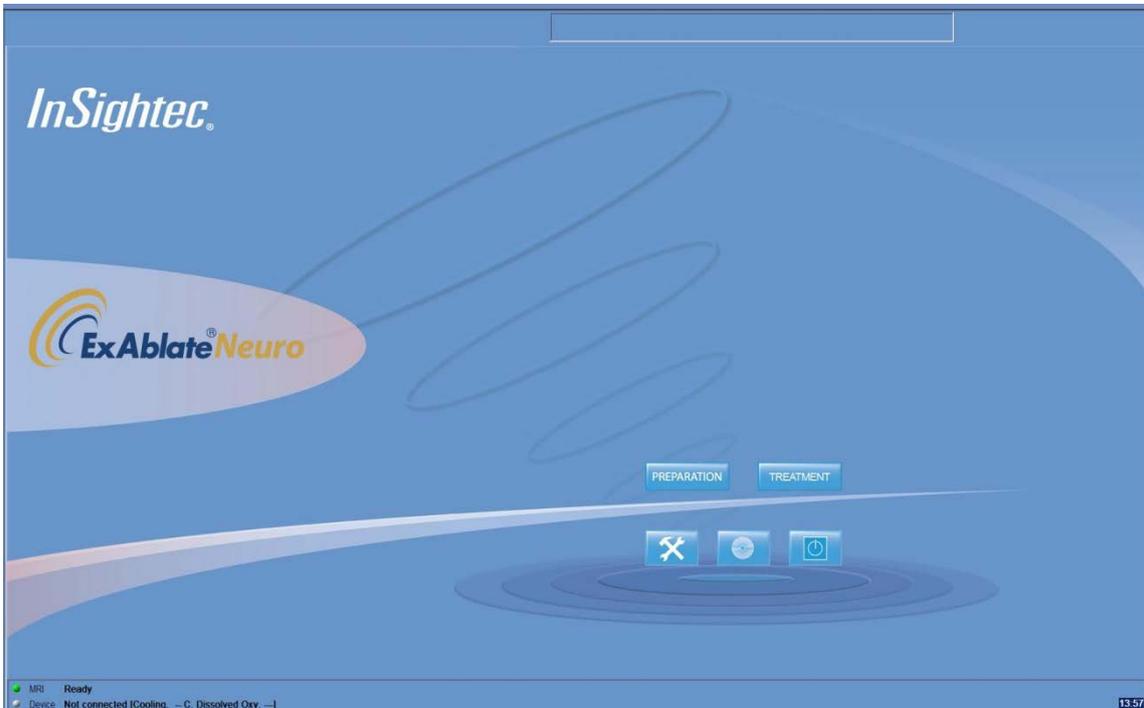


Figure 4-1: Start-Up Screen

The **Start-Up** screen contains a **Pre-Treatment Session** button, a **Treatment Start** button, Three **Command** buttons and a **Status Bar**.

4.1.1. Treatment Options

Pressing the **Treatment Start** button (see Section 4.1.1.1) activates the application-specific treatment.

4.1.1.1. Treatment Start



Prepare a Planning Session

Click this button to begin the Pre Treatment Plan session or to open existing session that was saved (see Appendix B)



Start Treatment

Click this button to begin the treatment

4.1.1.2. Command Buttons

The command buttons that appear in the lower half of the **Start-Up** screen are:



Utilities

Click this button to access **Utilities** mode (see Chapter 10)



Data Management

Click this button to access data management operations (see Chapter 11)



Shutdown

Click this button to shut down the ExAblate Neuro system (see Chapter 3)

4.1.1.3. Status Bar

The status bar shows the operational status of the ExAblate Neuro and the water system (**Device**), and the status of the MRI (**MR**).

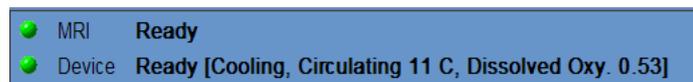


Figure 4-2: Device and MR Status Bar

Verify that the buttons in the status bar are green, and proceed to patient positioning. When the buttons are red, follow the system's instructions.

4.2. BEGIN TREATMENT PROCEDURE

After turning on power to the system and positioning the patient, the treatment procedure is initiated from the console.

1. Click **TREATMENT** on the **Start-Up** screen; the treatment data dialog box is opened (see Figure 4-3):
2. Type the physician's name in the **Physician Name** text box. This step is required, and the system will respond with an error message if you attempt to advance to the next stage without a name in this text box. The physician name consists of letters only (no numbers or symbols).

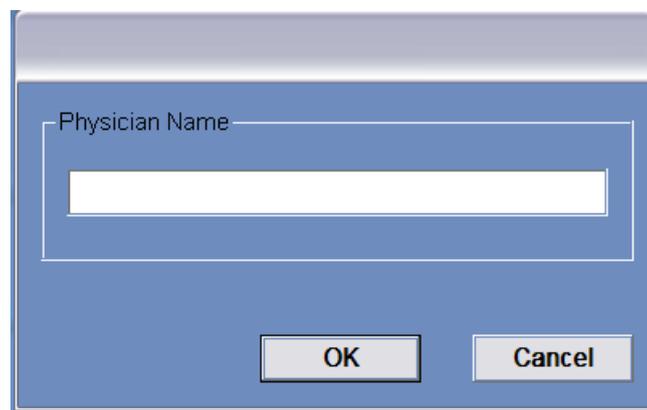


Figure 4-3: Treatment Data Dialog Box

Chapter 5

Treatment Tools

5.1. TREATMENT TOOLS - OVERVIEW

This chapter describes the elements, which appear on the **Treatment** screen throughout the treatment cycle. This includes **Treatment Stages**, **Utilities**, **Imaging**, **Navigation** and **Overlay** tools, **Cursor Coordinates**, **Image Strips** and the **Selected Image** window.

Along the left side of the **Treatment** screen, a number of tools are displayed to help plan and conduct the treatment. Different tools are available to the operator depending upon the stage of the treatment and are described in each of the following sections. The following descriptions refer to the general tools that are not specific to one stage or another.

5.2. TREATMENT SCREEN

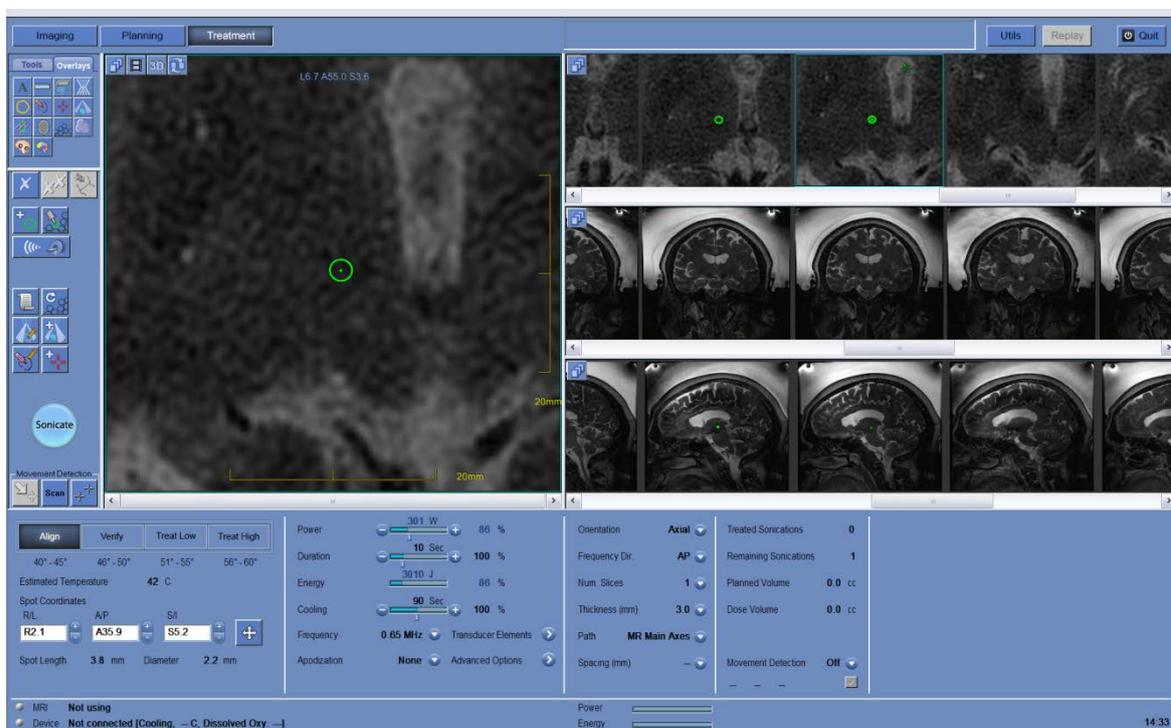


Figure 5-1: Treatment Screen

5.2.1. ExAblate Main Toolbar

This toolbar consists of buttons that correspond to the stages of the **Treatment** and the **Utilities** buttons.



Figure 5-2: The ExAblate Main Toolbar

5.2.2. Treatment Stages

Imaging Stage

This stage enables the operator to:

1. **Automatically track** and determine the transducer's home position and orientation relative to the patient's anatomy.
2. Determine and fix the **Central Frequency** (automatically or manually) that will be used in the MR images throughout the procedure, to minimize imaging and thermal shifts.
3. Define the required **Treatment Protocol** according to the specific target characteristics.
4. Plan and acquire **MR planning images** (or alternatively scan planning images on the MR and retrieve the relevant series to the ExAblate workstation).
5. Retrieve relevant range of images from a **CT exam** into the ExAblate workstation.
6. Upload **pre-Treatment Plan** into the ExAblate system (see Appendix B)
7. Determine the desirable **Target Center** and adjust the location of the transducer accordingly to match between its natural focus and the target.
8. Define sensitive areas that will limit or totally eliminate the acoustic energy from passing through them, by drawing **No Pass Region contours** upon the CT or MR images.

Planning Stage

This stage enables the operator to:

1. Automatically and/or manually **Register** between the different sets of images that were retrieved to the ExAblate workstation. This process matches between the coordinates of different sets of images using a controlled registration:

- CT to MR live (from the day of treatment) images.
 - MR preOP (pre-operative) to MR live images.
2. Examine the **Movement Detection Reference** images that were taken automatically during the Imaging stage.
 3. Add **Movement Detection Fiducial markers** to enable the system to identify and alert the user, if a patient movement occurred.
 4. Define the Region of Treatment (**ROT**) for larger treatment portions (optional).
 5. Run the **Automatic Calcification Detection** algorithm close to the target region, based on the CT image values.
 6. Define sensitive areas that will limit or totally eliminate the acoustic energy from passing through it, by drawing **No Pass Region contours** upon the CT or MR images.
 7. Define the required **Treatment Protocol** according to the specific target characteristics.

Treatment Stage

This stage enables the operator to:

1. **Adjust and Lock the spot coordinates** to match the desirable target location.
2. **Verify** that the location of the thermal focal point is in the selected target and that the sonication intensity levels deliver the expected results.
3. Define the **Spot's Parameters and Thermal scan parameters**
4. Perform therapeutic **Treatment Sonications**
5. **Optimize Acoustic Frequency** by performing sonication with sub-level of energy to determine the treatment sonication optimal parameters to be used per techno-clinical characteristics of the specific patient.
6. Refresh the spots' packing plan (**Re-plan**) within the predefined Region of Treatment (ROT).

5.2.3. Information Box

This box displays warning messages and treatment/progress status information to the operator.

5.2.4. Utilities

Utils – Provides access to optional tools during the **Treatment** stage.

Save – Enables to save the treatment plan.

Replay – Views and analyzes the results of previous sonications.

Exit – Aborts the treatment and returns to the **Startup** screen.

5.2.5. Image Strips

Three rows of image strips appear on the screen. Any content that has been loaded into the system can be displayed, using the navigation tools next to each strip (see Figure 5-1).

5.2.6. Selected Image Window

The **Selected Image** window is the "workspace" for planning and conducting treatments. When clicking on an image in the image strips, this image is displayed in the selected image window.

Note

All the user editing and interaction with graphical objects is performed *only* on the selected image window.

5.2.7. Imaging Tools

This section describes the button, name and function of each of the imaging tools.



Zoom

To see a close-up of an image, click this button. To zoom in, drag the mouse up. To zoom out, drag the mouse down. Any change in one image is automatically reflected in all the other images on the same type of strip. Alternatively, click the left mouse button and drag the mouse as above to change the zoom.



Pan

To navigate around a zoomed image, click this button and then move the cursor to the image you wish to navigate to. Drag to pan the image. Alternatively, right click and drag to pan the image. Any change is automatically reflected in all of the other images on the same type of strip.



Measure

Click this button to measure the actual distance between two points, the attributes of a drawn polygon, to measure an angle, or to place a right angle on the image. This function is applicable only to the selected image window.

To measure distance:

1. Click an image from the image strips to view in the selected image window.
2. Click on the first point to measure.
3. Move to the second point and click again.
4. Double click to complete the Measure command.

ExAblate calculates and displays the distance between the two points.

To measure an area, draw a polygon:

1. Click on the first point of the polygon to be measured.
2. Continue to draw the outline of the polygon with single clicks.
3. Close the polygon by clicking again on the first point.

The polygon's average pixel value, the standard deviation of pixel values within the polygon and its area are calculated and displayed.

Note

On a temperature map, the pixel value is the temperature value. The average temperature within a polygon is displayed in the temperature graph (See Section 8.3.6)

To measure an angle:

1. Click on the first point of the angle to be measured.
2. Move to the second and third point and click again
3. Double click to complete the **Measure** command.

ExAblate calculates and displays the angle

To place or measure a right angle:

- Click on the first point of the angle to be measured.

**Windowing**

To change the image windowing (brightness or contrast), click this button. Drag the mouse up to brighten and down to darken the image. Drag the mouse left to increase the contrast and right to decrease the contrast. The change is automatically reflected in all of the other images on the same type of strip.

Alternatively, click the middle mouse button and move the mouse as above to change brightness or contrast.

**Reset**

Click this button to restore all images to default zoom, pan, contrast, and brightness settings. **Reset** applies to the entire image slice in all strips simultaneously.

**Group Selection**

Click this button and then click on any number of the same type of drawn objects (in the **Selected Image** window) to create a group that can be controlled collectively.

**Centering**

Click this button and then select a location in any image. By clicking on it, the images with this point will appear at the center of the strips.

**Screen Snapshot**

Click this button to take a snapshot of the screen and save it with the treatment database. When that treatment is exported, the screen-dumps associated with that treatment are copied to the CD.

**Copy selected figure**

Select a graphic object in the main window. Click this button and then click on the image the object needs to be copied to.

5.2.8. Overlays

This section describes the overlay tools, which toggle the graphic overlays onto the MR images.



Treatment Envelope

Click this button to display a green parallelogram that defines the **Treatable area** (as governed by the extents of the transducer).



Text Overlay

Click this button to show or hide the **text overlays** on the images.



Measure

Click this button to show or hide the **Measurement** graphical overlays on the images.



Transducer Template

Click this button to show or hide the **Transducer's template** upon the MR images.



ROT

Click this button to show or hide the contours of the **Region of Treatment**.



Thermal Scan planes

Click this button to display the locations of the **MR thermal slices** on the selected image window and on the image strips. The lines display the intersection between the planned images and the thermal scan images for selected sonication spots.



Bony Tissue Contour

Click this button to show or hide the **bony tissue contours**.



Sonication Spots

Click this button to select **sonication spots display** (Show/Hide all spots)



Accumulated Dose

Click this button to show or hide the accumulated dose. The accumulated dose appears as a blue overlay on the image. In the **Thermal Evaluation** screen, the dose from the last sonication is displayed in green.

**Energy Pass Zone**

After calculating the transducer elements map of a sonication spot, you can view the rays from the transducer elements to the spot. A ray defines the acoustic path from a single element to the sonication spot.

Select a spot and click this button to select the rays display option from the pop-up menu:

Show All – displays all the rays from the transducer elements to the selected spot. Rays are colored according to their status (see Chapter 9).

Elements On – displays only the rays of the transmitting elements.

Elements Off – displays only the rays of the non-transmitting elements.

Selected Elements – displays only the rays of the selected elements in the transducer elements map.

Hide All – Hide all the rays.

**No Pass Regions (NPR)**

Click this button to show or hide the contours of the **No Pass Regions (NPR)**.

**Fiducials**

Click this button to show or hide the **Fiducial Markers**.

**Temperature Monitoring Volume**

Click this button to show or hide the **Temperature Monitoring Volume**.

**Target**

Click this button to show or hide the **Target marker overlay**.

**AC PC**

Click this button to show or hide the **AC and PC markers overlay**.

5.2.9. Navigation and Viewing Tools

Navigation and viewing tools are used to select the content of the image strips which will be displayed, to scroll within the strips and to activate various display functions.



Image Strip Selection

Click this button to choose the images in one of the three image strip windows to be displayed from the pull-down menu. Options may vary between stages depending on the data available.



Animation

Click this button to display the selected series as a cine



3D View

Click this button to show the treatment data in 3 dimensions, in order to clinically assess the treatment plan. The overlays include the skull, calcifications, region of treatment, sonications and treatment progress.



Image Flickering

Click on the image flickering button to iteratively show 2 different images in the selected image window, as follows:

The reference and current movement detection images.

The orthogonal frequency scans for manual central frequency calculations (optional)

5.2.10. Image Overlays

5.2.10.1. Image Annotations

The image annotations consist of the orientations, patient details, scan parameters, scaling bar and image type. MR magnitude images consist of slice location and temperature maps consist of the acquisition time.

5.2.10.2. Cursor Coordinates

The cursor coordinates show the location of the anatomical feature pointed in three axes on all image windows.

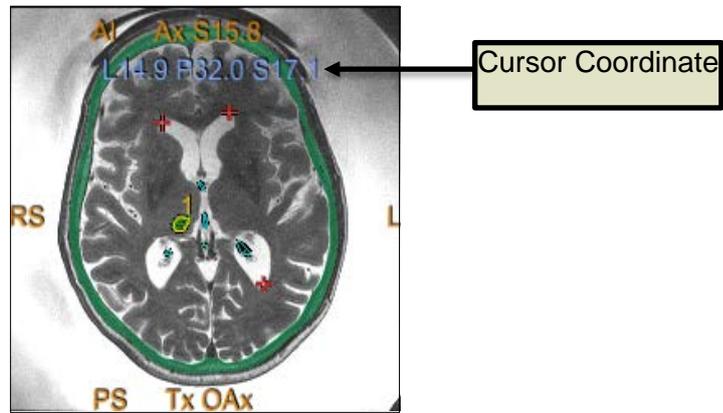


Figure 5-3: Cursor Coordinates

5.2.10.3. Shadow Cursor

While pointing the cursor at any image location, an additional small green cursor will appear on all images in which this point appears in all orientations.

Chapter 6

Imaging Stage

6.1. IMAGING STAGE - OVERVIEW

The **Imaging** stage is the first stage of an ExAblate Neuro treatment procedure. This stage provides the system with the necessary data relates to imaging, prior to treatment planning.

Note

During **Imaging** stage, there are several different treatment flows that can be executed by the operator. This chapter reviews a suggested treatment flow in order to cover all the features that were integrated within this stage.

Operator is not obliged to follow this suggested flow but must complete the following tasks in order to proceed to the next stage:

1. **Automatically track** and determine the transducer's home position and orientation relative to the patient's anatomy.
2. Determine and fix the **Central Frequency** (automatically or manually) that will be used in the MR images throughout the procedure, to minimize imaging and thermal shifts.
3. Plan and acquire **MR planning images** (or alternatively scan planning images on the MR and retrieve the relevant series to the ExAblate workstation).
4. Retrieve relevant range of images from a **CT exam** into the ExAblate workstation.
5. Determine the desirable **Target Center** and adjust the location of the transducer accordingly to match between its natural focus and the target.

The rest of tasks and features within **Imaging** stage can be performed either on the next stage (**Planning**) or can be considered as optional:

1. Define the required **Treatment Protocol** according to the specific target characteristics.
2. Upload into the ExAblate system **Treatment Plan** that was prepared and saved prior to treatment (optional - see Appendix B).
3. Define sensitive areas that will limit or totally eliminate the acoustic energy from passing through it, by drawing **No Pass Region contours** upon the CT or MR images.
4. Define **Temperature Monitoring Volume** that enables the operator to monitor the rise of temperature within a predefined region, during the action of sonication.

