INSIGHTEC

# Exablate Neuro

## For Neurological Disorders

## INFORMATION FOR PRESCRIBERS

September 2023

Exablate 4000 Cradle Type 1.0 and 1.1, Information for Prescribers, PUB41008291, Revision 2

**This document is based on the English source PUB41008291, Revision 2 (in the target language)**

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**InSightec, Ltd.**

5 Nachum Heth St. PO Box 2059
Tirat Carmel 39120 Israel
www.insightec.com

CE 0344

EC REP Obelis s.a.
Bd. General Wahis 53,
1030 Brussels, Belgium

**The Exablate Transcranial MR guided focused ultrasound system described in this document is also referred to as Exablate 4000 or Exablate Neuro**

**Warning**

**Treating physician must be trained and certified by local law for performing neurosurgical procedures.**

**The device is restricted to the use of a physician trained in MRI and who has completed training in the use of the device.**

**The Exablate device requires preventive maintenance that can only be performed by INSIGHTEC or INSIGHTEC's certified providers. The device should not be operated if the required maintenance is not performed.**

**If the device is not functioning appropriately, do not use and notify INSIGHTEC to determine if the device can be used or if it requires servicing by INSIGHTEC prior to use.**

**Using the device when not under valid maintenance may result in serious injury.**

**Read all instructions, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, prior to use. Failure to follow these instructions could result in serious patient injury.**

**Specialized 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 the required certification.**

**This document and instructions are not to be used in the United States of America.**

# Table of content

# CHAPTER 1: OVERVIEW

## 1.1. Device Description

InSightec's Exablate Neuro delivers focused ultrasound energy into a focal a brain tissue through an intact skull. 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 focused ultrasound system operates inside a Magnetic Resonance Imaging (MRI) scanner. The MRI provides images of the patient's anatomy that are used to define the target area and plan the treatment. During the procedure, the MR images are used by the Exablate system to create a real-time thermal map for monitoring of the thermal rise.

| Table 1: Exablate system configuration | |
|---|---|
| Generic name | MRgFUS |
| Trade Name | Exablate Neuro |
| Model | 4000 |
| Cradle Type | 1.0 and 1.1 |
| Application | Neuro |

## 1.2. Intended Purpose

Exablate System 4000 transcranial MR guided focused ultrasound system (Type 1.0 and Type 1.1) is intended for thermal ablation of targets in the thalamus, sub thalamus and pallidum regions of the brain using thermal focused ultrasound energy under full MR planning and thermal imaging control, for the treatment of Essential Tremor (unilateral and/or staged bilateral treatments), Idiopathic Parkinson's Disease (unilateral treatments), and Neuropathic Pain.

## 1.3. Target Group

Patients suffering from neurological disorders as Essential Tremor, Idiopathic Parkinson's disease, or Neuropathic Pain.

# CHAPTER 2: PATIENT SELECTION CRITERIA

## 2.1. Patient Selection Criteria

- Patient is able to undergo a high-resolution CT scan
- Patient is able to fit into MRI unit and comply with all contraindications for the specific MR system including and limited to contrast medium should there be needed.
- The thalamus, sub-thalamus and the pallidum must be apparent on MR imaging.
- Patient is able to communicate sensations to the physician during the procedure; Procedure does not require general anesthesia.
- Patient must be able to use the Stop Sonication button freely.
- Patient must be shaved prior to the actual treatment.
- Patient has no history for claustrophobia which is not responding to medications.
- For Parkinson's disease patient with motor symptoms and dyskinesia:
    - Patient is Levodopa responsive, having at least a 30% reduction in MDS-UPDRS motor subscale in the ON vs OFF medication state
- Patient intended for a staged bilateral treatment should have at least 9 months period from previous treatment (relevant only for thalamotomy performed for essential tremor).

## 2.2. Contraindications

- Patients with MRI related contraindications (e.g. presence of metallic implants incompatibility with MRI, severe claustrophobia, reaction to contrast medium)
- Patients in whom it is not possible to avoid energy absorbing structures or sensitive tissues (e.g., skull implants, surgical clips, shunts, electrodes, dura patch, skull patch, electrodes, etc.) from the path of the ultrasound beam
- Patients with concurrent active infections disease and/or severe allergies with fever
- Patients that have been diagnosed with brain tumors or a vascular anomaly

- Patients with a history of seizures, brain hemorrhages, stroke within the past year, or any coagulopathy
- Patients under anticoagulants and/or anti-platelets drugs known to increase bleeding risk within the duration defined by the half-life of the specific drugs.
- Patient that has been given any contrast agent (e.g., CT, MRI), within 24 hours before treatment
- Severe unstable hypertension that cannot be controlled by medications (diastolic BP > 100 on medication)
- Patients with unstable cardiac status
- Patients exhibiting any behavior(s) consistent with ethanol or substance abuse
- Cerebrovascular disease (multiple CVA or CVA within 6 months)
- Patients with risk factors for intraoperative or postoperative bleeding
- Imaging show abnormal finding in CT or/and MRI (e.g., brain tumor, brain vascular malformation, shunt, etc.)
- For Parkinson's disease patient with motor symptoms and dyskinesia:
    - Hoehn and Yahr stage in the ON medication is of state of 3 or greater
    - Presence of significant cognitive impairment using MMSE ≤ 24
    - Patient with unstable psychiatric disease, defined as active uncontrolled depressive symptoms, psychosis, delusions, hallucinations, or suicidal ideation and is not stable on antidepressant medications for at least 3 months.
- For patients intended for a staged Bilateral Essential Tremor treatment:
    - Patient has physical subscale score ≥ 16.5 on the Dysphagia Handicap Index or has been diagnosed with dysphagia
    - Patient has score <22 on the Montreal Cognitive Assessment (MoCA)
    - Patient with clinically significant abnormal speech function as determined by a speech pathologist

## 2.3. Warnings

**Note**: For precautions and warnings regarding the technical operation of the Exablate system refer to the Operator's Manual.

- Prolonged immobilization may lead to increased risk of deep venous thrombosis (DVT) or pulmonary embolism (PE). To avoid this, exclude patients where this

risk cannot be mitigated, and treated patients should be wearing compression stockings through the entire procedure time in the MRI

- Incorrect target determination may lead to treatment failure and side effects. It is important to monitor real time feedback from the patient and the system throughout treatment, to confirm the target location and adjust it, if needed.
- Ensure that the transducer interface is filled completely with water without air bubbles to provide adequate acoustic coupling and that the transducer and head frame are mechanically secured in place.
- Ensure that the patient can activate the Stop Sonication button before initiating treatment. In the event of pain, failure to do so may result in injury
- Ensure that the patient's scalp is shaved well, and that any scars or scalp lesions are marked for avoidance in the treatment beam path to minimize heating/burning at the scalp.
- A CT must be performed prior to this procedure to identify skull parameters and calcifications in the treatment path. These images are loaded into the MR unit and synched with real-time MR images.
- 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 is not available or not reliable.
- Ensure that only degassed water is used in the circulating area between the transducer and the patient's skull to avoid air bubbles in the system which might result in skin burn.
- 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, bone tissue and 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).

# CHAPTER 3: ANTICIPATED SIDE EFFECTS

The frequent anticipated potential side effects that might occur after MRgFUS treatment are: Gait disturbance (imbalance / ataxia /unsteadiness), dysmetria, dizziness/ fatigue, sensory disturbance as paresthesia, speech disturbance (dysarthria), swallowing or taste disturbance (dysphagia / hypogeusia/dysgeusia) and weakness.

Summary of safety events from clinical studies and post marketing surveillance data is presented in Chapter 4.

# CHAPTER 4: EXPECTED CLINICAL BENEFITS

The expected clinical benefit in Essential Tremor and Tremor Dominant idiopathic Parkinson's Disease is tremor relief, in Parkinson's Disease pallidotomy – tremor relief, reduction in muscle rigidity and in Neuropathic pain is pain relief. The information presented in this chapter is derived from clinical studies and post marketing surveillance data, describes its efficacy, safety and durability.

## 4.1. Essential Tremor

### 4.1.1. Pivotal Clinical Study

Study Design – a prospective, randomized, double-blind, 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.

Study included 76 qualified subjects with idiopathic medication-refractory Essential Tremor that were randomized at a 3:1 ratio to either Exablate treatment arm (56 patients) or sham control arm (20 patients).

Study Endpoints –

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

***Effectiveness Endpoint:*** The effectiveness was evaluated using a validated, tremor rating scale: the Clinical Rating Scale for Tremors (CRST) for ET subjects. The Tremor assessments was done by CRST Part A & B. In addition, the Durability (as measured by CRST upper arm extremity questions) and the subject daily functionalities (as measured by CRST Part-C) were also followed during the study.

Study Results – [1]

***Safety Results:*** Overall, the summary of safety demonstrated that no Serious or Life-threatening events related to device or procedure occurred. There were no unanticipated adverse device events reported, for the either the Exablate group or the Sham group, during the pivotal study.

For the patients under the "Exablate group", adverse events included gait disturbance in 36% of patients and paresthesia or numbness in 38%; these adverse events persisted at 12 months in 9% and 14% of patients, respectively. Gait disturbances also occurred, with ataxia noted on postoperative neurologic examination (in 20%) and at 12 months (in 4%).

One patient had a transient ischemic attack 6 weeks after undergoing thalamotomy that was deemed Unrelated to the Exablate procedure.