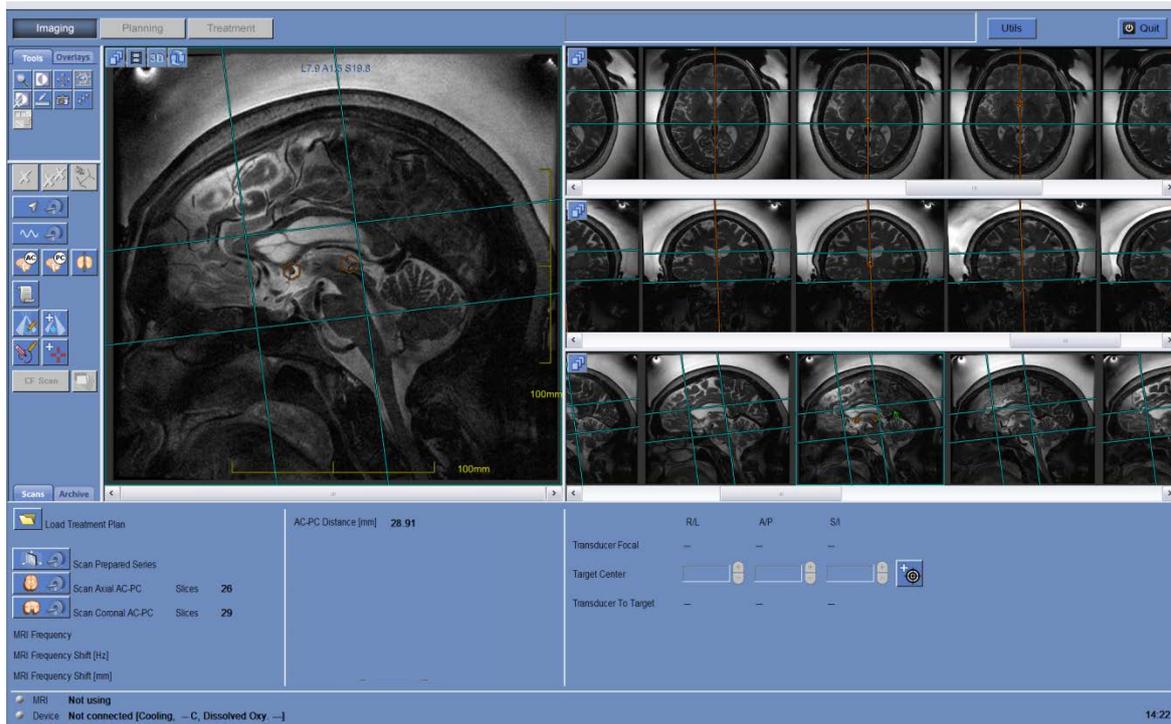


Figure 6-1: Imaging Screens (“Scans” tab)

6.2. IMAGING STAGE GENERAL ACTION ELEMENTS

During **Imaging** stage the following new general Action tools elements are used (see Chapter 5 for an explanation of the **Imaging** tools previously used).



Delete Selected Object

Click this button to remove the selected object.



Delete All Objects

Click this button to remove all objects of the same type as the selected object.

- Interpolate** Use this feature to interpolate graphic elements that were drawn on non-adjacent slices:
1. Click on the graphic element you want to interpolate.
 2. Click the **Interpolate** button; the drawn element is interpolated into a continuous surface or a 3D volume.
-  **Add Fiducial Marker** Use this feature to monitor patient movement during a treatment session. Click this button and then point and click in the **Selected Image** window to create a marker.
-  **Temperature Monitoring Volume** Use this feature to add a region in which the temperature rise will be monitored during the sonication.
1. Click on this button
 2. Draw a closed contour region upon the MR image
 3. Re-click the **Temperature Monitoring Volume** button.

6.3. TRANSDUCER CALIBRATION PROCEDURES

6.3.1. Transducer Location Tracking and Calibration

Under the procedure of the **Transducer Location Tracking and Calibration**, the following elements are used:



Automatic Transducer Tracking

Click this button to perform a scan on the MR that will track automatically the transducer's current location and update its focal coordinates on screen.

Note

Clicking this button fixes the new transducer location, eliminating the ability to return back to previous calibration or display the previous Transducer Focal coordinates.

Note

In case of non-clinical research configurations the transducer calibration can be set to **Manual mode** in **Utilities** stage (see Section 10.2.11) to allow a wider coverage of the imaging and to avoid tracking coils based calibration.

1. On the MR workstation, start a new MR exam and perform a localizer scan to define the patient's entry and position.
2. Click  and confirm the patient's name and position, as they appear in the pop-up message on the operating console screen.
3. The MR performs tracking scans in order to automatically detect the transducer location.
4. Once the tracking procedure ended, the **Transducer Focal** coordinates will be updated to this section under the “Scans” tab (See Figure 6-2)

	R/L	A/P	S/I
Transducer Focal	L18.1	A42.8	I0.8

Figure 6-2: Transducer Focal Coordinates

Note

Clicking the **Automatic Transducer Tracking** button fixes the new transducer location, eliminating the ability to return back to previous calibration or display the previous Transducer Focal coordinates.

Note

In case of non-clinical research configurations the calibration can be set to **Manual** mode in **Utilities** stage (see Chapter 10) to allow a wider coverage of the imaging and to avoid tracker based calibration.

6.3.2. Manual Transducer Calibration (Research Optional)

In case of a need to perform calibration without relying on tracking information, the calibration can be set to **Manual** mode in **Utilities** stage (see Chapter 10)



Calibrate

Click this button to set the transducer's home position and orientation.



Transducer Template

Click this button and click again on the image to position the transducer template.

In order to perform **Manual Transducer Calibration**:

1. Click  and confirm the patient's name and position, as they appear in the pop-up message on the operating console screen.
2. The MR then performs three scans (sagittal, coronal and axial) visualizing transducer's home position. These images appear in the image strips. The Transducer Template is displayed as a yellow overlay.
3. Click  and the system will perform trackers scan to locate transducer location based on the tracking information without performing imaging.
4. Move the template until it will be in the right location or click  and click on the image to position transducer template in the desired location.
5. Click .

Caution



Perform calibration correctly, with special attention to **Roll** and **Pitch** corrections. Inaccuracies in the transducer tilt will result a misallocation of the spot.

6.4. SCAN AND DETECT MRI FREQUENCY

Detecting the correct value of the MRI Central Frequency prior to the treatment can reduce thermal imaging shifts during sonications.

6.4.1. Automatic Detection of MRI Central Frequency

This feature enables to scan and detect the MRI Central Frequency. This procedure will occur automatically by the system.

During the procedure of **detecting the MRI Central Frequency** values, this element is used:



Scan and Detect MRI Frequency

Click this button to perform a scan on the MR to automatically detect the corrected MR Central Frequency values, in order to minimize imaging frequency shifts.

To use this feature:

1. Click  to scan and detect the value of the Central Frequency adequate for the scans throughout the treatment. The results will appear on screen (See Figure 6-2)

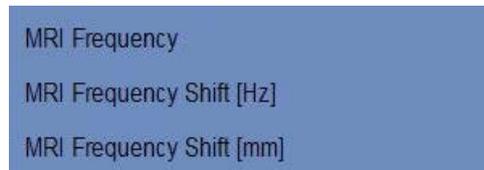


Figure 6-3: Detected MRI Frequency Frame

6.4.2. Manual Detection of MRI Central Frequency (Optional feature, may not be available in all system configurations)

This feature enables to scan and detect the MRI Central Frequency and adjust its value if necessary.

During the procedure of **detecting the MRI Central Frequency** values, the following elements are used:



Scan and Detect MRI Frequency (Adjustable option)

Click this button to scan and load MR Central Frequency images. Those images will be used to determine the corrected frequency value for the treatment.

Note: This feature is disabled under the nominal system configuration and functions as a backup (adjustable manual option) for the **Scan and Detect MRI Frequency** feature, using a different scan type.



Edit Central Frequency shift

Click this button to visually verify that the results of the automatic central frequency calculation are correct.

Use the keyboard or the on screen arrows to move the base image over the tracked image, to fine tune the results.

Note: This feature is disabled under the nominal system configuration and functions as a manual backup for the **Automatic Central Frequency Detection**.

1. To use this feature: Click  to perform 2 axial scans for determining the Central Frequency adequate for the scans throughout the treatment.
2. The 2 scans are done with orthogonal frequency directions.
3. Click  to view and edit the Central Frequency calculation outcome. A central region of one image will be displayed above the other image. Verify anatomical matching between the images by using  to iteratively replace between the 2 images.
4. If fine-tuning of the anatomical accuracy is required, use the on-screen or the keyboard arrows to move the central region of the upper image above the other image.
5. MRI Frequency value, shift between the two images in [Hz] and shift between the two images in [mm] will appear on screen (See Figure 6-3)

6.5. TREATMENT PROTOCOL

Choosing a Treatment Protocol is necessary to enable the system to adjust parameters according to the treatment specific target characteristics or while performing Daily Quality Assurance (**DQA**).

To choose or update the **Treatment Protocol**, use the following element:



Treatment Protocol

Click this button to access the treatment protocol dialog box.

1. Click  to open the **Treatment Protocol** Dialog box:

Figure 6-4: Treatment Protocol Dialog Box

2. From the **Treatment Protocol** pull-down list, select the Treatment or DQA protocol, per the specific procedure you would like to perform; the default parameters for the selected protocol appear in the sonication parameters frame.
3. From the **Treatment Type** drop-down list, choose the type of target you would like to treat. This will enable the system to initialize specific parameters which characterizes this type of target.
4. In order to change the status (On/Off) of the **Automatic Movement Detection** feature, choose the specific option from the drop-down list (See Section 7.3)
5. To change the default range for scanning the planning images using the **AC-PC** feature, enter the specific distance from AC-PC in [mm]. (See Section 6.6)
6. Use the typing **Remarks** area in order to keep your notes per Treatment Protocol.
7. Click the  button to change the sonication spot parameters (Advanced Mode):
 - **Max Energy** (in Joules): this is the energy for planning the treatment.
 - **Cooling Duration** (in seconds): this is the default required cooling period for a sonication energy pulse of the default value displayed. Actual cooling for each spot will be scaled automatically according to the actual energy applied.
 - **Sonication Duration** (in seconds): this is the length of time the ultrasound energy is applied to the target tissue in each **Nominal** sonication.
 - **Sonication Grid Density**: this determines the degree of planned spot overlap of adjacent sonications. There are three possible settings: low, medium and high. The spot overlap is an important consideration, particularly in determining the overall length of a treatment session and completeness of ablation.
 - **Spot Size**: this determines the dimensions of the spot along the propagation direction:
 - **Nominal** - the energy is delivered continuously
 - **Apodization**: this determines the effective transmitting area of the transducer.
 - **Body Temperature**: the default is normal body temperature. Change this value to the temperature of the organ treated.
 - **Spot Geometry Parameters**: enables to control manually the size of the predicted spot (Height and Diameter)

Click the  button to close this advanced mode of the Treatment Protocol.

Note

The selected sonication parameters are used for all treatment spots in the selected **ROT**.

8. Close the **Treatment Protocol** Dialog box:
 - If no changes were made to the protocol, click **Apply**.
 - If changes were made to the protocol, click **Save As** to access the **Save Protocol** dialog box.
 - Type in the name of the new **Treatment Protocol**.
 - Click **Save** to save the new values.
 - Click **Delete** to delete current user-defined protocol.
 - Click **Cancel** to discard the new information and return to the **Main** screen.

Note

The system's preset treatment protocols cannot be deleted from the list of protocols, and if edited they must be saved under a different name.

6.6. ACQUISITION OF ANATOMICALLY ALIGNED MR PLANNING IMAGES (BASED ON AC-PC)

This feature enables to plan and acquire the MR planning images from the ExAblate workstation, while enabling the operator to:

1. Ensure that one of the Axial planning images will intersect with the Anterior and Posterior Commissures line.
2. Ensure that all the Axial images will be taken aligned with the AC-PC plane.
3. The series of Axial images will be acquired perpendicular to the Midline (in coronal view), so the Axial and Coronal planning images will be acquired perpendicular to each other.
4. The treatment region of interest around the target will be covered by planning images of all three orientations.

6.6.1. User Interface Elements

During the procedure of acquiring the MR Planning images based on the **AC-PC** and **Midline** markers, the following elements are used:



Anterior Commissure Marker

Click this button to mark the Anterior Commissure upon the MR Sagittal images in order to enable the system to align the Central Axial planning image with the AC-PC plane.

To use this marking tool:

1. Click on the AC marker button
2. Navigate through the Sagittal images to find the exact location of the Anterior Commissure.
3. Place the marker upon the MR image where the center of the Anterior Commissure is clearly seen.



Posterior Commissure Marker

Click this button to mark the Posterior Commissure upon the MR Sagittal images in order to enable the system to align the Central Axial planning image with the AC-PC plane.

To use this marking tool:

1. Click on the PC marker button
2. Navigate through the Sagittal images to find the exact location of the Posterior Commissure.
3. Place the marker upon the MR image where the center of the Posterior Commissure is clearly seen.



Midline Orientation

Click this button to mark the Brain Midline and define the range of Axial and Coronal images to be scanned through the ExAblate work station.



Scan Prepared Series

Click this button to run the Sagittal scan, after preparing it on the MR.

1. Click the *Auto Pre-scan* button on the MR workstation. Wait until the MR will complete the pre-scan.
2. Click the *Scan Prepared Series* button on the ExAblate workstation. The planned sagittal scan will start to run on the MR.
3. Once scan ended, the new scanned MR series will appear on one of the ExAblate workstation image strips.

Note

This button enables running a scan in a more generic use for all different scan orientations. (See Section 6.6.2)

**Scan Axial**

Click this button to run the Axial scan from the ExAblate workstation, based on the AC-PC, Midline and scanning range inputs.

**Scan Coronal**

Click this button to run the Coronal scan from the ExAblate workstation, based on the AC-PC, Midline and scanning range inputs.

6.6.2. Acquire the Sagittal planning images

1. Acquire a **3D Localizer** scan on the MR workstation.
2. Prepare MR imaging Sagittal scan on the MR.
3. Select sequences that clearly show the region of treatment and include the entire skull anatomy.
4. Make sure the range of Sagittal images covers the desirable treatment region and that at least one image intersect with both the AC and PC anatomical structures. Adjust the scan parameters, such as slice thickness and FOV to optimize the imaging quality.

Warning



Inaccuracy in acquiring the series of Sagittal Planning images will disrupt the perpendicularity between the three different orientations and may lead to inaccuracies in locating the desirable target (if was not done purely based on anatomy). Verify that both the AC and PC can be clearly visible on the same sagittal image or reacquire the Sagittal Scan.

5. Run an **Auto Pre-scan** for this series from the MR workstation and wait until the MR will be ready to scan.
6. Click  in order to perform the scans with the optimal Central Frequency value that has been previously found (see Section 6.4).
7. Once the MR completed scanning this series, the set of images will be retrieved automatically and displayed on one of the **Image Strips** of the ExAblate workstation.
8. Review the images to confirm that:
 - The target to be treated is clearly identifiable
 - The patient is correctly positioned so that the target is in a treatable position
 - Closely examine each image and verify that there are no air gaps visible along the entire acoustic path from the transducer to the target

- Carefully check each image to verify that the patient has not moved during imaging
- Verify that both Anterior and Posterior Commissures clearly appear on the Sagittal images

6.6.3. Place the AC-PC and Midline markers

1. On the Sagittal series, look for the image where you can see clearly the anatomical structures of the AC and PC.

2. Use the  tool to mark the Anterior Commissure.

3. Use the  tool to mark the Posterior Commissure.

4. Click on . A new Coronal partial image will appear on the main image window (See Figure 6-5). The system uses the Sagittal Planning images to reconstruct a temporary Coronal series on the ExAblate workstation.

- Place the mouse cursor (**Midline marker**) upon one of the Coronal reconstructed MR images, where you can see clearly the brain's midline. The Midline plane will automatically intersect with both the AC and PC markers.
- In order to rotate the midline Plane, click on the **Midline graphic object** and rotate the element by using the **green control stick**, attached to it.
- Navigate through the Coronal reconstructed images to ensure that the **Midline graphic object** is aligned with the anatomical brain midline structure upon the MR images.

Note

To return back to the display of the reconstructed Coronal series, either click on the **Midline Marker** button or choose the series from the **Image Strip Selection** drop down menu.

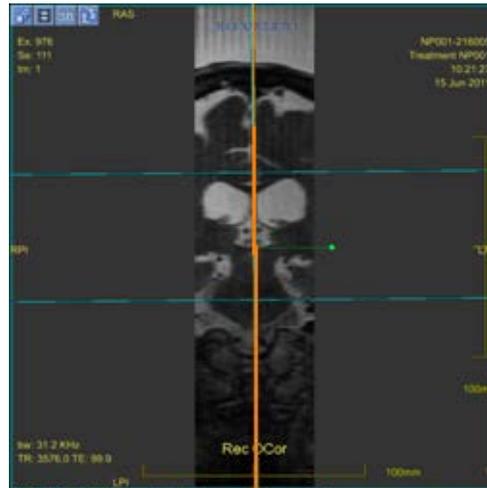


Figure 6-5: Reconstructed Coronal Image

The reconstructed image includes: (a) Midline graphic object – Orange vertical line (b) Axial scanning range - two azure horizontal lines (c) Rotation control stick – green dashed line with a spherical knob

Note

You can see the distance between the AC and PC markers (as were placed upon the Sagittal images) on the **Scans** tab beneath the main image window.

6.6.4. Define the Axial and Coronal Scanning Range

In order to define the **Scanning Range** for the **Axial** series of images which is about to be executed by the ExAblate workstation, the operator should perform the following actions:

1. Click on the more **superior** line from of the two graphical line objects upon one of the **Reconstructed Coronal** images. (see Figure 6-5)
2. Drag the graphical line object to the **Scanning Range Superior limit**.
3. Repeat actions 1 & 2 for the **Inferior line** as well.

Note

You can see on screen the number of slices that are ready to be scanned, next to its related scan button (Axial and Coronal). It is recommended to select the minimal number of slices requires to fulfill the clinical needs, in order to minimize the expected scanning duration.

4. Click on one of the Sagittal images in the **images strip** (or select the Sagittal series using the  drop down menu).

5. Repeat the previous actions for defining the **Scanning Range** of the **Coronal** series using the **Anterior** and **Posterior graphical line objects**.
6. Once the **Scanning Range** has been defined, click on the  button to run the Axial scan on the MR.
7. When Axial images has been retrieved, click on the  button to run the Coronal scan on the MR.
8. Once the Axial and Coronal images have been retrieved and uploaded to the ExAblate workstation, review the images to confirm that:
 - The target to be treated is clearly identifiable
 - The patient is correctly positioned so that the target is in a treatable position
 - Closely examine each image and verify that there are no air gaps visible along the entire acoustic path from the transducer to the target
 - Carefully check each image to verify that the patient has not moved during imaging
 - Verify that the actual Scanning Range meets the expected one.

Note

The range of Axial and Coronal Images must cover both the AC and PC markers otherwise the system will not enable you to perform the scans using this feature. As an indication that either the AC or the PC marker is not within the range of images to be scanned, the **Slices No.** will appear with a minus sign (“-”).

Same behavior of system limitation will occur when the Superior line was dragged below the Inferior line or when the anterior one was dragged more posteriorly than the Posterior line.

Note

Alternatively, use the **From-To** filed within the **Treatment Protocol** to define the **Scanning range** (See Section 6.5)

Note

While the Coronal MR scan has been acquired, an additional scan will start running sequentially on the MR.

This scan is the **Movement Detection Reference Scan**. (See Section 7.3)

6.7. MANUAL ACQUISITION OF MR PLANNING IMAGES (BASED ON MR USER INTERFACE)

As an alternative to option for acquiring the Planning images from the ExAblate workstation based on the AC-PC and Midline markers (as described in Section 6.6), you may either:

- Prepare and acquire the planning images completely using the MR workstation user interface.
- Prepare and acquire the planning images using the MR workstation, but initialize the scans from the ExAblate workstation that will ensure the use of the same adequate MRI Central Frequency values for the scans throughout the treatment.

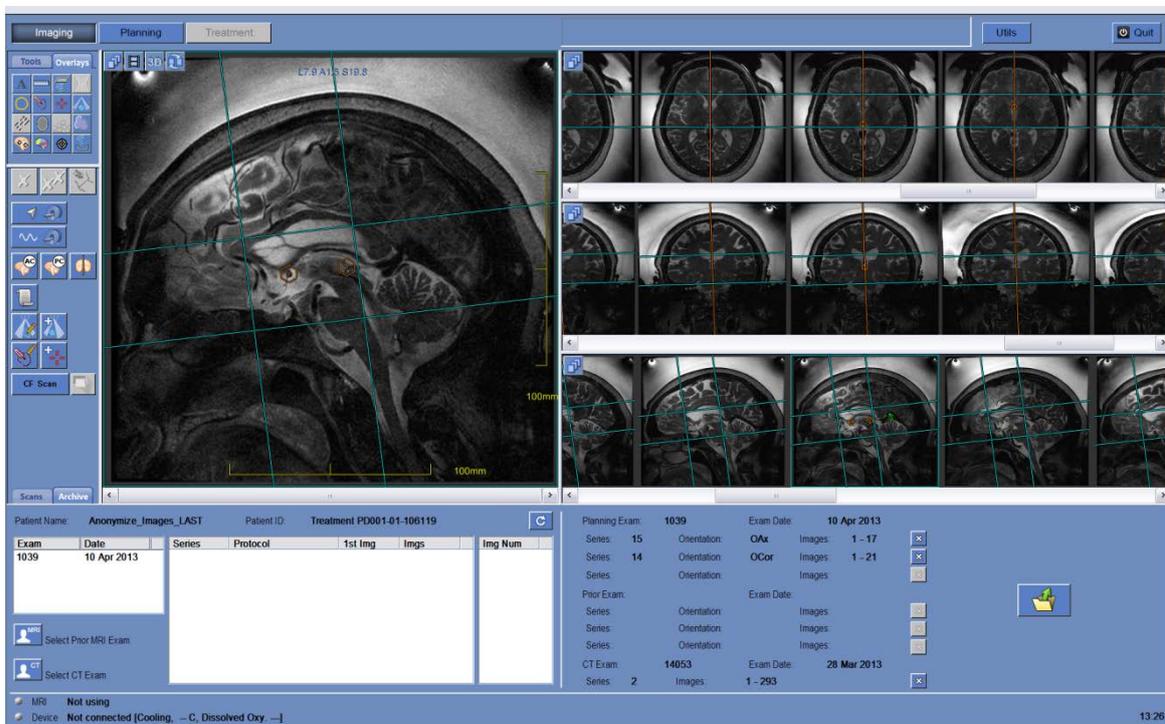


Figure 6-6: Imaging Screens (“Archive” tab)

6.7.1. Option A: Acquire Images from MR workstation

1. Prepare and scan all three planning orientations on the MR. Follow the imaging guidelines which were described on the document: “**ExAblate Neuro Imaging Guidelines**”
2. After acquiring each one of the scans, confirm that:

- The target to be treated is clearly identifiable
 - The patient is correctly positioned so that the target is in a treatable position
 - Closely examine each image and verify that there are no air gaps visible along the entire acoustic path from the transducer to target
 - Carefully check each image to verify that the patient has not moved during imaging
3. Enter the  tab (Figure 6-6)
 4. After acquiring each one of the scans (or alternatively after all were scanned), click on the  button. The new series that has just been scanned on the MR will appear on the *List of Images of the Selected Exam*.
 5. Click on each one of the selected series you would like to upload as a Planning Images. As a default, all images within the selected series will be used by the system.
 6. If only part of the series is needed, Click the desired image numbers as follows:
 - Select an image and then press **Shift** and select another image, to select any number of contiguous images.
 - Select an image and press **Ctrl** to select additional non-contiguous images.
 7. The selected series will appear on the *Selected Images Section*.
 8. To change the selection, click  and select a different set of images. These images replace the previously selected ones.
 9. Click on the  button to upload and display the selected images.