Detailed list of all adverse event appears in **Table 2**:

| Adverse Event | | FUS Thalamotomy Procedure (N = 56) | | | | Sham (N = 20) |
|---|---|---|---|---|---|---|
| | | Immediate | 7 Days | 3 Months | 12 Months | Immediate |
| | | *Number of patients (percent)* | | | | |
| Paresthesia or numbness | Both face and hand | 6 (11%) | 5 | 5 | 5 (9%) | |
| | Face, lips, and tongue | 8 (14%) | 6 | 6 | 2 (4%) | |
| | Hand and fingers | 6 (11%) | 5 | 2 | 1 (2%) | 1 (5%) |
| | Leg | 1 (2%) | 1 | 1 | | |
| Taste disturbance | | 3 (5%) | 2 | 2 | 2 (4%) | |
| Gait disturbance | Ataxia, noted objectively on examination | 11 (20%) | 10 | 2 | 2 (4%) | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | "Unsteady" or "unbalanced," reported subjectively | 9 (16%) | 8 | 7 | 3 (5%) | 1 (5%) |
| Dysmetria, limb | | 7 (12%) | 7 | 5 | 2 (4%) | |
| Weakness, contralateral | | 2 (4%) | 2 | 2 | 1 (2%) | |
| Dysarthria | | 1 (2%) | 1 | 1 | | |
| Dysphagia | | 1 (2%) | 1 | 1 | | |
| Headache lasting >1 day | | 8 (14%) | 4 | 2 | | 4 (20%) |
| Fatigue | | 3 (5%) | 3 | 1 | | 1 (5%) |
| Disequilibrium sensation | | 5 (9%) | 5 | 3 | 1 (2%) | |
| Tinnitus | | 3 (5%) | 3 | | | |
| Intraprocedural sensations or events | Head discomfort: "heat" or "pressure" | 17 (30%) | | | | |
| | Vertigo: "dizzy" | 12 (21%) | | | | |
| | Nausea | 11 (20%) | | | | 2 (10%) |
| | Vomiting | 2 (4%) | | | | |
| | Scalp tingling | 4 (7%) | | | | 1 (5%) |
| | Back pain | 5 (9%) | | | | 1 (5%) |
| | Anxiety | 3 (5%) | | | | 2 (10%) |
| | Pin-site pain, edema, or bruising attributable to placement of the stereotactic frame | 17 (30%) | | | | 7 (35%) |

***Table 2: adverse events reported in the pivotal study up to 12 months***

***Efficacy results***: The mean score for hand tremor (highest possible score, 32) improved by 47% at 3 months in the thalamotomy group and by 0.1% in the sham-procedure group. The improvement persisted throughout the 12-month study period.

Mean total tremor scores on the CRST improved by 41% at 3 months and by 35% at 12 months. This improvement was not observed with the sham procedure. Data is presented in the graph below (**Figure 1**).

Total disability score from Part C of the CRST was significantly improved at 3 months (a 62% reduction in the score from baseline to 3 months) and the improvement was sustained at 12 months.

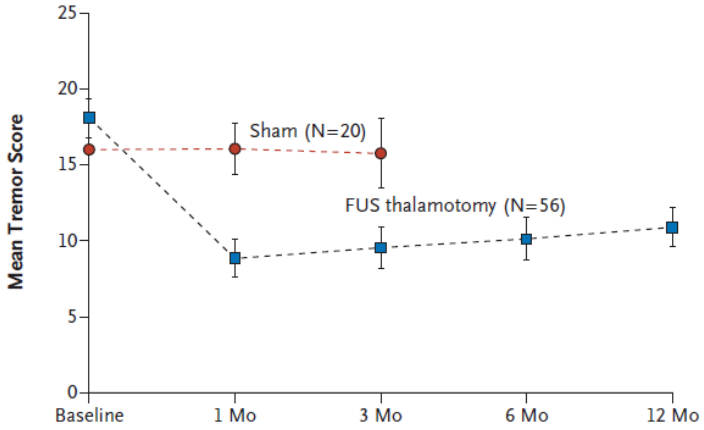



***Figure 1: CRST reported in the pivotal study up to 12 months***

### 4.1.2. Post Marketing Surveillance Data

**Safety aspect** -

1) Safety analysis of 186 patients with ET that were treated under FDA Premarket Approval submission (P150038) at 14 centers with MRgFUS thalamotomy with one-year follow-up (Fishman et al. 2018 [2]).
   - Most of treatment related AEs resulting from these studies were mild (79%) or moderate (20%). Only 5 cases (1%) were rated as severe.
   - Of the 5 severe cases, 2 were transient lasting less than 3 days post procedure (general fatigue and sonication related head pain resolved the same day). In addition, 2 cases of imbalance and 1 case of ataxia persisted for more than 12 months. **Table 3** summarizes the AEs after MRgFUS thalamotomy by type and level of severity (N=186 subjects/443 events)

| | Mild | Moderate | Severe |
|---|---|---|---|
| Frame-related | 39 (9%) | 3 (0.7%) | 0 |
| Sonication-related | 132 (30%) | 55 (12.4%) | 2 (0.4%) |
| Thalamotomy-related | | | |
| Sensory | 84 (19%) | 8 (2%) | |
| Speech | 15 (3%) | 2 (0.4%) | |
| Balance | 59 (13%) | 14 (3.2%) | 3 (0.7%) |
| Strength | 23 (5%) | 4 (1%) | |
| Totals | 352 (79%) | 86 (20%) | 5 (1%) |

***Table 3: Adverse events reported in multiple premarket approval studies up to 12Months***

2) Anecdotical safety information encountered after the pivotal study:

- A single center published data on 2 patients experiencing dystonia following treatment (Martino et al, 2019[3]).
  Authors recommend that patients should be carefully examined for accompanying dystonia and warned about the potential risk of worsening or unmasking of dystonia despite tremor improvement.
- In a local ET trial in Japan in 2018, one patient reported post treatment thalamic pain for 1 year, presented as Cheiro-Oral Syndrome and Hyperalgesia.

**Efficacy aspect** -

Efficacy analysis of 179 ET patients treated with unilateral thalamotomy at international multi centers under the pivotal and post pivotal studies with one-year follow-up (Krishna et al. 2019 [4]).

- Overall, the mean tremor improved by 60.7% at 3 months. The improvement persisted throughout the 12 months study period (57.9%). There was a statistically significant difference in outcomes between the pivotal and the post pivotal groups, with more tremor improvement in the post pivotal cohort potentially reflecting a learning curve with FUS Thalamotomy.
- Quality of Life, as measured by CRST Part C, improved by 70.7% at 3 months and was sustained at 1 year.
- Lower age and shorter disease duration were observed as significant predictors of outcomes after MRgFUS, similar to the reported effect of disease duration in DBS treatments for Parkinson disease.

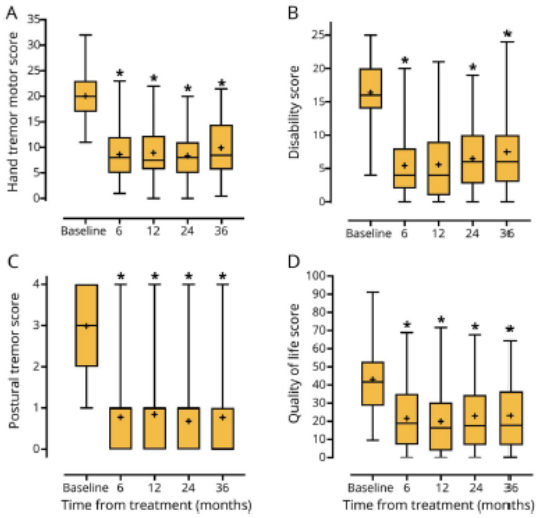
**Durability aspect** -

The effectiveness and durability of MRgFUS treatment for ET patients were assessed at 3 years follow up of patients treated under the pivotal study. 52 out of 75 patients have reached 36 months (Halpern et al. 2019 [5]).

- The median score improved from a baseline value of 20 points to 8 points at 6 months and remained at 8 at 36 months, a 56% median reduction from baseline.

- The disability score (measured by the CRST Part C) decreased by 63% at 3 years after MRgFUS treatment. The total QUEST score showed an improvement of 50% at 36 months.

  The change in tremor and quality of life scores after MRgFUS treatment presented in the graphs below (**Figure 2**).




The horizontal line in the center of each box represents the median value, and the box extends from the 25th to 75th percentiles. (Halpern et al, 2019)

***Figure 2: Tremor measures in the pivotal study up to 3 years***

## 4.2. Bilateral Essential Tremor

### 4.2.1. Summary of Clinical Study

Study Design - Prospective, open-label, multi-center, single arm, staged clinical trial. 51 subjects that have received a previous unilateral Exablate procedure, were recruited to the study in 7 centers in the USA.

Study Endpoints –

***Safety Endpoint:*** Clinical assessments and neurological examinations from the bilateral treatment day through the 12 Month post-treatment visit.

***Effectiveness Endpoint:*** Percent change at 3 months post procedure of the CRST for the secondary tremor side treated during this study.

Study Results –

***Safety Results:*** No severe or Life-threatening events related to device occurred. There were no unanticipated adverse device events reported.

During the first month post treatment, main adverse events included paresthesia or numbness (33%), dysarthria (29%), ataxia (23%), imbalance (18%) and Dysgeusia (14%). As some of these events are temporary in nature (e.g., due to post treatment edema), looking at the 6-months on going adverse events profile may be more adequate, showing paresthesia or numbness (in 16% of patients), dysarthria (14%), ataxia (14%) and Dysgeusia (6%).
All ongoing related adverse events are mild except for one moderate event in each of the following categories: dysphagia, unsteadiness/imbalance, dysgeusia.

One patient had a severe Urinary Tract Infection that was deemed procedure related (from the use of foley catheter during procedure) and was resolved 2 weeks after.