6.7.2. Option B: Initial acquirement of images from ExAblate workstation

During this procedure, the following ExAblate workstation element is used:



**Scan
Prepared
Series**

1. Click this button to run a prepared scan on the MR.
2. Then, click the  button on the ExAblate workstation, to run the prepared scan.

3. Prepare a planning series on the MR. Follow the imaging guidelines which were described on the document: “*ExAblate Neuro Imaging Guidelines*”.

4. When scan is ready to be scanned click the *Auto Pre-scan* button on the MR workstation.
5. Once pre-scanning ended, click the  button on the ExAblate workstation, to run the prepared scan.
MRI Central Frequency adequate values will be used automatically.
6. After acquiring each one of the scans, confirm that:
 - The target to be treated is clearly identifiable
 - The patient is correctly positioned so that the target is in a treatable position
 - Closely examine each image and verify that there are no air gaps visible along the entire acoustic path from the transducer to the target
 - Carefully check each image to verify that the patient has not moved during imaging
7. Once each one of the scans completed it will be retrieved automatically to the ExAblate workstation and will be displayed on one of the *Image Strips*.

Warning



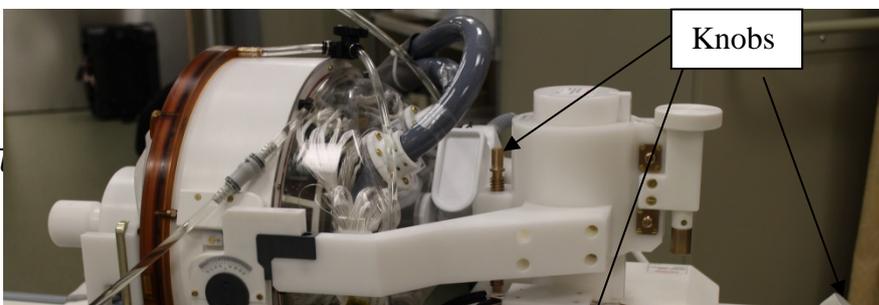
Closely examine each image along the entire acoustic path from the transducer to the target. Verify that there are no air gaps visible. If air gaps are visible, add water, as needed, or perform circulation.

6.8. DETERMINE THE TARGET CENTER

The **Target Center** is the center of the anatomical exact location of the desirable region to be treated. Therefore, it should be determined to be as aligned as possible with the Transducer's Natural Focus (*Transducer Focal*), to ensure an optimal and adequate delivery of energy to the target.

6.8.1. Mechanical Positioning of the transducer

The transducer's location is set by a mechanical positioning unit. This unit is manually adjusted by the operator in order to move the transducer, so that its Natural Focus (**Transducer Focal**) will be in the anatomical target. The transducer's adjustment can be done in 3 directions and an angle by using 3 specific knobs and 4 sets of locks (see Figure 6-8).



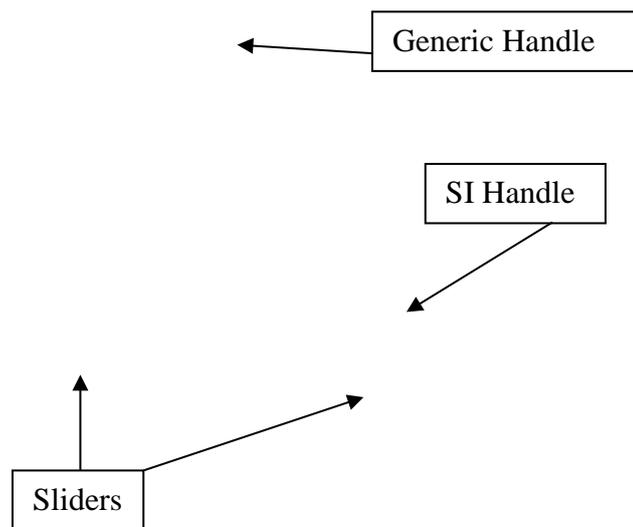


Figure 6-7: Mechanical Positioning unit

6.8.2. Determine the Target Center

The workstation presents the **Sliders Section** within **Scans** tab where you can notice: (a) the **Transducers Focal** values (b) the **Target Center** values and (c) the **Transducer to Focal** distance of which the transducer should be moved in order to be aligned with the **Target Center** location (see Figure 6-9).

	R/L	A/P	S/I
Transducer Focal	L18.1	A42.8	I0.8
Target Center	L21.5	A47.6	S8.6
Transducer To Target	L61.2	P71.1	S17.8

Figure 6-8: Sliders section

To treat a specific anatomical location (as seen on the MR images), do the following:

1. Click and then place the marker (by click) on the anatomical location seen on the MR planning images.
2. The system will presents on screen what the direction and required distance [in mm] the transducer needs to be moved to, in order to have the **Transducer Focal** aligned with the desirable **Target Center** location.
3. Use this data to move the mechanical positioning unit to the proposed position.

Note

Alternatively, instead of placing the  marker, it is possible to enter the **Target Center** coordinates (manually or using the  buttons) in order to calculate the **Transducer to Focal** required movement.

6.8.3. Adjustment of the Transducer Focal location

In order to align the Transducer Focal with the desirable Target Center, you should move the transducer using the positioning slider mechanism.

Note

Make sure you write down each one of the initial sliders' values before moving the transducer.

In order to move the transducer on a specific axis do the following:

1. Screw the knob counter clockwise to open the slider on the relevant axis.
2. Use the generic handle (placed free on a stand upon the positioner) to screw the relevant knob and move the transducer on the desirable direction.

Note

Moving the transducer on the SI axis should be done by using a dedicated handle (See Figure 6-8).

Note

You may use the Axes directions labels upon the sliders in order to make sure you move the transducer to the correct location.

3. Once the transducer reached the desirable location on each one of the axis, lock the knob clockwise to eliminate transducer movements along the sliders during the treatment.

Warning



Automatic Tracking procedure must be repeated after any change of the mechanical positioning unit location by clicking the  button.

6.9. LOAD A PREPARED TREATMENT PLAN (OPTIONAL)

For instruction on how to prepare a Treatment Plan prior to treatment, see Appendix B.

This section describes the way of uploading a prepared Treatment Plan that was saved to the system archive. In order to do so, follow these steps:

1. Under  **Scans** tab, click the  button; the system will prompt you to select a prepared Treatment Plan that was saved to the system archive.
2. Choose the **Treatment Plan** you wish to upload from the dialog box that was opened. Make sure the date, time and name of the selected **Treatment Plan** is the correct one.

Note

If a **Treatment Plan** was loaded, its planning images and CT images appear in the **Prior Exam** section and the **CT Exam** section, under **Archive Tab**.

6.10. LOAD CT SCAN AND PRIOR EXAMS

Both functions appear under **Archive Tab**.

6.10.1. Loading CT Images

Use CT images to register the location of the bony tissues with the MR coordinate system.

1. Click the  button; the system will prompt to select a stored CT exam from the ExAblate Neuro workstation or from the MR:
 - To select CT images from the console, click **Browse CD** and select the desired CT images directory in browser.
 - To select CT images from MR, first select the desired exam from the MR workstation (by clicking on it). Then click **MR Archive** in the dialog box that appears on the ExAblate workstation.
2. The CT exam information appears in the **CT Exam** frame. Verify that the correct images are used.

Warning



Make sure you choose the range of CT images to cover one slice above the head apex and down, to enable the system to use adequate parameters of aberration correction of the acoustic beam (automatically) throughout

the treatment, based on the specific skull characteristics.

Note

Due to system technical storage limitations you should use not more than 200 CT images. System will alert if more than 200 CT images were chosen and will suggest sampling selectively (every odd image) the range of CT images to fulfill the storage limitations. This should pose no safety or usability risks, as user is requested to confirm entire acoustic interface is represented in the selected CT series.

6.10.2. Using Prior Exams (optional)

If necessary, use images that were acquired in a past pre-treatment session, to aid in defining the region of treatment (see appropriate application guide).

1. Click  button; the system will prompt you to select a previously stored exam from the MR workstation browser.
2. Review the series of exams stored in the MR workstation and select the desired one by clicking on it. Click **OK** in the dialog box that appears on the ExAblate workstation. The selected exam will be added to the **Exam List**
3. The series numbers and types appear in the **Series List**.
4. Repeat Section 6.7.1 steps 5-8; the selected image numbers appear in the **Prior Exams** frame. Verify that the correct images are used.

6.11. DRAW NO PASS REGIONS (NPRs) CONTOURS

When there is a need to prevent the beam path from passing through sensitive regions, **NPR** (No Pass Regions) contours should be drawn on all relevant images.

After drawing these contours, the system will automatically update the beam path to each sonication spot and will prevent the beam from passing through the NPR contours.

Warning



Make sure you are using both the MR and CT images to identify carefully sensitive regions and mark them with NPRs.

During the procedure of **Drawing the NPRs** the following new elements are used:



**Draw Polygon
No Pass
Regions
(NPR)**

Define **NPR (No Pass Regions)** as follows:

1. Click on the image to display it in the **Selected Image** window.
2. Click the **Draw No Pass Regions** button; draw **NPR** contours around the sensitive tissues.
3. If required, continue to define the **NPR** on additional slices (interpolate if necessary).
4. Move the **NPR** by clicking it and dragging. Delete the **NPR** by clicking it and then clicking the **Delete** button.



**Draw
spherical No
Pass Regions
(NPR)**

Click this button to define spherical **NPR (No Pass Regions)** with specific radius from the drop down menu.

Warning



Drawing **NPR** contours may be used to prevent injury to the patient during treatment. The treating physician should identify and draw the regions that the beam should not pass through.

Warning



In case **NPR** contours are changed during treatment, a geometric verification procedure must be repeated before treatment is resumed.

Examine the sensitive anatomical structures on the images, and draw their **NPR** contours as follows:

1. Select an imaging strip where the regions that the beam should not pass through are best identified.
2. Click , and draw **NPR** contours around the sensitive tissues, where appear in the images. Click  for drawing spherical **NPR**s around round sensitive areas.
3. Use  to interpolate the **NPR** contours to define the volume of the **NPR**.

Warning

If **Interpolate** was used on **NPR**, manually check the interpolation results in all slices. If the interpolation action failed to achieve the desired results, delete the interpolated contours, and manually draw additional **NPR** contours in the necessary locations.

Note

Drawing NPR contours can be performed during **Planning Stage** as well, after using the **Automatic Calcification Detection** feature (See Section 7.4)

6.12. ADVANCING TO PLANNING STAGE

Click the  button on the main toolbar to advance to the next stage in the treatment procedure.

Note

If Planning images were not acquired through the AC-PC feature, the system will have to acquire the Reference Movement Detection scan, while entering the **Planning Stage**. In this scenario, the system displays a message "System is about to start movement detection reference scan". Click Yes to take reference MR images for **Movement Detection** feature. Do not interact with the MRI during the reference scan acquisition.

Chapter 7

Planning Stage

7.1. PLANNING STAGE - OVERVIEW

The **Planning** stage is the second stage of the ExAblate Neuro treatment procedure. This stage provides the system with the necessary data, based on the MR and CT images that were uploaded on the first stage.

Note

During **Planning** stage, there are several different treatment flows that can be executed by the operator. This chapter reviews a suggested treatment flow in order to cover all the features that were integrated within this stage. Features that appear both under **Planning** and **Imaging** stage were covered in Chapter 6.

These are the tasks that must be completed prior to proceeding to the next stage:

1. Correlate between two frames of coordinates by applying a manually controlled or automatic **Registration** between the corresponding set of images:
 - CT to MR live (from the day of treatment) images.
 - MR preOP (pre-operation) to MR live images.
2. Scan the **Movement Detection Reference** sequence. This scan will be taken automatically while entering **Planning** stage, upon operator's approval.
3. Add **Movement Detection Fiducial markers** to enable the system to identify and alert if patient movement occurred.
4. Define the Region of Treatment (**ROT**) for larger treatment volumes (optional).
5. Run the **Automatic Calcification Detection** algorithm close to the target region, based on the CT image values.
6. Define **Temperature Monitoring Volume** that enables the operator to monitor the rise of temperature within a predefined region, during the action of sonication. (See Section 6.2)
7. Define the required **Treatment Protocol** according to the specific target characteristics. (See Section 6.5)
8. Define sensitive regions when there is a need to prevent the beam path from passing through them, by drawing **NPRs** (No Pass Regions) **contours** upon the CT and MR images. (See Section 6.12)

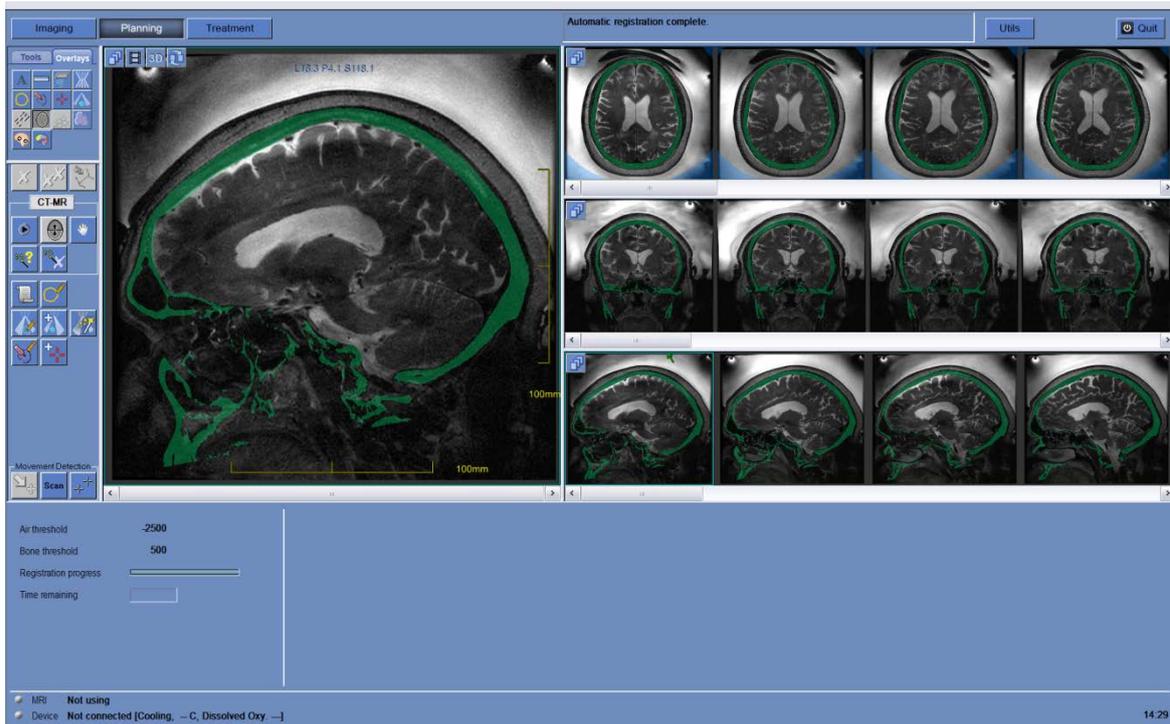
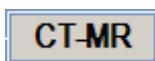


Figure 7-1: Planning Stage Screen Elements

7.2. REGISTRATION PROCEDURE

During the procedure of performing a registration between the different set of images, the following elements are used (see Section 5.2.4 for an explanation of the **Imaging** tools previously used):

7.2.1. Action Tools



Registration Type

The tag displays the image registration type. Click this button; from the drop down menu select one of the followings:

- **CT-MR** - to register the MR coordinates system of the planning MR images with that of the loaded CT images.
- **MR-MR** - if a **Treatment Plan** was loaded, MR coordinates system should be register with the pre-treatment loaded MR images.



Registration Options

Click this button to access the registration options dialog box

**Perform Automatic Registration**

Click this button to perform automatic images registration. Click again to stop the registration process.

**Manual editing of Registration Mask**

Use this button to edit the location of the CT segmentation mask on the MR image:

1. Select a MR image and click **Manual Registration**; the segmentation mask and a registration box will appear on the image.
2. Drag and/or rotate the registration box in order to move and/or rotate the segmentation mask.
3. Overlap between the segmentation mask and the anatomical bony structures on the MR images.

**Adjust Segmentation**

Click this button to adjust the CT image segmentation, based on bone and air thresholds:

1. Select the CT image to display it in the selected image window.
2. Click this button to change the thresholds of bone and air:
 - Drag the mouse up to increase and down to decrease the bone threshold.
 - Drag the mouse left to increase and right to decrease the air threshold.
3. The change is automatically reflected in all the CT images (bone is colored in green and air in blue).

**Cancel Registration**

Click this button to cancel the performed registration.

7.2.2. Registration Status Frame

For the registration process, this displays:

- The **Air and Bone Thresholds** for the CT image segmentation
- The time left to complete the registration progress, by **Registration Progress bar** and **Time Remaining**

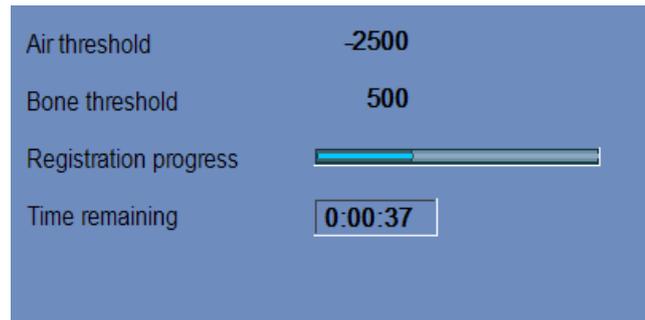


Figure 7-2: Registration status Frame

7.2.3. Perform CT-MR Registration

To enable the system to profile bony tissue, register the MR coordinates system with that of a loaded CT image.

Before the registration process, verify that the CT images segmentation is valid.

7.2.3.1. Perform Automatic Registration

1. Click  to initiate an automatic registration process; the registration is performed automatically and an indication of the progress is displayed in the **Registration Status Frame** (see Section 7.2.2).
2. If required, use  to match the registration mask with the bony tissue on the MR images.
3. Repeat step 4 on all 3 orientations until CT segmentation mask fully corresponds to the anatomy on the MR images
4. If needed, click  to define the registration parameters; modify the parameters in the **Registration Options** Dialog box (see Section 7.2.3.2).

Note

In case the registration results are satisfactory even before the registration process is completed, it is possible to stop the process using the  button.

7.2.3.2. Edit Registration Options

If needed, edit the registration options as follows:

1. Click  to open the **Registration Options Dialog** box (see Figure 7-3).

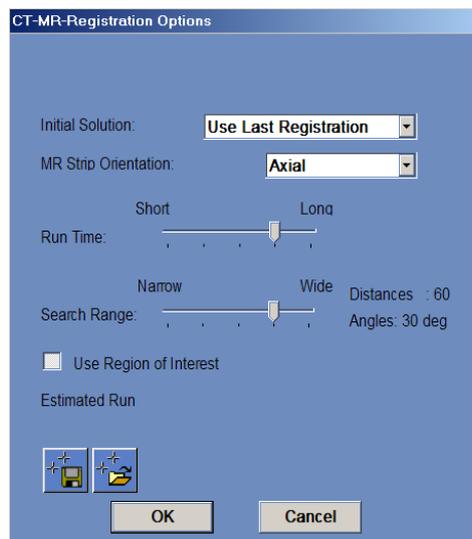


Figure 7-3: Registration Options Dialog

2. Set the following parameters:
 - **Initial Solution** – defines the initialization of the registration
 - **MR Strip Orientation** – defines the orientation of the created volume during the registration process. Select the required orientation from the pull down list.
 - **Run Time** – defines the registration process time. For setting the run time, change the timing bar.
 - **Search Range** – defines the search space for the registration. For setting the search range, change the range bar.
 - **Use Region of Interest** – defines if the ROI is used in the registration process. Click the button to enable or disable this mode.

3. Click ; save the last image registration that was performed through the displayed browser file.

4. Click ; select the required registration file from the displayed browser file.

5. Close the **Registration Options** Dialog box:
 - If no changes were made to the registration, click **Cancel**.
 - If changes were made to the registration, click **OK**.