A detailed list of all adverse event at 6 months visit appears in the table below:

| AE Description | Prevalence ≤1M | Prevalence ≤3M | Prevalence ≤6M | Prevalence Ongoing >6M |
|---|---|---|---|---|
| Numbness/Tingling | 17 (33.4%) | 11 (21.6%) | 9 (17.6%) | 8 (15.7%) |
| Dysarthria | 15 (29.4%) | 10 (19.6%) | 8 (15.7%) | 7 (13.7%) |
| Ataxia | 12 (23.5%) | 9 (17.6%) | 8 (15.7%) | 7 (13.7%) |
| Unsteadiness / Imbalance | 9 (17.6%) | 5 (9.8%) | 3 (5.9%) | 1 (2.0%) |
| Dysgeusia | 7 (13.7%) | 7 (13.7%) | 7 (13.7%) | 3 (5.9%) |
| Gait Disturbance | 5 (9.8%) | 3 (5.9%) | 2 (3.9%) | 1 (2.0%) |
| Dysphagia | 4 (7.8%) | 4 (7.8%) | 3 (5.9%) | 3 (5.9%) |
| Hypogeusia | 4 (7.8%) | 4 (7.8%) | 4 (7.8%) | 4 (7.8%) |
| Dysmetria | 2 (3.9%) | 1 (2.0%) | 1 (2.0%) | 1 (2.0%) |
| Fatigue | 2 (3.9%) | 1 (2.0%) | 1 (2.0%) | 0 |
| Voice Change | 1 (2.0%) | 1 (2.0%) | 0 | 0 |
| Sialorrhea | 1 (2.0%) | 1 (2.0%) | 1 (2.0%) | 1 (2.0%) |
| Hypoesthesia | 1 (2.0%) | 1 (2.0%) | 1 (2.0%) | 1 (2.0%) |
| Dry Mouth | 1 (2.0%) | 1 (2.0%) | 1 (2.0%) | 1 (2.0%) |
| Dizziness | 1 (2.0%) | 0 | 0 | 0 |
| Diplopia, Intermittent | 1 (2.0%) | 0 | 0 | 0 |
| Decrease in Synchronicity | 1 (2.0%) | 1 (2.0%) | 1 (2.0%) | 1 (2.0%) |
| Weakness | 1 (2.0%) | 1 (2.0%) | 1 (2.0%) | 1 (2.0%) |
| UTI | 1 (2.0%) | 0 | 0 | 0 |
| Headache | 1 (2.0%) | 0 | 0 | 0 |
| Facial Droop | 1 (2.0%) | 0 | 0 | 0 |

***Table 4: Adverse events reported in the Bilateral ET study***

***Efficacy results***: The mean score for tremor/motor function (CRST parts A+B) improved by 66%, from 0.6±0.2 baseline score to 0.2±0.2 at 3 months. The improvement persisted in 6-months follow up (Figure 3).

Mean Upper extremity posture score on the CRST (part A) improved by 81.2%, from 2.5±0.8 baseline score to 0.6±0.9 at 3 month and was kept the same also in 6 months visit.

Total disability score from Part C of the CRST improved by 73.1%, from 10.3±4.7 baseline score to 2.2±2.8 at 3 months and sustained at 6 months.

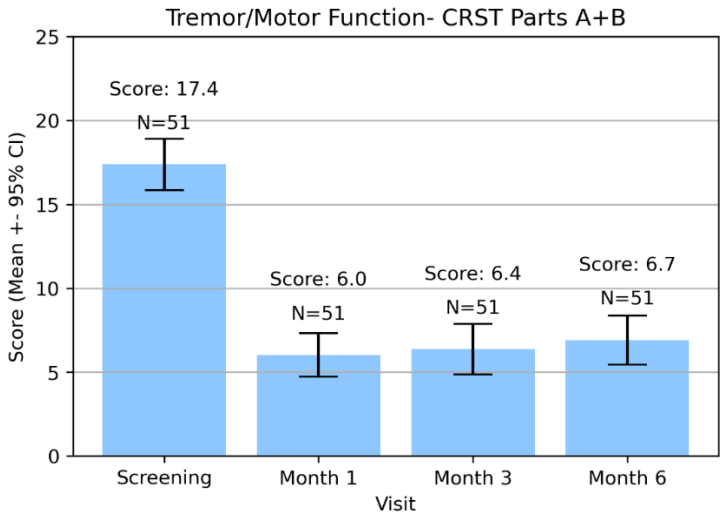



***Figure 3: CRST part A+B Tremor/Motor Function Average Score reported in Bilateral staged ET treatment***

## 4.3. Tremor-Dominant Parkinson's Disease

### 4.3.1. Summary of Clinical Study

Study Design – a prospective, multi-center, randomized, sham-control, double-blinded clinical trial. 27 subjects with idiopathic TDPD with medication-refractory tremor were recruited into the study and were randomized at a 2:1 ratio to either active Exablate treatment arm or Sham control arm. At the Month 3 visit, Sham subjects were permitted to Crossover to an active Exablate treatment. All subjects were followed to Month 12 following an Exablate treatment.

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 12 months post-treatment time point.

***Effectiveness Endpoint:*** The effectiveness was evaluated using a validated, tremor rating scale: The Clinical Rating Scale for Tremors (CRST) for ET subjects. The Tremor assessments was done by CRST Part A & B.

Study Results –

***Safety Results:*** the data of this study shows a very favorable safety profile of the Exablate procedure in the TDPD population. Of all events in the Exablate TDPD Cohort, 71% were transient and were no longer present 72 hours later. All events are detailed in ***Table 5***.

Two subjects experienced Thalamotomy-related Serious Adverse Events. Both resulting from local cerebral edema and trailing of the lesion toward the internal capsule:

- One subject experienced hemiparesis with expression of ataxia, and the patient required a walker after discharge. The event resolved after 30 days.
- One subject experienced developed hemiparesis 1 day post treatment.

| Relation to Device | Body System | Adverse Event Term | Incidence # (%) | | |
|---|---|---|---|---|---|
| | | | Mild | Moderate | Severe |
| **Procedure Related** | General | Fatigue | 2 (10%) | 0 | 0 |
| | Musculoskeletal | Musculoskeletal weakness | 1 (5%) | 0 | 0 |
| | Nervous | Dysgnosia | 1 (5%) | 0 | 0 |
| | Vestibular | Dizziness | 1 (5%) | 0 | 0 |
| **Thalamotomy Related** | Musculoskeletal | Dysmetria | 1 (5%) | 0 | 0 |
| | | Gait disturbance | 2 (10%) | 0 | 0 |
| | | Hemiparesis | 0 | 2 (10%) | 0 |
| | | Imbalance | 4 (20%) | 0 | 0 |
| | Nervous | Dysmetria | 1 (5%) | 1 (5%) | 0 |
| | | Ataxia | 1 (5%) | 0 | 1 (5%) |
| | | Numbness/tingling | 6 (30%) | 0 | 0 |
| | Neurological | Numbness/tingling | 1 (5%) | 0 | 0 |

| | | | | | |
|---|---|---|---|---|---|
| | | Unsteady | 1 (5%) | 0 | 0 |
| **Transient (≤3 days)** | Cardiovascular | Hypertension | 1 (5%) | 0 | 0 |
| | | Syncope | 1 (5%) | 0 | 0 |
| | Dermatologic | Sonication related flushing | 0 | 1 (5%) | 0 |
| | Eye | Visual Field Defect | 1 (5%) | 0 | 0 |
| | Gastro | Nausea/Vomiting | 3 (15%) | 2 (10%) | 0 |
| | Musculoskeletal | Imbalance | 1 (5%) | 0 | 0 |
| | | Positional pain | 2 (10%) | 1 (5%) | 0 |
| | Nervous | Imbalance | 1 (5%) | 0 | 0 |
| | | Anxiety | 0 | 2 (10%) | 0 |
| | | Dysgnosia | 2 (10%) | 0 | 0 |
| | | Numbness/tingling | 5 (25%) | 0 | 0 |
| | Pain/ Discomfort | Headache | 5 (25%) | 6 (30%) | 0 |
| | | Sonication-related scalp pain | 0 | 1 (5%) | 0 |
| | | Sonication-related head pain | 2 (10%) | 2 (10%) | 1 (5%) |
| | Vestibular | Dizziness | 6 (30%) | 1 (5%) | 0 |

***Table 5: adverse events reported in the TDPD clinical trial***

***Efficacy Results:*** [6]

- The Hand tremor, as measured with the CRST A+B sub scores in the on-medication state, improved 62% from a baseline of 17 points following FUS thalamotomy (n=20) and 22% from a baseline of 23 points after sham procedures (N=7) (***Figure 4***)
- Improvements at 3months were observed in all secondary-outcome CRST, UPDRS, and PDQ-39 scores in the treatment group.
- A notable placebo response was observed, which diminished at 3 months.