Warning

Inaccuracy in the registration may generate suboptimal computation of focusing correction and skull heating temperatures. Verify that the registration results accurately match between CT images and MR images.

7.2.4. Perform MR-MR Registration

If a **Treatment Plan** was loaded, the CT-MR registration will be done between the CT images and the pre-treatment MR images. Then, registration between Live MR coordinates system with the pre-treatment loaded MR images needs to be done.

7.2.4.1. Perform Automatic Registration

1. Click **Registration Type** to change to MR-MR
2. Select one of the Live-MR series to be presented in image strip. On a second image strip select one of the Pre-Op series.
3. Click  to initiate an automatic registration process; the registration is performed automatically and an indication of the progress is displayed in the **Registration Status Frame** (see Section 7.2.2)
4. If required, use  to match the registration mask with the bony tissue on the MR images.
5. If needed, edit the registration options as mentioned in Section 7.2.3.2

7.3. AUTOMATIC MOVEMENT DETECTION

Automatic Movement Detection feature can assist the operator in detecting a patient movement during the treatment. Acquiring the Movement Detection

Warning

Make sure you monitor patient movements during sonications using the real time anatomy images to confirm no movement, use **Automatic Movement Detection** feature as an additional advisory element

The following elements can be used while using the **Movement Detection** feature:

**Add Fiducial Marker**

Use this feature to monitor patient movement during a treatment session. Click this button and then point and click in the **Selected Image** window to create a marker.

**Scan and detect patient movement**

Click this button to start a new movement detection scan and determine if movement occurred

**Detect patient movement**

In case an erroneous fiducial location was detected, manually edit this fiducial and then use this feature to re-calculate movement.

Add one or more fiducial markers on anatomical distinct edges as reference markers. In total, at least 3 fiducials need to be placed on at least 2 orientations. Monitor the fiducial markers during the course of the treatment to facilitate the detection of patient movement.

1. Click on the image strip selection button to select Movement Detection Reference images from the drop-down menu. On the movement detection reference images, choose the relevant anatomic image.
2. Click .
3. Point and click in the Selected Image window to create a marker on the anatomical edges of the relevant organs.
4. Click again at another location to add as many fiducial markers as required.
5. Repeat on other movement detection reference images orientation. If required, move or delete the fiducials from the reference images.

Warning



Monitoring patient movement is important in order to assure accurate sonication targeting.

Monitor the fiducial markers during the course of the treatment to facilitate the detection of patient movement.

7.3.1.1. *Initiate manual movement detection (Optional)*

At any stage during the treatment, movement detection can be done to verify patient's positioning

1. Click  to start a new movement detection scan.
2. System will calculate the movement and inform in case a large movement was detected.
3. In case an erroneous fiducial location was detected, delete the erroneous fiducial from the reference images, and click  to re-calculate movement.

7.3.1.2. *Tracking Movements Manually*

At any stage during the treatment, patient's positioning tracking (detect movements) can be done based on the **Anatomy Real Time images** (during the delivery of sonications).

To assist in manually tracking the patient's positioning, you may use the fiducial markers to mark anatomical edges that will appear on the real time images (should be intersected with the thermal map plane).

To add these fiducial markers:

1. Select a relevant Planning Image to the Main Image window.
2. Click  to add new fiducials.
3. Point and click in the Selected Main Image window to create a marker on the anatomical edges of the relevant organs.
4. Click again at another location to add as many fiducial markers as required.
5. Repeat on other Planning images orientation. If required, move or delete the fiducials.

7.4. **AUTOMATIC CALCIFICATION DETECTION**

To enable the system to compute and detect automatically bony structures which are located around the target, the operator can run the **Automatic Calcification Detection** feature.

This feature will identify bony structures in a specific radius around the Transducer's Natural Focus (Transducer Focal) on demand, based on the CT images characteristics.

The system will automatically mark the detected regions by NPRs.

To run the algorithm:



1. Click the button.
2. Review the results to verify correct marking of the sensitive areas.
3. If needed complete the NPR contour for full coverage.

Warning



This *Automatic Calcification Detection* algorithm can only assist the operator in marking the bony structures around the Transducer Focal. Therefore, after running this feature, pay strict attention and review all the CT images to ensure that:

- a) All sensitive regions were identified and marked correctly.
- b) No regions were marked unnecessarily.

After each running of this feature, you must review the computation result otherwise you may risk the patient and cause a severe damage to the structures throughout the acoustic beam's path.

7.5. DEFINE THE REGION OF TREATMENT (ROT)

Drawing the Region of Treatment (**ROT**) can be used to define a large treatment volume (multiple adjacent target spots).

7.5.1. Action Tools



Draw ROT

Click this button to draw the outline of the volume to be treated (**ROT**) on the slice in the selected image window.

In the selected image window, click on the desired location to start the **ROT** outline.

Move the cursor in one direction, while pressing the left mouse button or by clicking on successive points to create the **ROT** outline.

Complete a non-intersecting polygon.

Click the box at the end of the line to close the **ROT** polygon.

Continue to define the **ROT** on all additional necessary slices.

Move the **ROT** by clicking and dragging it. Delete the **ROT** by clicking it and the **Delete** button.

7.5.2. Define the ROT

1. Click on an image to display it in the selected image window.
2. Click  and trace the Region of Treatment (**ROT**) on the selected image.
3. Toggle  to display the treatment limits and verify that the **ROT** is within the effective treatment area of the transducer. If this situation cannot be reached in the desired transducer tilt settings, reposition the transducer mechanically and repeat to Calibrate Stage to locate transducer by calibrating the system again
4. Repeat on additional slices if necessary, click on the ROT and click  to interpolate.

The system will automatically pack the ROT with treatment spots while entering the next stage (**Treatment Stage**)

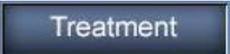
Warning



Carefully examine the ROT and spots within the volume, on all relevant images to ensure a safe treatment plan before applying each one of the sonications.

7.6. ADVANCING TO THE TREATMENT STAGE

Before advancing to the **Treatment Stage**, you must confirm that both the patient and the nurse have been instructed in the use of the **Stop Sonication** button and that the patient is holding it and understands how to operate it. Also, the Operator's console Stop Sonication button needs to be checked to assure it is working properly.

Click  on the main toolbar to advance to the next stage in the treatment procedure.

Note

The system will not continue to the **Treatment Stage** without testing the **Patient Stop Sonication** button.

Note

If no registration was performed, a message is displayed inquiring whether proceeding without registration is desired. At this point consider performing registration, or proceed on to the **Treatment Stage**.

Chapter 8

Treatment Stage

8.1. TREATMENT STAGE - OVERVIEW

Treatment stage is the stage of where the actual treatment is performed. If needed, the user can change the plan and the sonication parameters throughout the treatment.

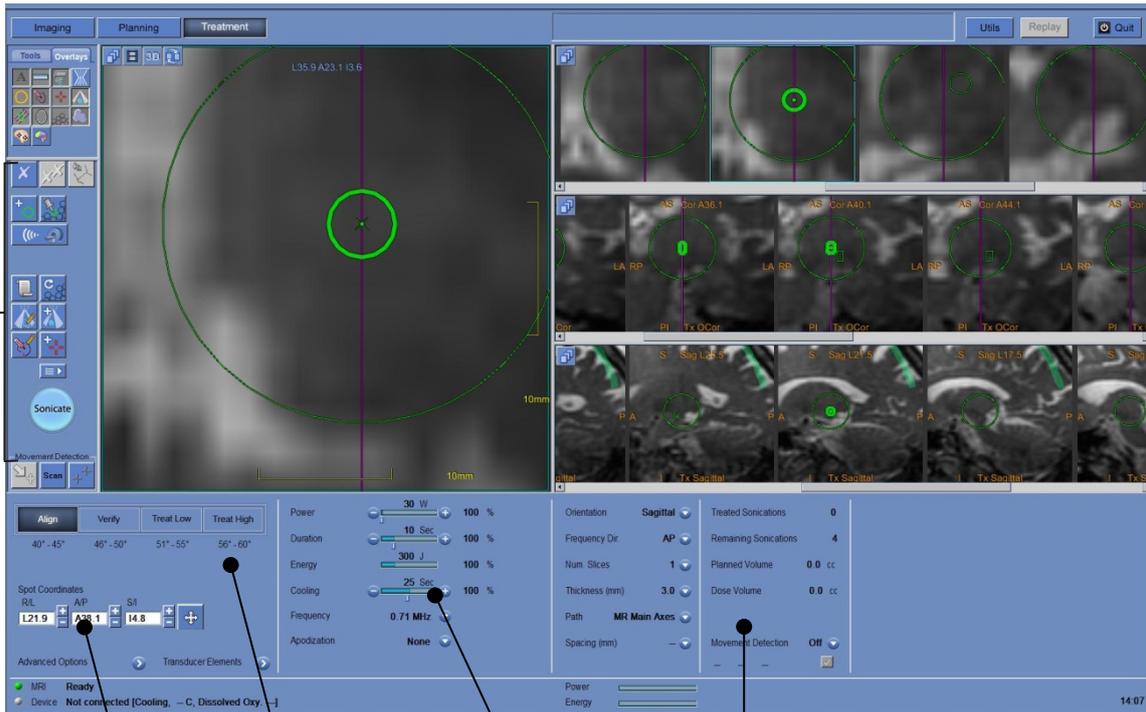
Treatment Stage includes two screens which cover the three phases within the sonication cycle:

1. **Treatment Stage Main Screen:** This screen (see Figure 8-1) enables to conduct the **Pre Sonication phase** and provides the means to prepare and plan the spot prior to the actual delivery of energy.
2. **Thermal Evaluation Screen:** This screen (see Figure 8-5) enables to conduct the **During & Post Sonication phases**. During the sonication time, the system displays the temperature maps and anatomy images acquired in real time. When the act of applying the energy has been completed, the system provided a set of tools to perform retrospective analysis and adjustments as necessary.

8.2. TREATMENT STAGE MAIN SCREEN

The **Treatment stage** contains the following new elements (see Chapter 5 for an explanation of the **Imaging** tools previously used).

Action Tools



Treatment Levels

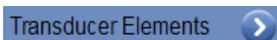
Spot Coordinates

Selected Spot Parameters

General Information and thermal scan parameters

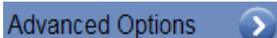
Figure 8-1: Treatment Stage Elements

8.2.1. Action Tools



Transducer Elements Window

Select a sonication spot and click this button to view the **Transducer Elements** window.



Advanced Option Mode

If the **Advanced Option Mode** is available on the system, and if required, click to open the **Advanced Option** dialog box (refer to Appendix A for details).



Add Sonication Spot

Use this button to add a sonication spot; the spot is added to the location selected on the MR image or to the selected **ROT** group.



Re-Plan ROT

Click this button to create a new plan for the selected **ROT**. The new plan will be set according to updated **ROT** parameter setting and the displayed selected spot parameters.

Note

A change in the treatment protocol or preparing a new **ROT Plan** at any stage causes all previous changes that were manually introduced in the current plan to be lost.



Set Spot As Current Spot

Click this button to set the selected spot as the **Current Spot** to be treated.



Move to next Spot

Click this button to select automatically the next planned spot to be treated.

Note

This option is available only while choosing the **Brain DQA protocol** from the **Treatment Protocol** dialog box. (See Section 6.5)



Suggest Optimal Acoustic Frequency

Click this button to perform an acoustic test to determine the optimal acoustic frequency for maximum intensity on target

Note

Frequency optimization should be performed only after Geometrical verification of the spot (**Align Mode**), to confirm targeting as well as average, or sub-average tissue response.



Start Sonication

Click this button to perform a sonication. This command is enabled only after a sonication spot is defined in the **Treatment stage** and both the MR and device lights in the status bar are green.



Image Flickering

If a movement detection scan was performed, click on the image flickering button to iteratively show in the selected image window the reference and actual movement detection images.

The blue fiducials represent the reference images, while the azure fiducials are the actual images.

8.2.2. Treatment Levels (Temperature Estimator)

This feature enables the operator to get an initial suggestion of the required sonication parameters in four treatment levels:

Align: where the hot spot center location is being evaluated and adjusted.

Verify: where the hot spot size and shape are being evaluated.

Treat Low: where the target is being stimulated to generate a clinical feedback that will ensure proper targeting of the expected anatomical structure.

Treat High: where the system aims to reach an adequate level of temperatures within the target that will ensure permanent controllable ablation of the anatomical structure.

Align	Verify	Treat Low	Treat High
40° - 45°	46° - 50°	51° - 55°	56° - 60°
Estimated Temperature		42 C	

Figure 8-2: Treatment Levels and Estimated Temperature

1. To generate an initial suggestion of the next sonication parameters, click the desirable treatment mode (temperature level).
2. The sonication parameters will be updated according to the predicted desirable temperature levels.
3. The Estimated Temperature field of the next spot (using the selected parameters) will be updated.

Note

Changing the spot parameters manually does not affect the Treatment Levels. In order to refresh the suggested sonication parameters, switch to new Treatment Level and get back to the current Treatment Mode.

Warning



While switching between Treatment Levels, confirm a moderate, gradual increase in energy with respect to previous observed peak temperature in the target.

Warning



Do not change the Treatment Level to increase the energy, unless you are certainly sure that the heated area is within the expected target (anatomical structure).

Caution



In case the sonication parameters have exceeded the system performance or safety limits, updated parameters will be presented.

8.2.3. Spot Information Frame

This frame displays the current spot coordinates and dimensions that are calculated from spot plan: **Length**, **Diameter**, and **Coordinates**.

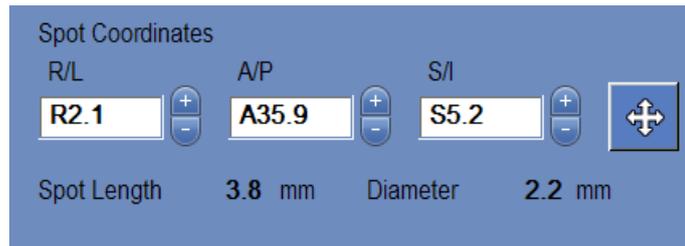


Figure 8-3: Spot Information Frame



Click the  button to lock all the planned spots. Lock state is eliminating spot location editing during the procedure.



Re-click this button () will enable editing the spot location.

To change the selected spot's coordinates, you may either drag the spot to the desirable location upon the MR images or alternatively insert the required spot coordinates.

Note

Pay attention to signs while inserting the spot coordinates. (i.e. L/R, A/P and S/I).

8.2.4. Sonication Parameters Frame

If necessary, change the parameters as described below. All changes to the spot parameters affect all sonication spots in the selected **ROT**. Confirm the changes by clicking the **Apply** button or cancel them to retrieve previous parameters.



Change the Power percentage of sonication by clicking the  or  buttons. Click the **Center Marker** on the scale to reset to 100%.



Change **Sonication Duration** by clicking the  or  buttons. Click the **Center Marker** to reset to 100%.

For **Burst** sonications, the sonication duration is automatically defined by the **Energy, Duty Cycle** and the **Peak Power**. (This sonication mode are not available in all system

configurations)



Displays the **Acoustic Energy** of next sonication (for **Nominal** sonications).



Change the **Cooling Duration** by clicking the **+** or **-** buttons. Click the **Center Marker** to reset to **100%**.



Select **Frequency** from the pull-down menu.



Select **Apodization percentage** to determine the effective transmitting area of the transducer out of the total active elements.

Caution



Verify desired sonication parameters before performing sonication. Unintended sonication parameters may result in ablation of unintended tissue. Check Temperature estimation (see 8.2.2) and confirm spot location before each sonication.

Caution



In case the sonication parameters have exceeded the system performance or safety limits, updated parameters will be presented.

Caution



Make sure you verify the spot's location upon the MR images after inserting a set of coordinates manually.

8.2.5. Thermal Scan Parameters Frame



Orientation	Axial
Frequency Dir.	AP
Num. Slices	1
Thickness (mm)	3.0
Path	MR Main Axes
Spacing (mm)	-

Figure 8-4: Thermal Scan Parameters

This section controls the parameters of the thermal scan to be taken during the next planned sonication.

Orientation:

Select one of the following for scan orientation:

- In case of **MR Main Axes**: One of the three main orientations (Axial, Coronal or Sagittal).
- In case of **Planning images**: One of the three main orientations (Axial, Coronal or Sagittal), or in case planning images were taken as oblique - one of three oblique orientations (OCor, OAx, OSag).

Freq. Dir:

Select the frequency direction from one of three settings: **RL**, **AP**, or **SI**.

Num. Slices:

Select **Number of Slices** for single-slice or multi-slice thermal imaging:

- **1** (Single-Slice) is using protocols of **Single Echo** (SE) thermal imaging intersecting with the center of the planned spot.
- **3 or 5** (Multi-Slices) protocols are for volumetric **Echo Planar Imaging** (EPI) thermal imaging. A few parallel scan slices will be taken while the center slice will intersect with the center of the planned spot.

Note

There is an option to use Multi Echo thermal imaging with Single slice protocol.
See section 10.2.13

Thickness:

Select the slice thickness from one of the settings: **3, 5, or 7** mm.

Path:

Select one of the following options:

- **MR Main Axes** – scan direction will be defined by the MR main axes.
- **Planning Images** – scan direction will be defined by the Planning images direction.

Spacing: (for multi slice thermal imaging)

Select the spacing between the slices

Note

For each selected sonication, the thermal scan grid lines (purple color line/s) are automatically displayed on the screen, according to the thermal scan parameters.

8.2.6. General Information Frame

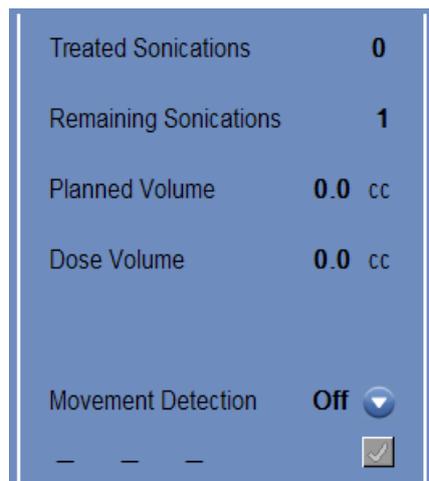


Figure 8-5: General Information Frame

Treated Sonications:

The system automatically indicates the number of sonications already conducted.

Remaining Sonications:

The system automatically indicates the number of remaining sonications in the treatment plan.

Planned Volume:

The system automatically calculates the planned volume based on the predefined **ROT** volume.

Dose Volume:

The system automatically calculates and indicates what volume has been treated so far, based on the accumulated dose volume that was accepted by the operator in previous sonications.

The thermal dose is defined as the volume that has reached a temperature of 54°C for a duration of 3 seconds (or thermally equivalent values), based upon the real time thermal images.

Movement detection:

When **Movement detection** option is turned on, the system will automatically perform movement detection imaging ("*current image*") and analysis every few sonications, and will alert the operator in case of large movement.

Once a movement was detected, the evaluated direction of movement will be displayed (point in 3 axes represents the direction vector). If estimated movement is above 1mm, check movement detection images to verify the movement,

In case the movement detection occur due to artifact or noisy area, delete the faulty fiducial and place another one in a better location, then run the detection again (see section 7.3)

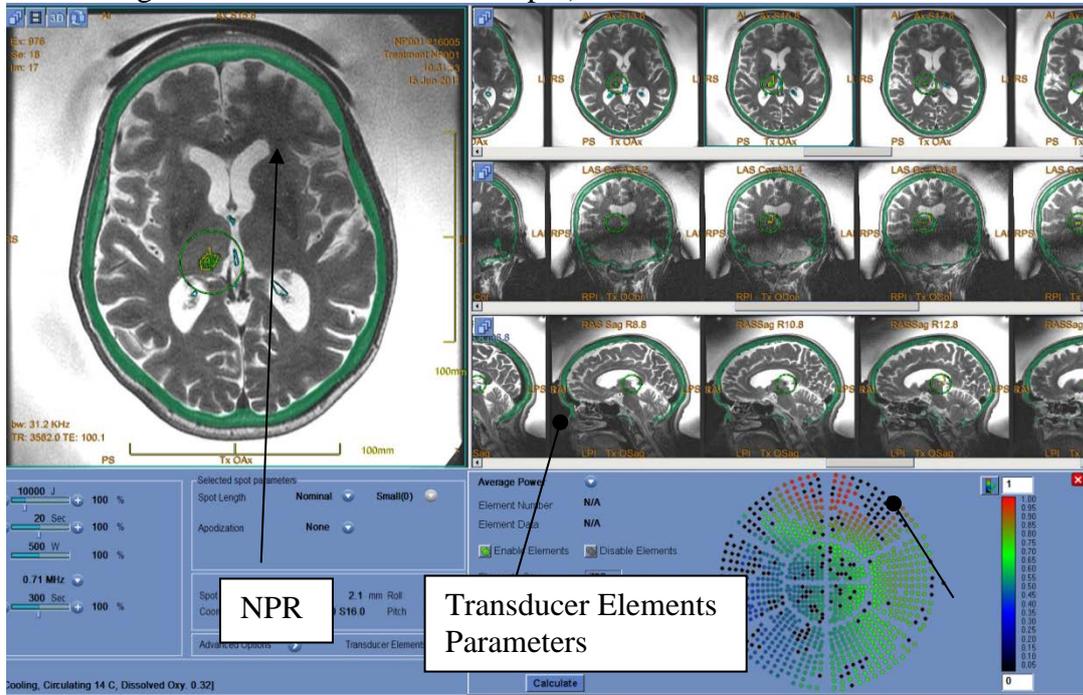
Warning



An automatic algorithm is used for movement detection. This algorithm is designed to assist an operator to identify movement. However, the Movement detection option does not replace the operator and does not relieve the operator from the responsibility to properly identify movement.

8.2.7. Transducer Elements Window

The transducer elements window displays the **Transducer Elements Map** and the **Transducer Elements Parameters** for the sonication spot. The rays from the transducer elements to the sonication spot can be seen on the images (a ray defines the acoustic path from a single element to the sonication spot).



Transducer Elements Map

Figure 8-6: NPR and Transducer Elements Window

8.2.7.1. Action tools

	Calculate Elements	Click this button to calculate the transducer elements map and parameters for a selected sonication spot.
	Set Map Range	Click this button to apply the scaling range of the transducer map.
	Enable/Disable Elements	Click these buttons to turn selected element(s) ON or OFF:
		<ol style="list-style-type: none">1. Select element(s) from the Transducer Elements Map by clicking on it.2. Click Enable Elements to turn on, or Disable Element to turn off.

8.2.7.2. Transducer Elements Map

For each sonication spot, it is possible to view its derived **Transducer Elements Map**.

Each of the following profiles can be displayed on the map:

- The **Average Power** (in Watts) transmitted from each element.
- The **Phase Correction** (in degrees) applied for skull aberration correction of each element.
- The **Thickness** (in mm) of the skull that the ray passes through.
- The **External Angle** (in degrees) between the ray and the skull surface at the intersection area.
- The **Air in Skull** (in mm) along the ray path.
- The **Internal Temperature** (in Celsius) estimation of the brain tissue temperature at the inner surface of the skull.
- The **External Temperature** (in Celsius) estimation of the temperature at the skin adjacent to the skull.
- The **Ray Shift** (in mm) as a measure of the ray refraction.
- The **Skull Average Intensity** (in Watt/cm^2) shows the average acoustic energy density on the surface of the skull.

- The **Manual Disabled** displays the elements that were manually turned off by the operator.

8.2.7.3. Transducer Elements Parameters

1. Click on a transducer element to view its parameters in the **Transducer Elements Parameters** frame. Each parameter value is displayed next to the corresponding profile (as detailed in section 10.2.8.2).
2. General parameters of the selected spot are displayed:
 - The **Elements On** displays the total number of the transmitting elements available for treating the current patient.
 - The **Skull Area** (in cm²) displays the total area on the skull available for the rays to pass through.
 - The **Focal Power** (in Watts) displays the estimated peak power that reaches the target location after traversing through the skull and brain tissue.

8.2.8. Spot and Ray Colors

The sonication spots and rays are colored to provide additional feedback about their status.

8.2.8.1. Sonication Spot Colors

- **Green** – untreated spots, which are valid and may be treated
- **Yellow** – warns the user that the energy density of the spot is above the threshold of the NPR
- **Red** – non-treatable spots (spot parameters are not valid)
- **Blue Outline** – next spot to be sonicated

Note

When the untreated spot is yellow or red, the reason will be displayed in the information box by pressing on the spot.

8.2.8.2. Ray Colors

The rays are colored to provide additional feedback about their status:

- Transmitting elements - **Green**
- Non-transmitting elements - **Azure**

Note

- For non-transmitting element, the reason will be displayed in the information box by selecting the ray.
- Selected sonication spots or rays are highlighted.

8.3. THERMAL EVALUATION SCREEN

After the sonication energy is applied, the system displays the **Thermal Evaluation** screen (see Figure 8-7).

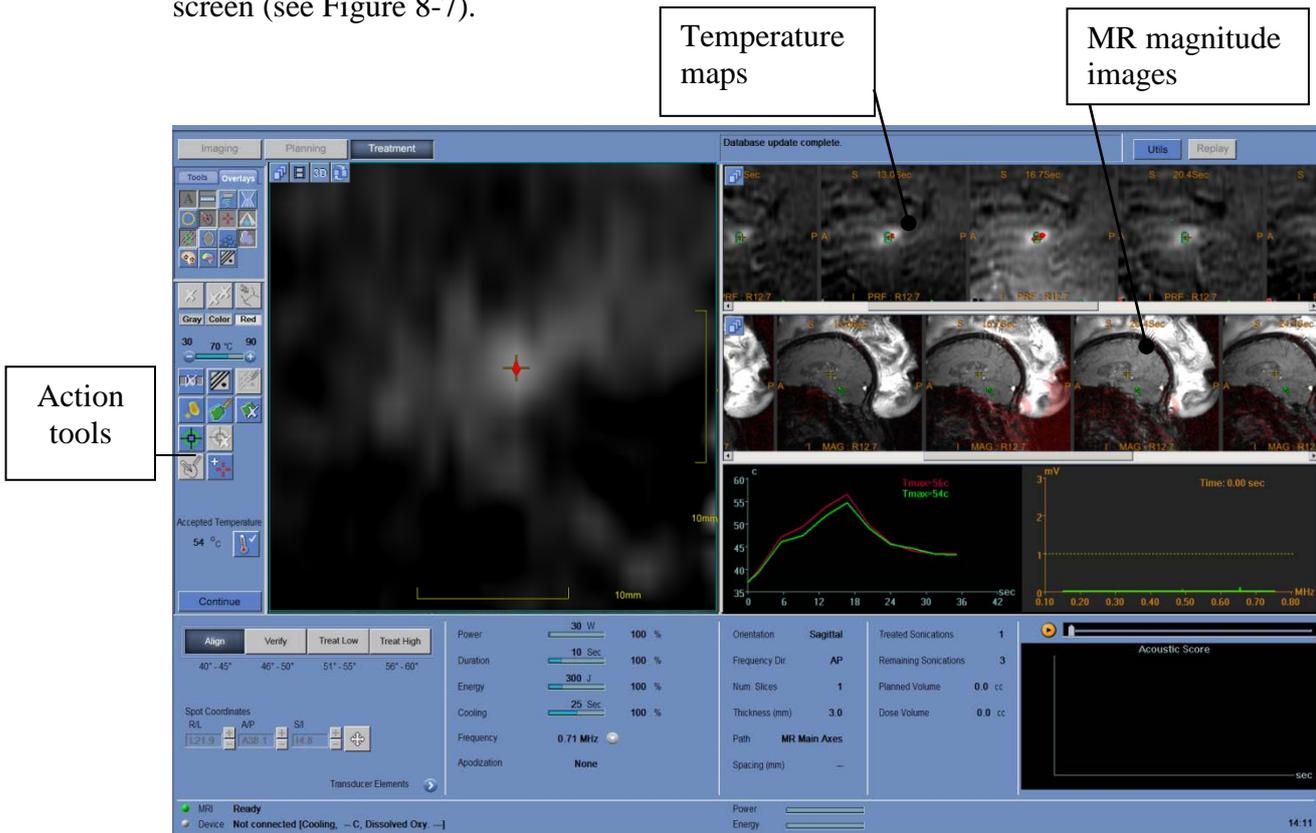


Figure 8-7: Thermal Evaluation Screen Elements

Warning



The ExAblate Model 4000 does not have an automatic user alert should the temperature reach high temperatures. Should the temperature reach high temperatures, the user should press the Stop Sonication at once.

8.3.1. Image Strips

The top image strip shows the temperature maps acquired during the sonication.

The bottom strip displays the set of MR magnitude images taken during the sonication.

The **Image Strip** selection menu  may be used to manually change this default setting.

For multi-slice thermal scans, the central slice is displayed.

The **Selected Image** window shows the MR image acquired closest to the end of the sonication. The calculated thermal dose contour is superimposed on the post-sonication temperature maps.

To navigate through the MR images along time, use the **Keyboard Right and Left Arrows** or alternatively click on the desirable image.

For multi-slice thermal scans, use the **Keyboard UP and Down Arrows** to navigate between different slices of the temperature maps. Annotation on the bottom of the selected image (main image) will indicate the scan location.

8.3.2. Thermal Evaluation Action Tools

Note

Some action tools may not be enabled when analyzing **Geometric Verification** results.



Background Temperature Correction

In case of background temperature change due to patient movement or MR central frequency shift, you can correct the background temperature.

Click this button to perform the background temperature correction, according to the **Background Polygons** displayed on the temperature maps.

The temperature maps and graphs are updated. Verify that the **Background Polygons** are located in soft tissue, which is **not** within heated or noisy areas. If necessary, move, delete or use the **Draw Background Polygon** button.

Note

If you selected the **Background Temperature** option, that button will remain pressed for the next sonication.



Draw Background Polygons

Use this button to draw polygons for the background temperature correction, after using the  button.

Click this button and draw the **Background Polygons** in soft tissue, which is **not** within heated or noisy areas.

Continue to define more **Background Polygons** (if necessary).

Move the **Background Polygon** by clicking it and dragging. Delete **Background Polygon** by clicking it and then clicking the **Delete** button.



Spot Location Adjustment

To perform spot location adjustment, select the temperature map with the hottest spot to the **Selected Image** window.



Reset Adjustment

Click this button to reset all accumulated adjustment of the treatment



Heat Estimation

Click this button to provide an automatic evaluation by the system of thermal heated regions, and mask out erroneous regions in the temperature maps.

Note

- This overlay provides only a suggestion for heated regions. Do not rely on the algorithm solely and carefully examine the entire thermal map to detect real heated regions.
- If you selected the **Heat Estimation** option, that button will remain pressed for the next sonication.



Draw Dose Polygon

In case of erroneous thermal dose regions (caused by artifacts) mark the thermal dose on the temperature map as follows:

Click on a temperature map with thermal dose to display it in the selected image window.

Click the **Draw Dose Polygons** button; draw polygons around the correct thermal dose regions.

Continue to define the **Dose Polygons** on additional slices (interpolate if necessary).

If it becomes necessary to refine or redefine the drawn polygon, move it by clicking it and dragging, or delete by clicking it and then clicking the **Delete** button.



When clicking on the **Continue** button, only the thermal dose inside the dose polygons will be accumulated.



Remove Noisy Image

In order to avoid an erroneous dose, it is possible to ignore entire noisy thermal image in temperature calculations:

Click on the noisy thermal image to display it in the selected image window.

Click the **Remove Noisy Image** button; the noisy temperature map is replaced by an interpolated map and the thermal dose calculations are updated accordingly.

To cancel the selection, click again.

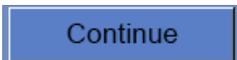


Add Fiducial Marker

Use this feature to add fiducial marker on anatomical features as reference marker. These fiducials will be seen on planning images as well.

Click this button and then point and click in the **Selected Image** window to create a marker.

8.3.3. Continue Treatment Tools



Continue to Treatment Main Screen

Click this button to continue to **Treatment Main Screen**.

Note

By clicking this button you accept the following **Thermal Outcomes** from this sonication:

- **Measured Thermal Dose** accumulation.
- **Accepted Peak Temperature**.

LEVEL

Update Accepted Peak Temperature

These parameters may affect the **Treatment Levels (Temperature Estimator)** and the **Accumulated Measured Thermal Dose**. Carefully examine the sonication outcomes before clicking the continue button.

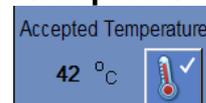
Click this button to update the **Accepted Average Peak Temperature** as the outcome of this sonication. This temperature will be selected as the inputs for the **Treatment Levels (Temperature Estimator)**.

As a default, the system will accept the average peak temperature calculated automatically by the system at the end of the sonication (Where the **Temperature Cursor** was located by the system).

To update the **Accepted Temperature**:

1. Drag the **Temperature Cursor** to where you think the peak temperature was reached, upon the **Thermal Maps**.
2. Make sure this location is indeed the center of the real thermal spot.
3. Click the  button.

The temperature will be updated to the **Accepted Temperature Field**.



Reject Thermal Outcomes

Click this button (toggle button) to **Reject All Thermal Outcomes** from last sonication.

Keep this button in “*pressed*” state before clicking the 

button, in order to reject the thermal outcomes.

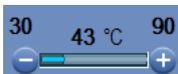
8.3.4. Temperature Scaling Tools



Temperature Scale Viewing

Click on different tabs for different scaling:

- **Gray** displays temperature maps in grayscale.
- **Color** displays temperature maps in color.
- **Red** displays a red overlay on the grayscale image. The red overlay displays all of the areas where the temperature is above a pre-determined temperature threshold.



Temperature Threshold

To view the desired temperature scale, set the temperature threshold by clicking the  or  buttons. The selected value appears on the scale.

8.3.5. Sonication Energy / Power Indicator

This frame indicates the measured acoustic power and energy of the last sonication.



Figure 8-8: Sonication Energy/Power Indicator

8.3.6. Temperature Graph

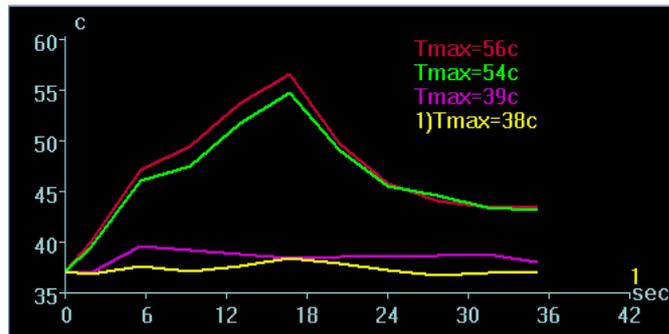


Figure 8-9: Temperature Graph

The temperature graph shows the temperature change during a sonication at the cursor location. During the sonication, a cross-shaped cursor automatically appears on the hottest spot.

The graph shows:

- **Red Line** – the evolution of the temperature at the cursor location, during and after sonication.
- **Green Line** – the average temperature around that cursor.
- **Yellow Line** – the average temperature within a measurement polygon.
- **Magenta Line** - the average temperature within the **Temperature Monitoring Volume**
- The highest temperature reached by each graph line is displayed on the upper right position of the frame.

Note

The graph may be used to display the temperature history of any location by moving the cross-shaped cursor with the mouse.

8.3.7. Acoustic Spectrum and Spectral energy Score

Two additional graphs are displayed during the course of the sonication; both are displayed as soon as sonication begins:

- **Acoustic Spectrum Data** – show the spectrum of frequencies that are transmitted back to the transducer
- **Spectral energy score** – show the intensity of these frequencies at each time point

The **Acoustic spectrum** and the **Spectral energy score** show graphs, which assist in detecting the creation of micro-bubbles associated with cavitation effect.

Acoustic high values in the the transmitting indicates possibility effect, and will result **energy score** above horizontal line. If this sonication, the system stop the energy



spectrum with range of half of frequency for cavitation in **Spectral** the dashed occurs during a will automatically transmission,

while the MR scan will continue as prescribed.

Figure 8-10: Acoustic Spectrum Graph



Figure 8-11: Spectral energy score graph

Both graphs are captured during the sonications and can be reviewed by the user in the thermal evaluation stage, by pressing the  button. The data will be played as cine.

Note: the ExAblate system is equipped with an automatic Cavitation related mechanism that once the cavitation signal reaches a certain threshold, the system will automatically stop the sonication followed with system alert to the user.

8.4. TREATMENT PROCEDURE

8.4.1. General Sonication Flow

1. Verify that the patient is comfortable.
2. Examine the next spot to be sonicated:
 - When highlighted in blue, the spot is valid and may be treated.
 - When highlighted in yellow, the spot is above the threshold on **NPR**. Cautiously try to optimize the location and/or the orientation. Check the parameters and assess if the clinical situation allows this sonication.

Note

When the untreated spot is not blue, the reason is displayed in the information box at the top-right side of the screen by clicking on the spot.

3. Based upon the examination of the actual dose and patient feedback, manual changes to the treatment plan are possible at any stage during a treatment:
 - Sonication parameters (such as **Energy, Duration, Frequency**)
 - Confirm estimated external and internal temperatures are adequate
 - Change Thermal scan parameters (MR protocol, scan orientation, Frequency direction)
 - Add/remove spots

Warning



Before each sonication, confirm that the water system is functioning properly and that:

- There are no water leaks from the transducer by visually inspecting the transducer area.
- The blue **Circulation Controller** on the operator's console is illuminated continuously. Blinking means that the water temperature or pressure has exceeded the limits.
- Degassing level is less than 1.5 ppm



4. Click  to apply the ultrasound energy.
5. During the sonication, the following factors should be monitored:
 - Patient discomfort or abnormal reactions
 - Energy transmission, as displayed by the energy bar
 - Spectrum signal during the transmission of the acoustic energy
 - Patient motion, by observing the fiducial markers or the CT mask on the updated MR anatomical images
 - The evolving temperature rise during sonication

Warning



If there is a need to stop the sonication process, press the **Stop Sonication** button.

Caution



In case the sonication parameters prescribed by the user have exceeded the system performance or safety limits, updated parameters will be presented before sonication will start.

Warning



Monitor the temperature maps during the sonication. If an unexpected thermal rise is found outside the target location, stop the sonication.

6. After the sonication, the **Thermal Evaluation** screen opens with the actual thermal dose contour overlaid on the image (see Figure 8-7). Review the results as described in **Performing Thermal Spot Verification** (see Section 8.4.6).

Warning

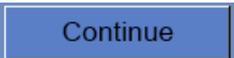


Monitor the thermal rise at the target location, and at the relevant pass zone with special attention to the interface with the skull and other sensitive regions.

If the patient moves or is repositioned you must return to the **Imaging Stage**, scan new planning images, and create a new plan based on these new images.

The geometric verification procedure must be repeated if one or more of the following incidents occur during treatment:

- Repositioning of the transducer or updating **Imaging Stage** parameters
- Modifying CT/MR registration
- Patient movement is detected and new planning images are loaded
- **No Pass Region** polygons have been modified
- Thermal hot spot is not noticed on thermal imaging sequence during treatment

7. Click  to continue to the next sonication.

Note

After continuing to the next sonication, the operator will not be able to edit the **Accumulated Measured Dose** of previous sonications or the **Accepted Peak Temperature** for the **Treatment Levels (Temperature Estimator)**.

Warning



If there is a need to increase treatment energy, do so in gradual steps and monitor thermal rise after each sonication.

8. Repeat the procedure until all the planned sonications have been performed, or alternatively repeat the selected spot until you have reached the desirable clinical outcome (for a single target).
9. If needed, click **Replay** to view the results of previous sonications.

8.4.2. Confirm Treatment Plan

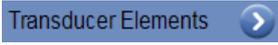
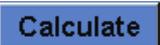
After examining the treatment plan in all orientations, verify that the sonication spots cover the target tissue (including the margins as required by clinical considerations). If necessary, edit the plan as follows:

1. Select sonication spots to edit by clicking on a spot for a single spot, clicking on  for a group of spots.
2. Change the **ROT** parameters or selected spot parameters (as explained Section 8.2.4).
3. To update the grid density according to the new parameters, you should prepare a new **ROT** plan, using the  button.
4. Add, move or delete a sonication spot / fiducial marker as required.

8.4.3. Adding a new Sonication Spot

1. Click  and add a reference sonication spot in the **Selected Image** window.
2. Verify that the sonication test spot is located within the **ROT**.
3. Verify that the position of the sonication spot is exactly within the desirable target location.
4. The system will warn you if the spot is technically invalid (e.g. spot is outside the treatment limits).

8.4.4. View Transducer Elements

1. Click  to view the **Transducer Elements** window.
2. Select a sonication spot in the center of the ROT from the **Selected Image** window.
3. Click  to view the **Transducer Elements Map**, according to the selected profile.

Warning



Please ensure minimum values of 700 calculated active elements and an available skull area of 250 cm² to ensure a safe and effective treatment. In case of marginal values, re evaluate pre-plan and placement of head frame.

Note

For optimized planning, confirm that the water temperature (displayed in the status bar) has been cooled to the defined values in the treatment protocol.

4. Select the **Elements-On** option from the **Pass Zone Overlay** menu to verify that the rays do not pass through sensitive tissues.

If required, click an element in the transducer map or on a ray in the selected image window, to view the element's profiles.

You can review the transducer elements map and the parameters of each element, for each sonication spot.

8.4.5. Geometric Verification (“Align” Level)

8.4.5.1. Perform a geometric verification sonication

Warning



In case of an unanticipated system action or patient reaction, the operator, the nurse or the patient can immediately stop the system at any time with the **Stop Sonication** button.

1. The system automatically defines sonication parameters and the temperature-sensitive PSD parameters for geometric verification, while using the  **Treatment Mode**, based on previous treatment's data from treatment of the same type of target. Sonication parameters should be examined in the **Sonication**

Parameters and the **Thermal Scan Parameters General Information and Treatment Options** frames.

Note

The default scan orientation will be axial.

2. Confirm that the sonication parameters are adequate to assure that the thermal rise will be below dose threshold.
3. Verify that the patient is comfortable, and notify the patient that verification is about to begin.

Warning



Before each sonication, confirm that the water system is functioning properly and that:

- There are no water leaks from the transducer by visually inspecting the transducer area.
- The blue **Circulation Controller** on the operator's console is illuminated continuously. Blinking means that the water temperature or pressure are exceeded the limits.
-



4. Click the  button to apply the ultrasound energy. The system transfers the sonication location to the MR.
5. The sonication will start with the MR scanning images and then starts transmitting ultrasound energy.
6. During the sonication, the following factors should be monitored:
 - Patient discomfort or abnormal reactions
 - Spectrum signal and spectral energy score during the transmission of the acoustic energy
 - Patient motion, by observing the fiducial markers or the CT mask on the updated MR anatomical images
 - The evolving temperature rise during sonication

Warning



- In case of an unanticipated system action or patient reaction, the operator, magnet room technician or patient can immediately stop the system at any time with the **Stop Sonication** button.
- Remind the patient to stop the sonication when feeling pain or heat.
- At any point if any undesired signs appear, the **Stop Sonication** button must be pressed immediately.