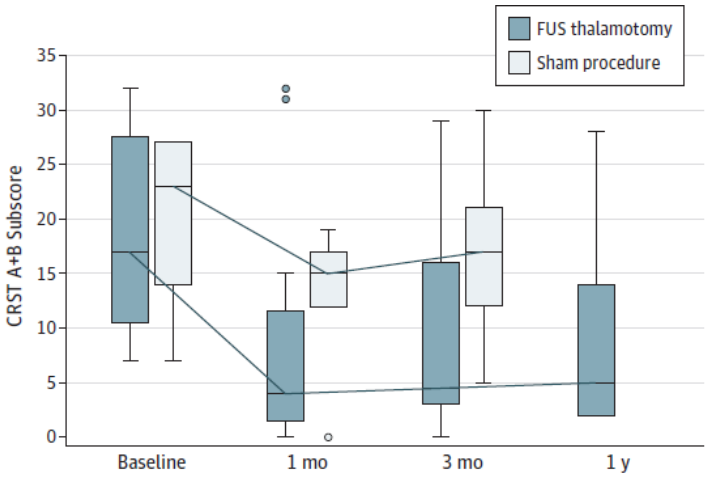



***Figure 4: CRST in the TDPD clinical study up to 1 year***

## 4.4. Parkinson's Disease

### 4.4.1. Summary of Clinical study

Study Design – a prospective, two-arm, sham-controlled, randomized (3:1), multi-center study to evaluate the safety and efficacy of unilateral Exablate pallidotomy for medication-refractory, advanced idiopathic PD. Subjects underwent (actual or sham, according to the randomization assignment) unilateral pallidotomy to the symptom-dominant side of the GPi.

Study Endpoints –

***Safety Endpoint***: The safety was determined by an evaluation of the incidence and severity of device-related adverse events and serious adverse events from treatment day through the 12 months follow up.

***Efficacy endpoint:*** the effectiveness was evaluated by the difference in the Responders Rate of the Exablate group Vs the Control group. Response to the treatment was based on whether a patient reached a minimally clinically important difference on either MDS-UPDRS Part III (OFF meds motor exam for extremities on the treated side) OR UDysRS Objective Impairment (ON meds) without worsening on the other assessment.

Study Results -

***Safety Results:*** The analysis of safety was based on 92 subjects (68 Exablate subjects and 24 Sham subjects), available through the 12 months follow up.

In the Exablate group, only one Serious event occurred. One subject had a pulmonary embolism that was coincident with immediate travel pre-and post-procedure Exablate. The DSMB ruled it as procedure-related out of abundance of caution.

The Procedure-related and Pallidotomy-related events are presented in **Table 6** below. Of the AEs that resolved, resolution generally occurred within 1 week to 3 months. AEs categorized as Procedure-related are generally those events that are non-transient and related to undergoing the procedure, such as fatigue, headache, etc. Other AEs listed as Pallidotomy-related are similar to the types of events that have been reported when ablation/stimulation of the globus pallidum is undertaken.

| Relation to Device | Body System | Adverse Event Term | EXABLATE ARM (N=68) | |
|---|---|---|---|---|
| | | | N | % |
| Procedure-related | Cardiovascular | Pulmonary Embolism | 1 | 1.5% |
| | General | Fatigue | 1 | 1.5% |
| | Nervous | Dizziness | 3 | 4.4% |
| | Pain/Discomfort | Headache | 3 | 4.4% |
| | | Sonication Related Pain | 1 | 1.5% |
| Pallidotomy Related | Nervous | Dysarthria | 2 | 2.9% |
| | | Facial Drooping | 1 | 1.5% |
| | | Gait Imbalance | 1 | 1.5% |
| | | Hiccups | 2 | 2.9% |
| | | Imbalance | 1 | 1.5% |
| | | Increased Salivation/Drooling | 1 | 1.5% |
| | | Numbness/Tingling | 1 | 1.5% |
| | | Paresthesia | 1 | 1.5% |
| | Vision | Blurred Vision | 1 | 1.5% |

***Table 6: adverse events reported in the study***

All Procedure related events resolved within the 12-months follow up. Of the Pallidotomy related events, three Mild/Moderate events were still on-going in

12 Months: 1 moderate dysarthria, 1 mild Increased salivation/drooling, 1 mild Numbness/tingling

***Efficacy Results:*** Out of 67 subjects randomized to the Exablate group, 46 (69%) subjects were Responders, whereas the Responder rate of the Sham group was 33.3%. (OR = 4.4, P=0.005).

The Exablate treated group showed 26% improvement in MDS-UPDRS Part III (OFF meds motor exam) for extremities on the treated side as compared to the Sham-treated group (6%) at 3 months. Additionally, the improvement in the Exablate Arm was stable through 12 months.