7. When the thermal imaging is complete after the sonication, the screen is automatically replaced by the **Thermal Evaluation** screen (see Figure 8-7).

Warning

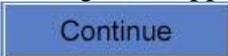


If the patient moves or is repositioned, you must return to the **Imaging** stage, scan new planning images, and create a new treatment plan based on these new images.

8.4.5.2. Geometric Adjustment

Every thermal image has a pre-set frequency direction, along one of the plane's axes. The frequency direction is indicated by an orange arrow located in the lower right corner of the thermal image. The location along this direction is sensitive to imaging shifts and may not represent the true location of the thermal spot, or of the displayed anatomical features. Therefore, adjustment should only be performed along the phase direction, which is perpendicular to the frequency direction. (see Figure 8-12).

1. If the thermal spot can be adequately identified, verify that it is within 1.0 mm of the planned location along the phase direction. If it is, continue to the **Thermal Spot Verification Procedure** (see Section 8.4.6).
2. If the thermal spot is over the 1.0 mm margin, click , and click on the hot spot center in the **Selected Image** window, to adjust to the correct position. The **Adjust** function automatically corrects the transducer's electronic position according to the offset between the sonication location and the planned spot location. A pop-up message will appear showing the adjustment. Click **Apply** and then click

 to continue.

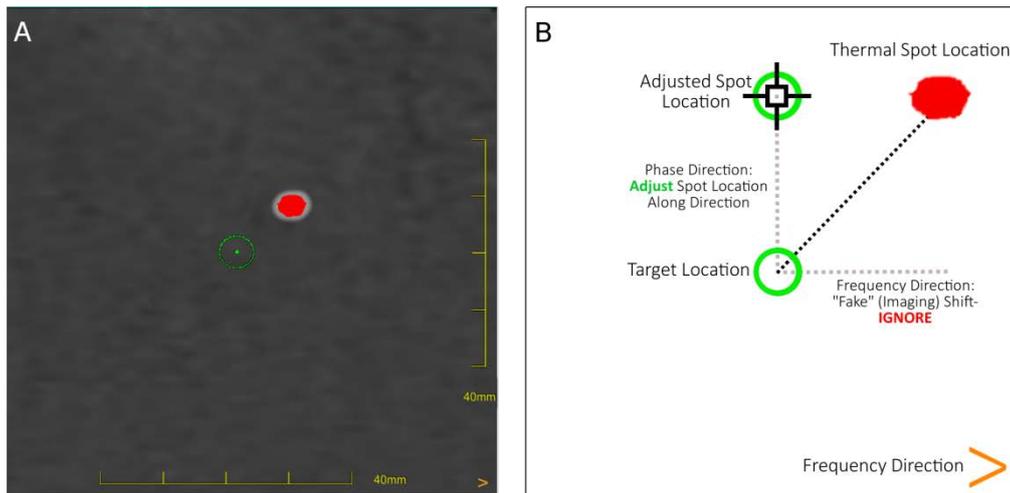


Figure 8-12: Alignment algorithm
A: Thermal image ; B: Schematic representation

3.

Warning



Take extreme caution before performing an adjustment:

If adjustment is required, it must be performed. However, do not perform an adjustment unless you can clearly see the entire hot spot and be absolutely certain that the adjustment is necessary.

If the adjustment is over 2mm, before performing it apply another sonication with different orientation (that shows the same direction) in order to confirm the necessity of the adjustment.

Failure to do so may increase the risk of unintentionally treating non-targeted tissue.

4. If a hot spot from the sonication cannot be adequately identified, do the following:

- Confirm that no air has entered the transducer interface and that it is completely filled with water.
- Verify that the energy accumulated in the last sonication, displayed in the **Sonication Energy / Power Indicator** (see Figure 8-8), is the same as the energy requested.
- Repeat the sonication while modifying scan parameters to different orientations.
- Increase the sonication energy level in small increments, repeating the geometric verification sonication until a hot spot is observed.
- Perform an additional MR scan to evaluate patient's movements or changes.

5. After the spot is aligned in the axial orientation, click  and repeat the **Geometric Verification Procedure** in a coronal or sagittal orientation (change the scan orientation in the **Thermal Scan Parameters General Information** frame).
6. After the **Geometric Verification Procedure** is successfully completed, advance to the **Thermal Spot Verification Procedure** (see Section 8.4.6).

Warning



Do not continue with the treatment if a hot spot is not adequately visible and confirmed to be well aligned with the planned target in all 3 dimensions.

Warning



The geometric verification procedure must be repeated if one or more of the following incidents occur during treatment:

- Repositioning of the transducer or updating **Imaging Stage** parameters
- Modifying CT/MR registration
- Patient movement is detected and new planning images are loaded
- **No Pass Region** polygons have been modified
- Thermal hot spot is not noticed on thermal imaging sequence during treatment
- Spot placed in new target location (e.g, bilateral treatment)

Note

- If the spot appears red, it is invalid and cannot be sonicated.
- If the spot appears yellow, be cautious. Try to optimize the location and or the orientation.

Warning



This is effectively the beginning of treatment. Select the spot parameters as though you are beginning treatment.

Confirm a moderate, gradual increase in energy with respect to geometric verification energy in which a hot spot was observed.

8.4.6. Thermal spot Verification (“Verify” Level)

Performing **Thermal spot Verification** is aiming to reach a peak temperature that will ensure a full evaluation of the thermal hot spot’s size and shape.

1. Switch to  mode on the **Treatment Levels** frame, to calculate an initial prediction of the required sonication parameters (Power, Duration and Energy) that will theoretically increase the level of the peak temperature to be within 46 to 50 degC.

Warning



Confirm a moderate, gradual increase in energy with respect to Geometric Verification energy (in **Align Mode**) in which a hot spot was observed.

2. Follow the same monitoring guidelines as in the **Geometric Verification Sonication Procedure** (steps 3 through 6).

3. Click  button to apply the ultrasound energy; the system transfers the sonication location to the MR.

3. Monitor the sonication:

- Patient discomfort or abnormal reactions
- Spectrum signal during the transmission of the acoustic energy
- Patient motion, by observing the fiducial markers and the CT mask on the MR anatomical images
- The evolving temperature rise during sonication

Warning



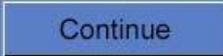
Monitor the temperature maps during the sonication. If an unexpected thermal rise is found outside the target location, stop the sonication.

4. After the sonication ends, the **Thermal Evaluation** screen opens (see Figure 8-7).
5. Check whether there has been patient motion by observing the location of the fiducials and the CT mask location on the Anatomical images from the sonication.
6. If needed, use  or  to correct the **Background Temperature**.

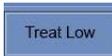
Warning



Monitor the thermal rise at the target location, and at the relevant pass zone with special attention to the interface with the skull and other sensitive regions.

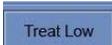
7. If needed, click  to **estimate the heated regions** on the temperature maps. Analyze the thermal results near the skull and the thermal dose in the sonication area.
8. If required, use  to draw **Measurement Polygons** near the surface of the skull to evaluate the temperature rise.
9. Analyze the results and compare the size of the obtained spot with the planned spot:
 - If they match, click  to accept the **Thermal outcome** and return to the **Treatment Screen** (see Figure 8-1).
 - If they don't match, change the sonication parameters and repeat the **Thermal Dose Verification Procedure**.

Note

- If the temperature map still contains an erroneous thermal dose (caused by residual artifacts), use the  button to define which regions should be considered as dosed regions.
 - To remove a specific noisy thermal image from the temperature calculations, use the  button.
 - If the temperature map contains artifacts, press  to reject the measured thermal dose and accepted peak temperature and then click the  button.
 - Repeat the procedure.
10. Once suitable parameters for treatment have been set and an acceptable spot size is achieved, switch to  Treatment Mode.

8.4.7. Target Stimulation (“Treat Low” Mode)

Performing Target Stimulation is aiming to reach a peak temperature that will enable to only stimulate the targeted anatomical structure and assess the required clinical feedback. This will enable the operator to ensure that the predefined targeted region is meeting the clinical expectations of targeting this anatomical structure.

Switching to  Treatment Mode will generate an initial prediction of the spot parameters that will theoretically increase the level of the peak temperature to be within 51 to 55 degC.

Warning



Confirm a moderate, gradual increase in energy with respect to Thermal Dose Verification energy (in **Verify Mode**) in which a hot spot was observed.

1. Follow the same monitoring guidelines as in the **Geometric Verification Sonication Procedure** (steps 3 through 6).

2. Click  button to apply the ultrasound energy; the system transfers the sonication location to the MR.

3. Monitor the sonication:

- Patient discomfort or abnormal reactions
- Spectrum signal during the transmission of the acoustic energy
- Patient motion, by observing the fiducial markers and the CT mask on the MR anatomical
- The evolving temperature rise during sonication

Warning



Monitor the temperature maps during the sonication. If an unexpected thermal rise is found outside the target location, stop the sonication.

4. After the sonication ends, the Thermal Evaluation screen opens (see Figure 8-7).

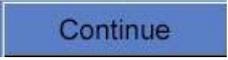
5. Check whether there has been patient motion by observing the location of the fiducials and the CT mask location on the Anatomical images from the sonication.

6. If needed, use  or  to correct the **Background Temperature**.

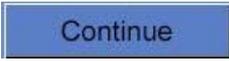
Warning



Monitor the thermal rise at the target location, and at the relevant pass zone with special attention to the interface with the skull and other sensitive regions.

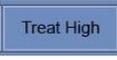
7. If needed, click  to **estimate the heated regions** on the temperature maps. Analyze the thermal results near the skull and the thermal dose in the sonication area.
8. If required, use  to draw **Measurement Polygons** near the surface of the skull to evaluate the temperature rise.
9. Analyze the results and assess the clinical feedback from the patient to ensure an accurate targeting of the desirable anatomical structure.
 - If the clinical assessment meets the expectations of targeting this anatomical structure, click  to accept the **Thermal outcome** and return to the **Treatment** screen (see Figure 8-1).
 - If they don't match, change the sonication parameters and repeat the sonication.

Note

- If the temperature map still contains an erroneous thermal dose (caused by residual artifacts), use the  button to define which regions should be considered as dosed regions.
- To remove a specific noisy thermal image from the temperature calculations, use the  button.
- If the temperature map contains artifacts, press  to reject the measured thermal dose and accepted peak temperature and then click the  button.
- Repeat the procedure.

Warning



Only once suitable parameters for treatment have been set and the actual clinical feedback meets the expected clinical outcome, switch to  mode.

8.4.8. Target Ablation (“Treat High” Mode)

Performing target ablation is aiming to reach a peak temperature that will enable to ablate the targeted anatomical structure (create a controlled ablation).

Switching to  Treatment Mode will generate an initial prediction of the spot parameters that will theoretically increase the level of the peak temperature to be within 55 to 60 deg C.

Warning



Confirm a moderate, gradual increase in energy with respect to Target Stimulating energy (in **Treat Low Mode**) in which a hot spot was observed.

1. Follow the same monitoring guidelines as in the **Geometric Verification Sonication Procedure** (steps 3 through 6).



2. Click  button to apply the ultrasound energy; the system transfers the sonication location to the MR.
3. Monitor the sonication:
 - Patient discomfort or abnormal reactions
 - Spectrum signal during the transmission of the acoustic energy
 - Patient motion, by observing the fiducial markers and the CT mask on the MR anatomical images
 - The evolving temperature rise during sonication

Warning



Monitor the temperature maps during the sonication. If an unexpected thermal rise is found outside the target location, stop the sonication.

4. After the sonication ends, the Thermal Evaluation screen opens (see Figure 8-7).
5. Check whether there has been patient motion by observing the location of the fiducials and the CT mask location on the Anatomical images from the sonication.
6. If needed, use  or  to correct the Background Temperature.

Warning



Monitor the thermal rise at the target location, and at the relevant pass zone with special attention to the interface with the skull and other sensitive regions.

7. If needed, click  to estimate the heated regions on the temperature maps. Analyze the thermal results near the skull and the thermal dose in the sonication area.
8. If required, use  to draw Measurement Polygons near the surface of the skull to evaluate the temperature rise.
9. Analyze the results and assess the clinical feedback from the patient to ensure an accurate targeting of the desirable anatomical structure.
 - If the clinical assessment meets the expectations of targeting this anatomical structure, click  to accept the **Thermal outcome** and return to the **Treatment Screen** (see Figure 8-1).
 - If they don't match, change the sonication parameters and repeat the sonication.

Note

- If the temperature map still contains an erroneous thermal dose (caused by residual artifacts), use the  button to define which regions should be considered as dosed regions.
- To remove a specific noisy thermal image from the temperature calculations, use the  button.
- If the temperature map contains artifacts, press  to reject the measured thermal dose and accepted peak temperature and then click the  button.
- Repeat the procedure.

8.5. CONCLUSION OF THE TREATMENT SESSION

At the conclusion of the treatment session, the patient may be released from the treatment table.

1. Cradle pulled out of the MR bore
2. Water drained from the transducer
3. Patient released from frame holder and membrane
4. Head frame removed
5. Patient examined in recovery room

6. Perform Cleaning / Disinfection procedure – See Cleaning and Disinfection procedure for more details.

Chapter 9

Replay

9.1. REPLAY - OVERVIEW

Replay mode enables the operator to analyze the results of previous sonications. **Replay** can also be activated from **Data Management** in order to view past treatments.

Click **Replay** in the main toolbar to access the **Replay** screen. This screen is similar to the **Thermal Evaluation** screen displaying the results of the last performed sonication (see Figure 8-7). This way the operator can observe the acquired temperature maps and the temperature graph of all previous sonications.

If you access **Replay** from **Data Management** (see Chapter 11), the **Replay** screen displays the first sonication in the treatment.

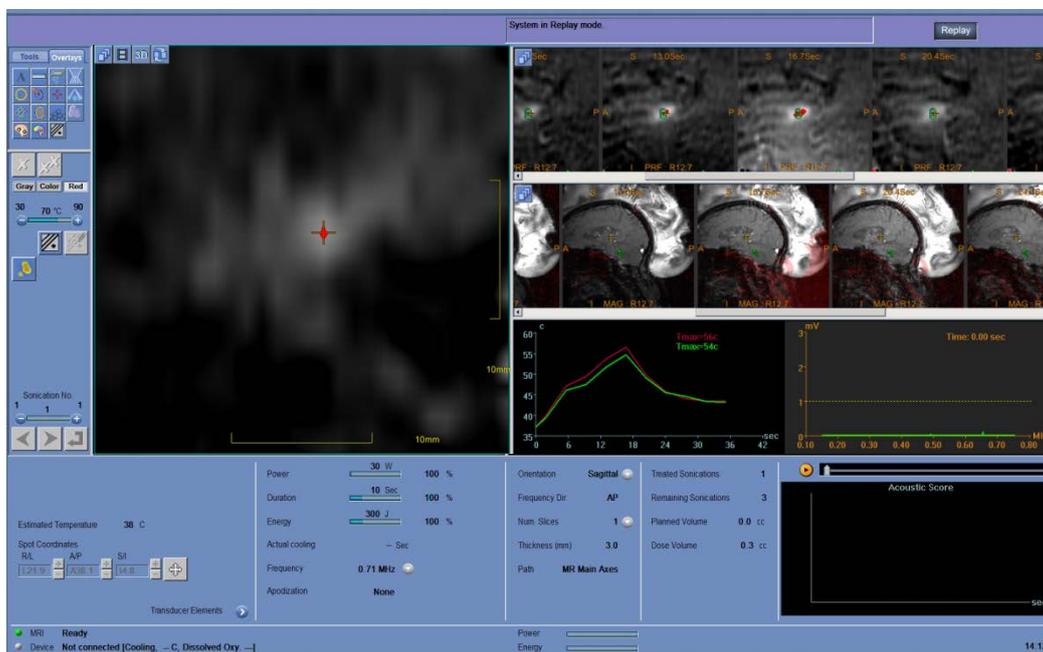


Figure 9-1: Replay Mode Screen

9.2. *REPLAY ACTION TOOLS*



Next or Previous Sonication

Click this button to scroll through the sonications. The current sonication sequence number appears in the middle of the sonication bar.



Sonication No. Bar

Use the  and  buttons in the **Sonication No. Bar** to choose to view a certain sonication, and click



9.3. *EXIT REPLAY*

To leave **Replay**, click  in the main toolbar; the system returns to the same screen from where you accessed **Replay**.

Chapter 10

Utilities

10.1. UTILITIES - OVERVIEW

The **Utilities** mode provides the means to perform actions that may be used during treatment but are not necessarily part of the nominal treatment flow.

These means include MR operations, turning device On/Off, operate water system, connection to the site network, Trackers use, and changing Calibration mode.

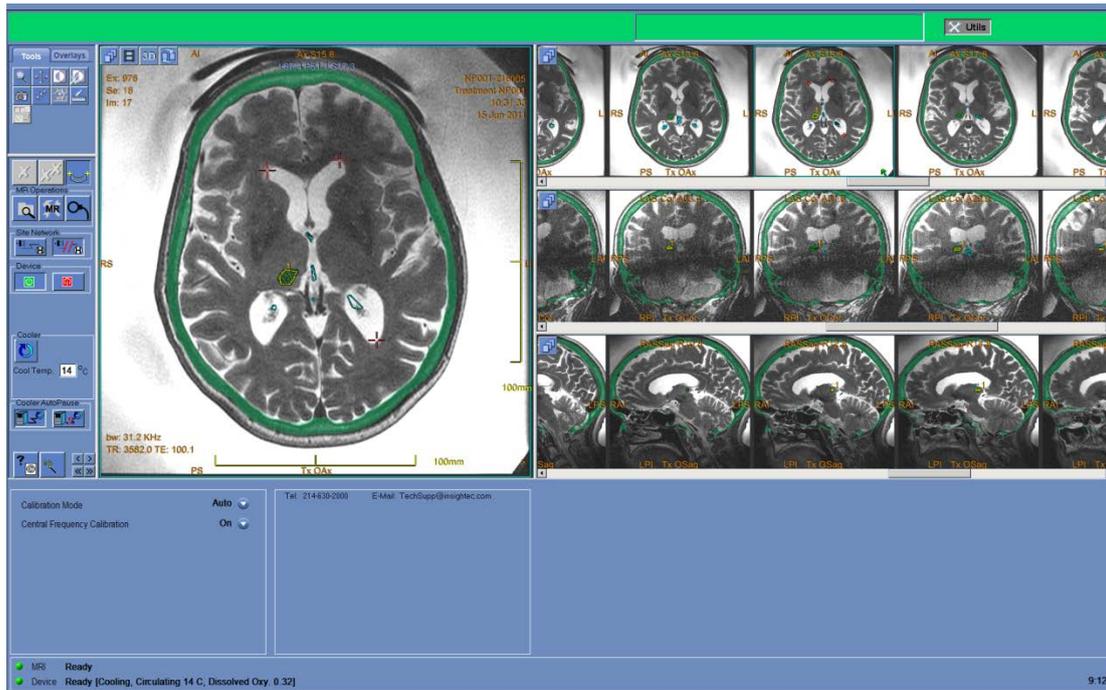


Figure 10-1: Utilities Screen

The elements are mostly the same as in the previous stages

10.1.1. Utilities Action Tools

The new tools are (refer to Figure 10-1):



MR Operations

Click the **Select Exam** button to select the active exam in the MR as the new treatment exam for the rest of the treatment.



Click the **Setup MRI** button to manually restore the connection to the MRI and/or the MR protocols in the GE MR system (in case they were



changed or removed).

Click the **Switch MR Coil** button to define the MR coil used for the treatment scans as the alternative coil.



Disable/Enable Trackers

Click this button to disable/enable the use in trackers to locate transducer's location.

Default option is ON.



Turn Device On/Off

Click  to turn the device off. Once shutdown is complete (as

appears in the status bar), click  to turn the device on.



Connect/Disconnect to the Site network

Click  to connect the MR system to the hospital network. Click  to disconnect from the hospital network.



Operate Water System options

Use  to:

Turn Cooler On/Off

Set Transducer temperature

Set preparation stage – transferring the system to degassing mode

Set Clean stage

Set Treat stage – this stage is automatically ON when treatment begins



Enable/Disable Water System Auto-Pause

Click  to manually control the water circulation.

Click  to automatically pause the water circulation whenever MR scan is performed.



Movement Detection

Click this button to:

Turn Movement detection feature On/Off or to scan new reference scan



Copyright Notice

Click this button to review the list of open source software that parts of the product may incorporate or be distributed with.

10.2. UTILITIES PROCEDURES

10.2.1. Select Exam (calibrate stage)

This procedure is used when the system selected an incorrect exam during calibrate stage (i.e. due to previous exam active). In order to continue treatment with the correct exam, a new MR exam must be opened and defined as the current exam.

1. Verify that a current MR exam exists

2. Click  in the **Utils** screen to select the correct MR exam.
3. Follow instructions according to the messages on the screen.

10.2.2. Select Exam (during the treatment)

This procedure also can be used when a new exam has been defined in the MR during treatment (usually due to the need to define a new MR exam). In order to continue treatment after such an event, a new MR exam must be defined as the current exam.

1. Confirm that a new exam with at least one series comprising of some images has been manually scanned in the MR.
2. Click on ; the system will automatically select the latest exam in the MR as the treatment exam. From this point on all thermal scans will be created using images from the new exam.
3. Before continuing treatment, the Geometric Verification Procedure must be repeated (see Section 8.4.5).

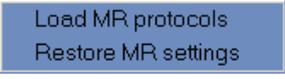
Warning



Before performing this procedure, the operator **must** confirm that both exams have the exact same landmark location and that there was no patient movement since the planning images were scanned.

10.2.3. Setup MR Protocols

This procedure should be used when the MR protocols stored in the GE MR system have been deleted or modified, or when communication with the MRI was lost.

1. Click  to open the Setup MRI drop down menu .
2. Choose the desired option:
 - Click **Load MR Protocols** to restore the MR treatment protocols from the workstation to the GE MR system.
 - Click **Restore MR settings** to restore the connection between the ExAblate system and the MRI, and to restore the MR treatment protocols.

10.2.4. Switch MR Coil (where applicable)

In some sites an alternative coil is defined during the installation process. The **Switch MR Coil** procedure is performed when there is a need to use the alternative coil instead of the default coil.

- Click on  and choose one of the existing coils you want to use; the system will automatically define the MR coil in use as the alternative coil. From this point on, all scans will be performed using the alternative coil.

To return to the default coil definitions, click  again and choose the correct coil or exit treatment

10.2.5. Disable/Enable Trackers

This procedure is to be used when there is a trackers scan failure or the trackers results are wrong and as a consequence the system interprets it as transducer movement.

The default option is ON  therefore Calibrate stage will be done with trackers and also trackers scan will be performed before each sonication.

Click this button to change it to OFF .

10.2.6. Turn System Hardware On/Off

This procedure is to be used when the equipment cabinet computer must be restarted in the middle of the procedure.

Click  to turn off the ExAblate Neuro system; when the device shutdown is complete, the **Device Status** (in the status bar) appears as **Not** connected. Click  to turn on the ExAblate Neuro system; when the device is on, the **Device Status** (in the status bar) appears as **Ready**.

10.2.7. Connect/Disconnect to the Site Network

The MR system should be disconnected from the hospital network during a treatment. In case of an urgent need to transfer data, use this option to connect/disconnect the MR to the site network.

1. Click  to connect to the hospital network.
2. As soon as the data transfer is completed, click  to disconnect the MR from the site network and continue the treatment.

Caution



Do not treat the patient while the MR is connected to the hospital network

10.2.8. Operate Water System

This procedure is used when the water system needs to be switched to degassing mode (before treatment or DQA), needs to set to cleaning stage or needs to be restarted in the middle of the treatment.

Click  and choose the preferred option:

1. Turn on/off the water system; the status bar indicates when the shutdown is complete. Click again to turn on the water system; the status bar indicates when the water system is activated.
2. Set preparation stage – transferring the system to degassing mode before treatment or DQA
3. Set Cleaning stage – transferring the system to cleaning mode after treatment

The option of “Set treat stage” is automatically chosen when treatment begins

In addition, you can set preferred cooling temperature by entering the degrees to

Cool Temp. °C and press **Apply**.

10.2.9. Enable/Disable Water System Auto-Pause

This procedure is used to control the water circulation. Disable **Water System Auto-Pause**, mainly when you acquire images through the MR (e.g. post-treatment imaging).

Click  to manually control the water circulation. Click  to automatically pause the water circulation whenever MR scan is performed. This will be indicated in the status bar.

10.2.10. Movement Detection menu

1. To take new reference scans, select .
2. To disable\enable the feature, click  to Set Movement detection OFF or ON.
3. To check for a movement on next sonication click  and select “Movement on Next Sonication”.

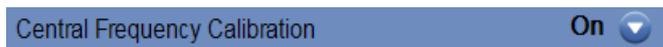
10.2.11. Change Calibration Mode

The calibration procedure is done automatically by the system.

This procedure is used when there is trackers scan failure or there is a need for wide imaging cover, when the narrow imaging cover of the default scan is not enough. The calibration can be set to a **Manual** mode by selecting it from the “Calibration mode” list.



10.2.12. Enable Central Frequency Manual Mode



Set this button to ON to enable the Image Central Frequency manual tool.

10.2.13. Enable Multi Echo Single Slice



Set this button to ON to enable using a scan type of Multi Echo for a single (“1”) slice. Otherwise, in OFF state the imaging option is set (by default) to use Single Echo scans.

10.2.14. Copyright Notice

Certain parts of this system may incorporate – or be distributed with – selected open-source software. Pressing the **Copyright Notice** button will open a Windows[®] text file listing such software.

10.3. EXIT UTILITIES

To leave **Utilities**, click  in the main toolbar; the system will return to the stage that was active prior to entering **Utilities**.

Chapter 11

Data Management

11.1. DATA MANAGEMENT OVERVIEW

Data Management provides the following options:

- Store treatment records
- Review treatment records
- Export treatment records to a CD-R or USB storage device
- Import treatment records from a CD-R or USB storage device

Note

This mode can be accessed only from the **Startup** screen and not during treatment by

clicking the **Data Management** button

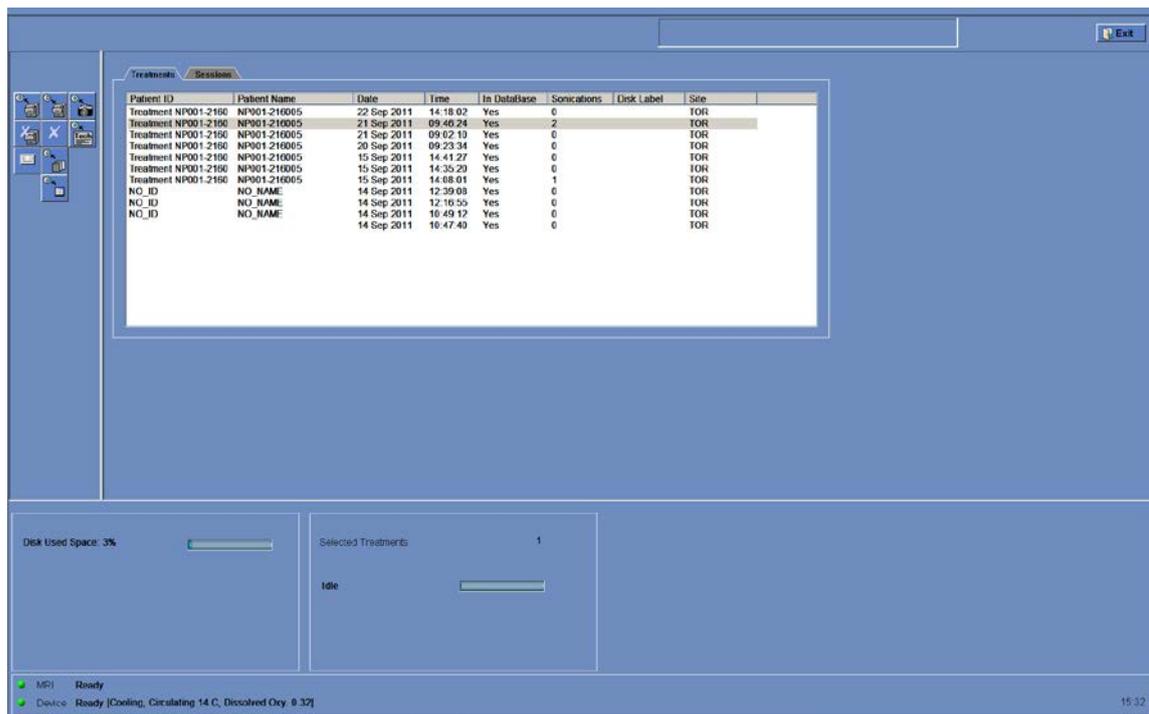


Figure 11-1: Data Management Screen

11.2. SELECTING A PATIENT

1. Click the **Patient ID** number to select the treatment record.
2. Hold down the **Shift** key to select a continuous list of patient IDs.

3. Hold down the **Ctrl** key to select specific patient IDs.

11.3. DATA MANAGEMENT ELEMENTS

11.3.1. Action Tools

The following commands appear on the **Data Management** screen (see Figure 11-1):

	Saved Treatments	Click this tab to view the saved treatments list.
	Saved Sessions	Click this tab to view the saved session's list.
	Export	Click this button to export all selected treatment records to the CD or USB device.
	Import	Click this button to import one or several treatment records that have been previously saved on a CD or USB device to the console, or treatments from another ExAblate Neuro console.
	Screen Dump	Click this button to send the snapshots associated with the selected treatments to the CD or USB device.
	Technical Export	Click this button to export technical log files to the CD or USB device.
	Replay	Click this button to access the Replay screen. Replay can be applied only if one treatment is selected.
	Get Images	Click this button to enter the Download MR Images dialog box. Images imported from the MR system can be copied using the ExAblate CD drive or USB storage device.

11.3.2. Export to CD or USB Storage Device

Export one or more treatment records to a CD-R as follows:

1. Insert a blank CD into the CD-R drive or connect a USB device.
2. Select a treatment or a set of treatments to export.

3. Click ; select **To CD/DVD** or **To USB** from the drop-down menu and click **OK** to start export. The system responds with the **Disk Label** dialog box (see Figure 11-2).
4. Type in a title for the disk/file and click **OK**.
5. Data will be exported to the CD or USB device. The export's progress can be viewed on the **Status Bar**.



Figure 11-2: CD Disk Label Dialog Box

6. The CD is automatically ejected from the CD-R drive when the data export is complete.

11.3.3. Import Treatment Records from CD or USB Storage Device

To import one or more treatment records:

1. Place the CD with the treatment files in the CD drive or connect the appropriate USB device.

2. Click ; select **From CD/DVD** or **From USB** from the drop-down menu;
3. The imported treatments will be copied to the local drive and will be shown in the Patient List.

11.3.4. Screen Dump to CD or USB Storage Device

To store snapshots associated with the selected treatment:

1. Insert a CD or connect a USB device.

2. Click ; select **To CD/DVD** or **To USB** from the drop-down menu.
3. The snapshots associated with the selected treatments will be copied to the selected storage option.

11.3.5. Technical Export to CD or USB Storage Device

Export one or more treatment technical log files to a CD or a USB device as follows:

1. Insert a blank CD into the CD-R drive or connect a USB device.

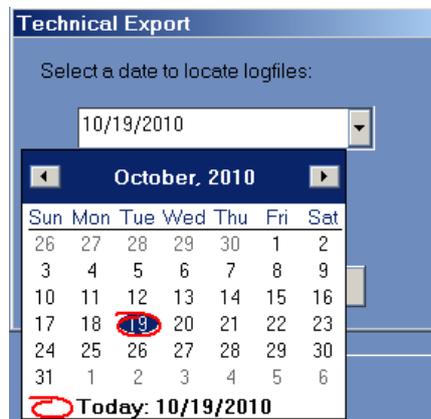


Figure 11-3: Technical Export Dialog Box

2. Click ; select To CD/DVD or To USB from the drop-down menu, and in the Technical Export dialog box select a date to locate log files and click OK to start the export.
3. Type in a title for the disk/file and click **OK**.

Technical data will be exported to the CD or USB device. The export progress can be viewed on the **Status Bar**.

11.3.6. Download MR images

The ExAblate Neuro system is equipped with a utility to export MR images to the CD or USB storage device.

To export MR images:

1. Click  and select **To CD/DVD** or **To USB** from the drop-down menu; the Download MR Images dialog box opens.
2. Select one exam from the Exam List; all relevant series will appear in Series List (this operation might take a while).
3. From the associated Series List select one or more series, using the Shift or Ctrl keys, or using the Select All option button.
4. Type in a new patient name and treatment ID or use the system default (patient's initials).

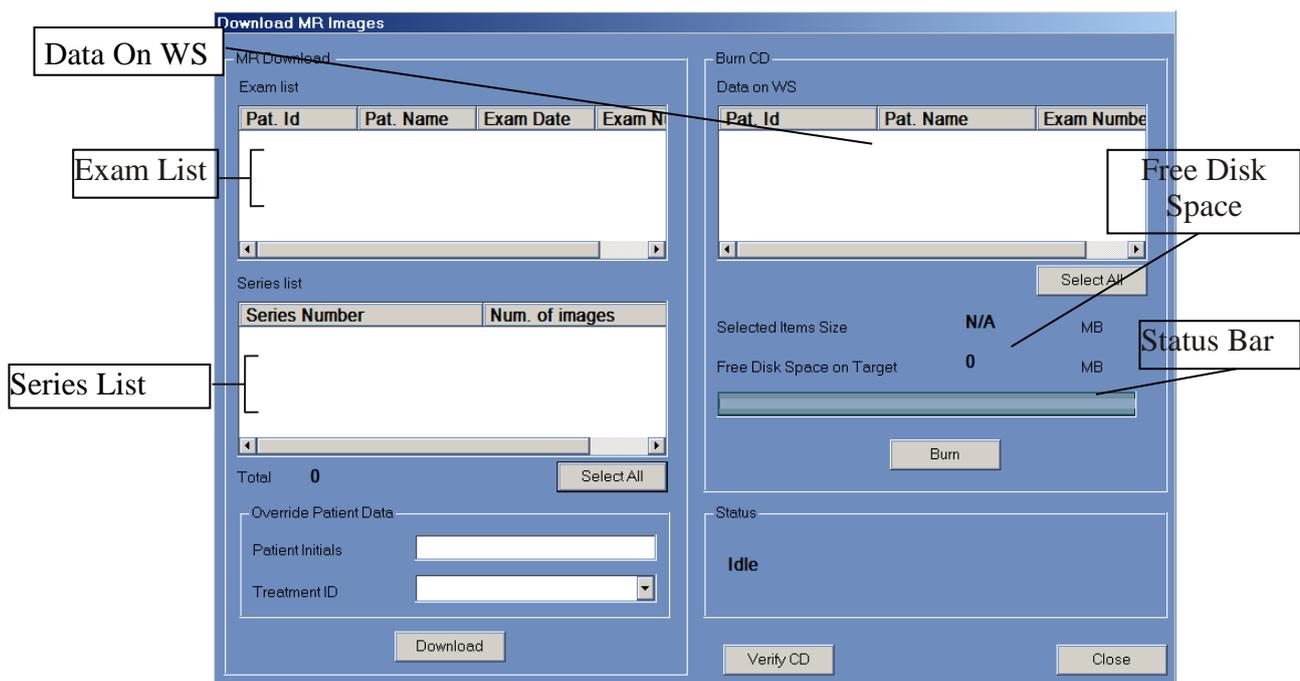
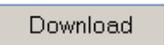
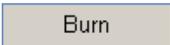


Figure 11-4: Download MR Images Screen

5. Click  to copy the images to the ExAblate Neuro system; the images will be stored on the work station and will appear in the Data on WS list.
6. Select the patients from Data on WS list and click  to export the images to the CD-R. The burning process can be viewed in the Status Bar.
7. The CD-R is automatically ejected from the CD drive when the data export is complete.

Note

The treatment files must come from an ExAblate Neuro console. When treatment files are recorded on a different console, the patient's name and ID are not displayed to retain privacy.

11.3.7. Export Summary File

Use this button to export a summary file of a selected treatment to a CD or USB device.

1. Select the treatment from the Patient list.

2. Click  and select **To CD/DVD** or **To USB** from the drop-down menu to create a treatment summary and export it.

11.4. EXIT DATA MANAGEMENT

To leave **Data Management**, click ; the system will return to the **Startup** screen.

APPENDIX A

Advanced Option Mode

A.1. Overview

Warning



Improper use of the **Advanced Option Mode** may degrade the quality of treatment and may even result in personal injury.

Advanced Option Mode enables the operator to override the automatically generated treatment plan and manually set the treatment parameters. This includes:

- Sonication parameters
- MR scan protocol parameters
- Adjusting Advanced Sonication Parameters
- Adjusting Acoustic Correction Parameters (**ACT**)

When you access the **Advanced Option** dialog box, all displayed values are the current treatment values.

To change a parameter:

1. Click the button next to the parameter to be changed or adjusted; the parameter's value text box is activated.
2. Type in or select the required value.
3. Click on:
 - **OK** to accept the changes
 - **Cancel** to reject all changes and close the dialog box
 - **Reset Values** to reset all changes

To return the parameter to system default:

1. Open the **Advanced Options** dialog box.
2. Click the box next to the parameter; the value text box is disabled and the value is automatically generated by the system.

Note

Manual changes made to parameters from the **Advanced Options** dialog box appear in the **Sonication Parameters** frame and the **Progress Parameters** frame in blue text.

A.2. Adjusting Sonication Parameters

The image shows a software dialog box titled "Advanced Options" with four tabs: "Sonication", "MR Scan", "Advanced", and "ACT". The "Sonication" tab is selected. The dialog is divided into three main sections:

- Sonication Parameters:** Contains four controls, each with a checkbox:
 - Acoustic Power: 36 W
 - Sonication Duration: 20 Sec.
 - Spot Type: Mode0 (dropdown menu)
 - Frequency: 0.710 MHz (dropdown menu)
- Thermal Dosimetry Parameters:** Contains one control with a checkbox:
 - Body Temperature: 37 °C
- Sonication Type:** Contains one control with a checkbox:
 - Sonication Type: Regular Sonication (dropdown menu)

At the bottom of the dialog are three buttons: "OK", "Reset Values", and "Cancel".

Figure A-1: Sonication Parameters Dialog Box

A.2.1. Changing Sonication Parameters

It is possible to change the following sonication parameters:

- duration
- Spot Acoustic power
- Sonication type
- Frequency
- Body temperature

- It is also possible to change the sonications type:
 - a. Regular Sonication
 - b. Spectrum receiver test (For verification of the cavitation mechanism)
 - c. Sham Sonication (if needed, for zero energy sonication)

Warning

Before applying each one of the Sham sonications, ensure that the sonication planned power value doesn't exceeds 1 Watt.

A.3. Adjusting MRI Scanning Protocol Parameters

Click the **MR Scan** tab to access the **MR Scan Parameters** dialog box.

Advanced Options

Sonication MR Scan **Advanced** ACT

Number of coil channels 1

Set central frequency Yes 127758342

MR Scanning Protocol

Protocol Name **TMAP3**

Profile		Settings	
Type	Single Echo	Pre sonication phases	1
Phase acquisition time	4 sec.	Post sonication phases	5
Images per phase/slice	3	CV thrctrl	29
Magnitude image index	1	CV rhtype	N/A
Real image index	2	External Trigger CV name	ext_trig
Imaginary image index	3	External Trigger CV Value	1
T1 magnitude index		Number of slices	1
Thickness	3.0 mm		
Spacing			

OK Reset Values Cancel

Figure A-2: MR Scan Parameters Dialog Box

A.3.1. Changing MR Parameters

1. Click the button next to Number of coil channels.
2. Select the number of coil channels.
3. Click the button next to Set Central Frequency.
4. Enable manual setting of MR central frequency to override automatic feature values.
5. Select a MR Scanning **Protocol**:
 - Select from the **Thermal Mapping Protocol** list in the pull-down menu.
 - Create a new thermal mapping PSD. Type the new protocol name in the **Protocol Name** text box.
 - The parameters of the selected protocol appear automatically. If a user protocol is created, manually set all values for the protocol profile.

Note

Ensure that the user-defined protocol profile is correct and complete.

A.3.2. Profile Parameters Elements

- **Type**

Select the sequence type: **Dual Echo**, **Single Echo**, or **EPI**.
- **Phase Acquisition Time**

The MR performs a single scan under the selected protocol in this time span.
- **Images per Phase**

This sets the number of images created by the MR for each phase.
- **Magnitude Image Index**

Determines which image in a series is the magnitude image.
- **Real Image Index**

Determines which image in a series is the real image.
- **Imaginary Image Index**

Determines which image in a series is the imaginary image.

- **T1 Magnitude Index**

For dual echo sequences, determines which image in a series is the echo 1 magnitude image.

- **Thickness**

For **EPI** sequences, determines the slice thickness.

- **Spacing**

For **EPI** sequences, determines the slice spacing.

A.3.2.1. Parameter Settings

- **Pre-Sonication Phase**

Use **Pre-Sonication Phase** to determine the number of “cold phases” created by the system before each sonication.

- **Post-Sonication Phase**

Use the **Post-Sonication Phase** to determine the number of cooling phases the system scans after each sonication.

- **CV rhrcctrl**

This defines the image types reconstructed for each phase. For reconstructing magnitude, real and imaginary images, use a value of **29**.

- **CV rhtype**

For **EPI** sequences, use a value of **8**. This applies only to **EPI** sequences.

- **External Trigger CV Name**

This defines the name of the external trigger.

- **External Trigger CV Value**

For sequences with the **ext_trig CV**, use a value of **1**.

For sequences **without** the **ext_trig CV**, use a value of **0**.

- **Number of Slices**

For multi-slice **EPI** thermal imaging, defines the number of slices per sonication.

A.4, Adjusting Advanced Sonication Parameters

Click the **Advanced** tab to access the **Advanced** dialog box.

Advanced Options

Sonication **MR Scan** **Advanced** **ACT**

Sonication Parameters

Sonication Focal Coordinates

RAS R A S

XYZ X Y Z

Thermal Scan Shift

Axial mm

Coronal mm

Sagittal mm

Thermal Dosimetry Parameters

Tissue Coefficient

Nominal Dose Threshold

OK Reset Values Cancel

Figure A-3: Advanced Sonication Parameters Dialog Box

A.4.1. Sonication Parameters

This defines the sonication focal point in RAS Coordinates. Click the button next to **Sonication Focal Coordinates**, and then **RAS** or **XYZ** to change the focal spot location in the selected coordinates.

A.4.2. Changing Thermal Scan Shift

This defines the sonication **Scan** shift in each scan orientation. Click the button next to **Axial**, **Coronal** and **Sagittal**. Then enter the shift value in **mm**.

A.4.3. Changing Thermal Dosimetry Parameters

- **Tissue Coefficient**

This defines the co-efficient of the tissue for temperature maps calculations. For soft tissue, use a value of **0.00909**.

- **Nominal Dose Threshold**

This defines the time in minutes to achieve a thermal dose at 43°C. The nominal threshold value is **240** minutes.

A.5 Adjusting Acoustic Correction Parameters (ACT)

Click the **ACT** tab to access the **ACT** dialog box.

Advanced Options

Sonication MR Scan **Advanced** ACT

ACT File ...

Skull Correction Parameters

Geometric Thresholds

External Angle ° Alg. Criteria ° Ray Shift mm

Ext. Angle Above Threshold Ext. Angle Above Threshold Skull Thickness mm

External/Internal Angle Diff ° Air in Skull mm

Speed of sound

Water m/s Brain m/s

Skull Longitudinal Wave $f(I=CT \text{ Intensity})$ I min V(I min) m/s

$\times I^2$ $\times I$ m/s

Skull Shear Wave $f(I=CT \text{ Intensity})$ I min V(I min) m/s

$\times I^2$ $\times I$ m/s

Sampling parameters

Surface sample mm

Density sample mm

Sample

Skull threshold

Save slices

Skull Heating Algorithm

Power Maximum external ° C

Maximum internal ° C

OK Reset Values Cancel

Figure A-4: Acoustic Correction Parameters Dialog Box

A.5.1. Changing ACT

The **ACT** file determines the amplitudes and the phases of the transducer elements. Click the button next to **ACT File** to load new **ACT** file. Click  to open the file browser, and select the required **ACT** file.

A.5.2. Changing Skull Correction Parameters

The skull correction parameters are used for the acoustic and thermal calculations. Click the button next to **Skull Correction Parameters** to set these parameters.

A.5.2.1. Geometric Thresholds

- **External Angle** (degrees): this threshold defines the transducer element's sound wave or controls the element state according to the **External Angle Above Threshold** key, as follows:
 - **Disable** – element with **External Angle** above this threshold is turned off.
 - **Use shear-wave velocity** – the sound wave of the elements with **External Angle** below this threshold is **Longitudinal**; otherwise it is **Shear**.
- **Algorithm Criteria** (degrees) – this threshold defines the model for the ray path in the tissue. If the external angle of the ray is above the **Algorithm Criteria** value, the ray will be refracted.
- **External and Internal Difference** (degrees) – if the **External and Internal Difference** is above this threshold, the transducer's element is turned off.
- **Ray Shift** (mm) – if the **Ray Shift** is above this threshold, the transducer's element is turned off.
- **Skull Thickness** (mm) – if the **Skull Thickness** is above this threshold, the transducer's element is turned off.
- **Air in Skull** (mm) – if the **Air in Skull** is above this threshold, the transducer's element is turned off.

A.5.2.2. Speed of Sound

- **Water** (m/sec) – defines the speed of sound in the water.
- **Brain** (m/sec) – defines the speed of sound in the brain soft tissue.
- **Skull** (m/sec) – defines the speed of sound in the skull as a function of the CT intensity: $aI^2 + bI + c$ (**a**, **b** and **c** are the coefficients. **I** is the CT intensity).

- **I min** – defines the CT intensity threshold that below it, the speed of sound in skull is equal to **V(I min)**.
- The first set of co-efficient and minimal values is for the **Longitudinal** wave and second is for the **Shear** wave.

Note

- The sound wave is defined as **Longitudinal**, if the **External Angle** was below the threshold value. **Otherwise**, it is defined as **Shear**.
- Do not change the **Sampling Parameters** values.

A.5.3. Changing the Skull-Heating Algorithm

Skull heating is an algorithm for temperature calculations near the skull during the sonication. The skull-heating algorithm determines the power distribution of the transducer elements. Click the button next to **Skull Heating Algorithm** to select one of the following options:

- **Disable Skull Heating** – for not using this algorithm
- **Uniform Intensity - display temperature only** – for uniform power distribution of the elements. The temperatures near skull will be displayed and won't affect the power.
- **Uniform Intensity - modify sonication power** – for uniform power distribution of the elements. If the temperatures near skull are above pre-defined thresholds, the power is cut off.
- **Distributed Intensity - display temperature only** – for **non**-uniform power distribution of the elements depends on the temperatures near skull.
- **Distributed Intensity - modify sonication power** – for **non**-uniform power distribution of the elements depends on the temperatures near skull. If the temperatures near skull are above pre-defined thresholds, the power is cut off.
- **Uniform Intensity on skull - display temperature only** – for power distribution of the elements depends on uniform intensity on skull.

If required, change the following thermal parameters that are part of the skull-heating algorithm:

- **Maximum External** – defines the external temperature threshold
- **Maximum Internal** – defines the internal temperature threshold
- **Water** – defines the temperature of bath

APPENDIX B

Treatment Preparation

B.1. Overview

The **Treatment Plan** can be performed prior to treatment day (offline) and has several objectives:

- Load or scan high quality (head coil) images for treatment planning and reference during treatment
- Analyze and consider the techno-clinical parameters of the specific case
- Perform tasks that can be performed prior to the treatment and make the treatment timeline more efficient. Typically, tasks such as:
 - Loading CT images
 - Scanning CT images for clips, scars or anything that may affect the treatment plan
 - Loading of high quality MR contrast images
 - NPR drawing
 - Target delineation, assessment of patient and transducer positioning

The **Treatment Plan** option can be prepared under **PREPERATION** stage on the main entrance screen and allows you to load Pre-Op imaging data (live or scanned) and to plan the treatment.

The **PREPERATION** stage allows you to review and edit **Treatment Plan** after it was saved.

B.2. Pre Treatment Plan

B.2.1. PREPERATION Screen

The Pre-Treatment Plan session consists of the same stages as in **TREATMENT (Imaging, Planning, and Treatment)**.

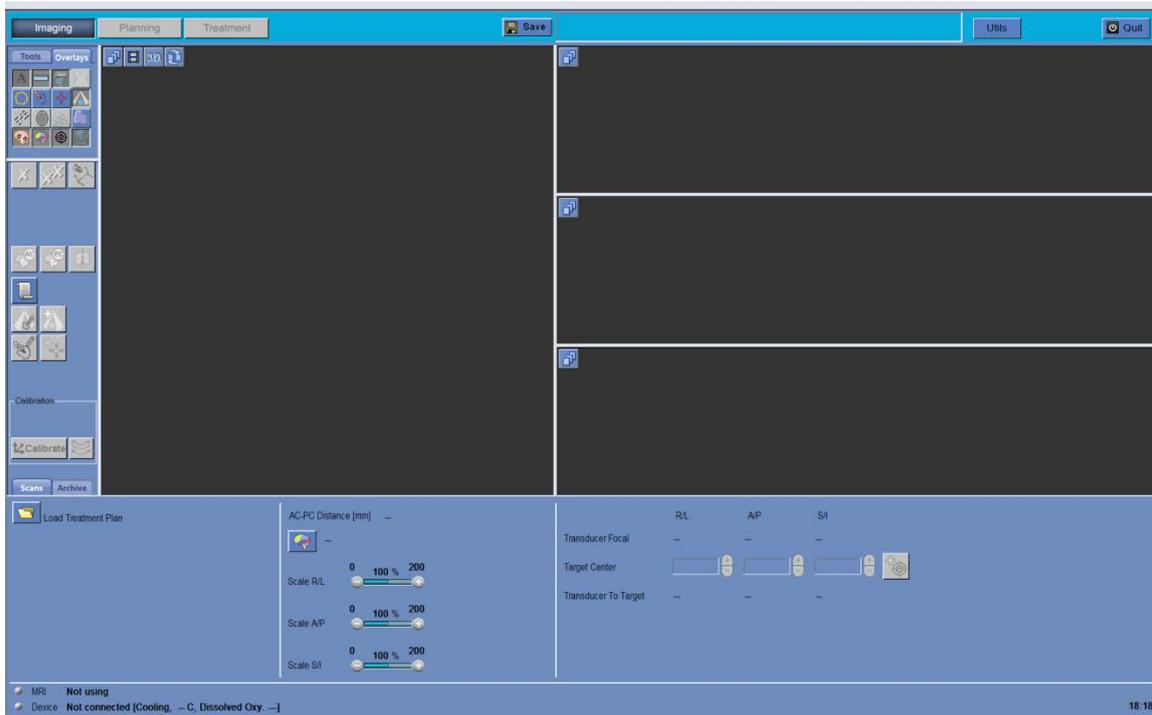


Figure B-1: Preparations Screen

B.2.2. Pre Treatment Session Procedure

Note

During the PREPARATION sessions there is no need for water filling in the interface or connecting the device to the table. Therefore, the **Device** status is not relevant to the sessions' procedures and there is no need to connect the MR scanner as well. Therefore, the **MR Status** has no effect on the **Treatment Plan** procedure.

1. Turn on the system (See Chapter 3, Section 3.1, steps 1-2, 5-8).
2. If the session is done with a patient, position the patient on the treatment table (See Chapter 3, Section 3.2.1, steps 1-7). If a patient is not present, make sure pre-operative data is located on the MR or on CD/USB.

3. Click  on the **Start-Up** screen and enter **Imaging** stage.

4. If a patient is attendant:

Scan 3D localizer images.

Follow the procedure of acquiring planning images using the AC-PC mechanism (see Section 6.6) or alternatively acquire the planning images on the MR console (see Section 6.7)

If the session is done without a patient:

- On the MR console, choose the exam with the relevant pre-operative images
 - Enter the  tab (Figure 6-6)
 - Upload Prior MR Exam:
 - Click  button; the system will prompt you to select a previously stored exam from the MR workstation browser.
 - Review the series of exams stored in the MR workstation and select the desired one by clicking on it. Click **OK** in the dialog box that appears on the ExAblate workstation. The selected exam will be added to the **Exam List**
 - The series numbers and types appear in the **Series List**.
 - The selected series will appear on the *Selected Images Section*.
 - To change the selection, click  and select a different set of images. These images replace the previously selected ones.
 - Upload CT images exam:
 - Click the  button; the system will prompt to select a stored CT exam from the ExAblate Neuro workstation or from the MR:
 - To select CT images from the console, click **Browse CD** and select the desired CT images directory in browser.
 - To select CT images from MR, first select the desired exam from the MR workstation (by clicking on it). Then click **MR Archive** in the dialog box that appears on the ExAblate workstation.
 - The CT exam information appears in the **CT Exam** frame. Verify that the correct images are used.
 - Click on the  button to upload and display the selected images.
5. Locate the transducer in the optimal location for the relevant target. When the transducer template is in place, click  to set the transducer's home position.

6. Switch to Planning Stage and perform the Registration procedure (CT-MR) as described in Section 7.2.
7. Draw the relevant NPRs as described on the procedure in Section 6.12.
8. Switch to Treatment Stage. Add new spot at the target and calculate the spot's technical parameters through the Transducer's Element frame, as described in Section 8.2.7.
9. Click  to save the **Pre-Treatment Plan** session.
10. Release the patient (if attendant).

Note

To upload a **Pre-Treatment Plan** session that was saved to the system for an offline editing (not under TREATMENT), enter the  screen, click the  button and select the relevant session.

Appendix C

Full ExAblate 4000 Accessory List

Table 1 - Full ExAblate 4000 Accessory List

NAME	P/N	DESCRIPTION
EXABLATE NEURO ACCESSORIES SET		
3.0T Neuro Patient Accessory Set	SET000902	The Accessory Kit includes the following items: A DQA gel, 1 helmet sealant tube, a cleaning kit , 5 protective frame pin caps, 4 Long Stereotactic Frame Pins Set and a 3.0T Silicone Membrane.
EXABLATE NEURO NECESSARY ACCESSORIES		
Neuro Patient Accessory Kit	SET400173	The Accessory Kit includes the following items: A DQA gel, 1 helmet sealant tube, a cleaning kit and 5 protective frame pin caps.
Emergency Drain Kit	SET00174	Used to manually drain water from transducer in the event of Mains power loss during procedure.
DQA SETUP KIT	SET000884/ASM001507	DQA setup is used as part of Daily Quality Assurance procedure for 3T.
Coil Holder Setup	ASM001517	For assembly of ASM002258 (see below) on DQA setup, to allow QA for specific Head coil.
Long Stereotactic Frame Pins Set	MPR000444	For Stereotactic frame fixation.
EXABLATE NEURO DISPOSABLES		
DQA Gel	SET000893	Tissue mimicking phantom gel, used for Daily Quality Assurance (DQA).
Protective Frame Pin Caps	MPR001164	Silicone protective caps used to cover the frame pins, for membrane protection. For single use. Supplied in groups of 5 units.
Helmet Sealant	BUY000180-AA	Tube containing sealant material for water-tight coupling to the transducer. For single-use.
Cleaning Kit	SET000870	A set of products used for cleaning the system after each treatment. For single-use.
Short Stereotactic Frame Pins Set	MPR000445	For stereotactic frame fixation.
Silicone Membrane	ASM000355	For coupling of patient head to FUS helmet. Allows multiple uses. For use only with a 3.0T MRI.
EXABLATE NEURO SPARE PARTS		
Stereotactic Frame Set	SET400168	The stereotactic Frame set includes the Stereotactic Frame, posts, screws, wrench and a case. One set is supplied with the system.
Stereotactic Frame	ASM001399	Stereotactic head frame, including adapters to ExAblate 4000 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 ASM001396 ASM001397	A part of the stereotactic head frame set. Includes 4 Posts (with separate P/N). One set is supplied with the system.

	ASM001398	
Stereotactic Frame Cross Bar	NO PN yet, Part of BUY40001	Enables alternate positioning of stereotactic head frame screws.
Frame Attachment Strap	MEC001647	Assists with stereotactic frame placement.

APPENDIX D

Guidance and Manufacturer's Declaration on Electromagnetic Compatibility

Table 1 – Guidance and MANUFACTURER’S declaration – ELECTROMAGNETIC EMISSIONS

Guidance and manufacturer’s declaration – electromagnetic emissions		
The ExAblate 4000 Medical System is intended for use in the electromagnetic environment specified below. The customer or the user of the ExAblate 4000 Medical System should assure that it is used in such an environment.		
Emissions test	Compliance	Electromagnetic environment – guidance
RF emissions CISPR 11	Group 1	The ExAblate 4000 Medical System uses RF energy only for its internal function. Therefore, its RF emissions are very low and are not likely to cause any interference in nearby electronic equipment.
RF emissions CISPR 11	Class A	
Harmonic emissions IEC 61000-3-2	Not applicable	
Voltage fluctuations/ flicker emissions IEC 61000-3-3	Not applicable	
	[See 5.2.2.1 c) and Figure 1]	<p>The ExAblate 4000 Medical System is suitable for use in all establishments other than domestic, and may be used in domestic establishments and those directly connected to the public low-voltage power supply network that supplies buildings used for domestic purposes, provided the following warning is heeded:</p> <p>Warning: This equipment/system is intended for use by healthcare professionals only. This equipment/ system may cause radio interference or may disrupt the operation of nearby equipment.</p> <p>It may be necessary to take mitigation measures, such as re-orienting or relocating the ExAblate 4000 Medical System or shielding the location.</p>

Table 2 – Guidance and MANUFACTURER'S declaration – electromagnetic IMMUNITY

Guidance and manufacturer's declaration – electromagnetic immunity			
The ExAblate 4000 Medical System is intended for use in the electromagnetic environment specified below. The customer or the user of the ExAblate 4000 Medical System should assure that it is used in such an environment.			
IMMUNITY test	IEC 60601 test level	Compliance level	Electromagnetic environment – guidance
Electrostatic discharge (ESD) IEC 61000-4-2	± 6 kV contact ± 8 kV air	± 6 kV contact ± 8 kV air	Floors should be wood, concrete or ceramic tile. If floors are covered with synthetic material, the relative humidity should be at least 30 %.
Electrical fast transient/burst IEC 61000-4-4	± 2 kV for power supply lines ± 1 kV for input/output lines	± 2 kV for power supply lines ± 1 kV for input/output lines	Mains power quality should be that of a typical commercial or hospital environment.
Surge IEC 61000-4-5	± 1 kV line(s) to line(s) ± 2 kV line(s) to earth	± 1 kV line(s) to line(s) ± 2 kV line(s) to earth	Mains power quality should be that of a typical commercial or hospital environment.
Voltage dips, short interruptions and voltage variations on power supply input lines IEC 61000-4-11	<5 % U_T (>95 % dip in U_T) for 0,5 cycle 40 % U_T (60 % dip in U_T) for 5 cycles 70 % U_T (30 % dip in U_T) for 25 cycles <5 % U_T (>95 % dip in U_T) for 5 s	N/A	Mains power quality should be that of a typical commercial or hospital environment. If the user of the ExAblate 4000 Medical System requires continued operation during power mains interruptions, it is recommended that the ExAblate 4000 Medical System be powered from an uninterruptible power supply or a battery.
Power frequency (50/60 Hz) magnetic field IEC 61000-4-8	3 A/m	3 A/m	Power frequency magnetic fields should be at levels characteristic of a typical location in a typical commercial or hospital environment.
NOTE U_T is the a.c. mains voltage prior to application of the test level.			

Table 3 – Guidance and MANUFACTURER'S declaration – electromagnetic IMMUNITY

Guidance and manufacturer's declaration – electromagnetic immunity			
The ExAblate 4000 Medical System is intended for use in the electromagnetic environment specified below. The customer or the user of the ExAblate 4000 Medical System should assure that it is used in such an environment.			
IMMUNITY test	IEC 60601 TEST LEVEL	Compliance level	Electromagnetic environment – guidance
<p>Conducted RF IEC 61000-4-6</p> <p>Radiated RF IEC 61000-4-3</p>	<p>3 Vrms 150 kHz to 80 MHz</p> <p>3 V/m 80 MHz to 2,5 GHz</p>	<p>3 Vrms 150 kHz to 80 MHz</p> <p>3 V/m 80 MHz to 2,5 GHz</p>	<p>Portable and mobile RF communications equipment should be used no closer to any part of the ExAblate 4000 Medical System, including cables, than the recommended separation distance calculated from the equation applicable to the frequency of the transmitter.</p> <p>Recommended separation distance</p> $d = \left[\frac{3,5}{V_1} \right] \sqrt{P}$ $d = \left[\frac{3,5}{E_1} \right] \sqrt{P} \quad 80 \text{ MHz to } 800 \text{ MHz}$ $d = \left[\frac{7}{E_1} \right] \sqrt{P} \quad 800 \text{ MHz to } 2,5 \text{ GHz}$ <p>where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer and d is the recommended separation distance in metres (m).</p> <p>Field strengths from fixed RF transmitters, as determined by an electromagnetic site survey, should be less than the compliance level in each frequency range.</p> <p>Interference may occur in the vicinity of equipment marked with the following symbol:</p> 
<p>NOTE 1 At 80 MHz and 800 MHz, the higher frequency range applies.</p> <p>NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.</p>			
<p>a Field strengths from fixed transmitters, such as base stations for radio (cellular/cordless) telephones and land mobile radios, amateur radio, AM and FM radio broadcast and TV broadcast cannot be predicted theoretically with accuracy. To assess the electromagnetic environment due to fixed RF transmitters, an electromagnetic site survey should be considered. If the measured field strength in the location in which the ExAblate 4000 Medical System is used exceeds the applicable RF compliance level above, the ExAblate 4000 Medical System should be observed to verify normal operation. If abnormal performance is observed, additional measures may be necessary, such as re-orienting or relocating the ExAblate 4000 Medical System. b Over the frequency range 150 kHz to 80 MHz, field strengths should be less than [V1] V/m.</p>			

Table 4 – Recommended separation distances between portable and mobile RF communications equipment and the ExAblate 4000

Recommended separation distances between portable and mobile RF communications equipment and the ExAblate 4000 Medical System			
The ExAblate 4000 Medical System is intended for use in an electromagnetic environment in which radiated RF disturbances are controlled. The customer or the user of the ExAblate 4000 Medical System can help prevent electromagnetic interference by maintaining a minimum distance between portable and mobile RF communications equipment (transmitters) and the ExAblate 4000 Medical System as recommended below, according to the maximum output power of the communications equipment.			
Rated maximum output power of transmitter W	Separation distance according to frequency of transmitter m		
	150 kHz to 80 MHz $d = \left[\frac{3,5}{V_1}\right]\sqrt{P}$	80 MHz to 800 MHz $d = \left[\frac{3,5}{E_1}\right]\sqrt{P}$	800 MHz to 2,5 GHz $d = \left[\frac{7}{E_1}\right]\sqrt{P}$
0,01	0.12	0.12	0.24
0,1	0.37	0.37	0.74
1	1.17	1.17	2.34
10	3.7	3.7	7.4
100	11.7	11.7	23.4
For transmitters rated at a maximum output power not listed above, the recommended separation distance d in metres (m) can be estimated using the equation applicable to the frequency of the transmitter, where P is the maximum output power rating of the transmitter in watts (W) according to the transmitter manufacturer. NOTE 1 At 80 MHz and 800 MHz, the separation distance for the higher frequency range applies. NOTE 2 These guidelines may not apply in all situations. Electromagnetic propagation is affected by absorption and reflection from structures, objects and people.			