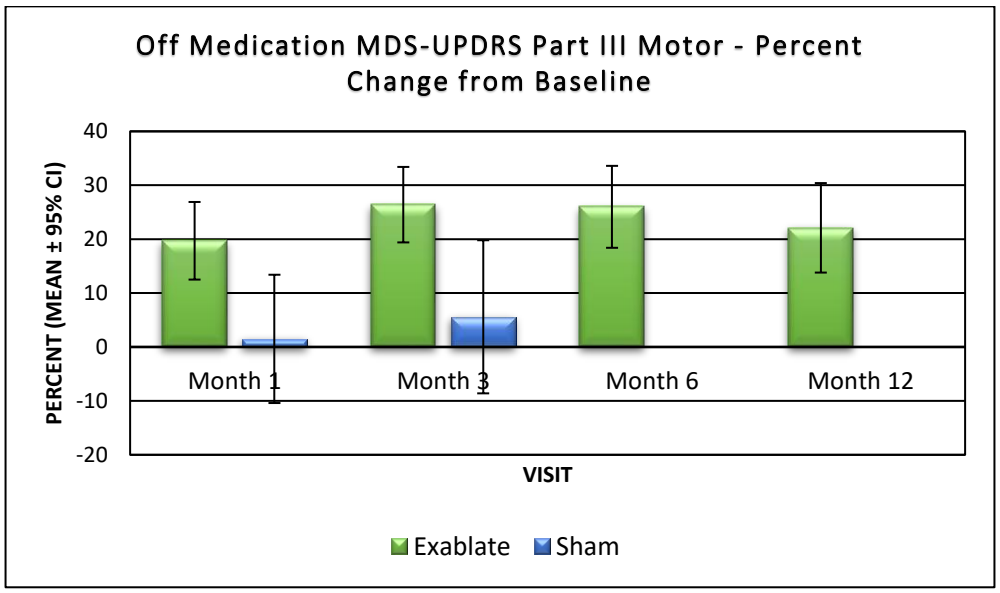



***Figure 5: Off Medication MDS-UPDRS GPi clinical study up to 1 year***

The Exablate treated group showed 46% improvement in MDS-UPDRS Part IV - Motor Complication Score as compared to the sham-treated group (2%) at 3 months:

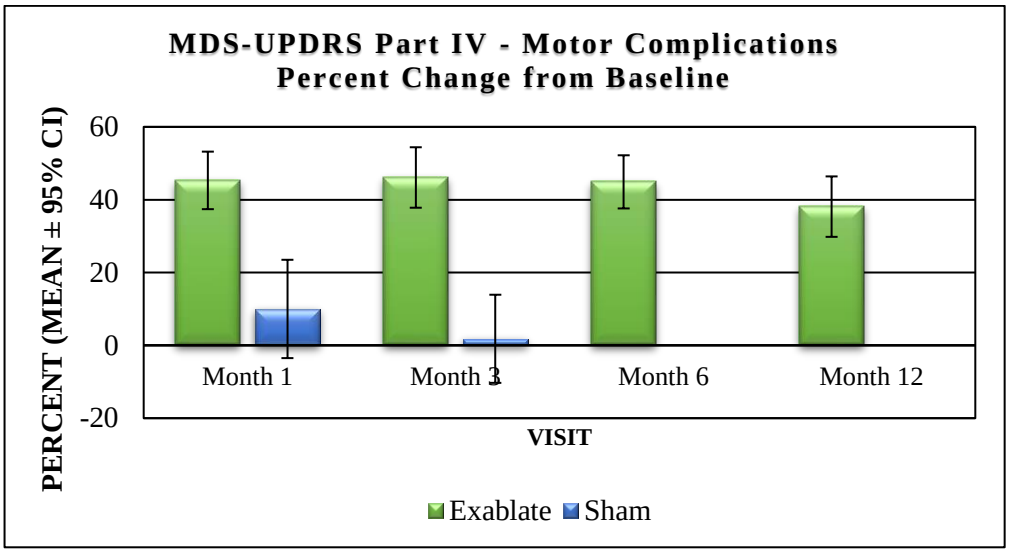



***Figure 6: MDS-UPDRS GPi clinical study up to 1 year***

## 4.5. Neuropathic Pain

### 4.5.1. Summary of Clinical Study

Study Design [7] –

Twelve patients with chronic therapy-resistant neuropathic pain were enrolled for MRgFUS Central Lateral Thalamotomy (CLT).

Pre- and postoperative pain assessment was performed using a detailed questionnaire. The VAS rating of pain intensity was noted for the least and worst pain intensities on a scale between 1 and 100. In addition, patients provided a global percentage value of postoperative pain relief as compared with the preoperative state.

Study Results –

***Safety Results:*** One patient (8%) experienced right sided motor hemineglect and dysmetria of the arm and leg as well as dysarthria secondary to an 8-10 mm bleeding in the center of the CLT target with ischemic changes extending into the Vim. By 24 hours, 70-80% of the motor symptoms had reduced and with time all dysmetric symptoms cleared except when the subject tried to write or speak. At 1-year post-treatment, the subject remained impeded during demanding and stressful interactions.

***Efficacy Results:*** An analysis of global pain relief percentages as reported by the patients and of VAS values was performed for 9 patients.

Significant pain relief (mean group value 55%) was reported during and at the end of the procedure. More reliable pain relief percentages were collected at 2 days (mean group value 71.1%, 9 patients), 3 months (mean group value 49.4%, 9 patients), and 1 year (mean group value 56.9%, 8 patients) after treatment.

The postoperative mean VAS score was 34.3/100 at 3 months and 35.3/100 at 1 year, representing a 42.3% and 40.7% postoperative improvement, respectively.

# CHAPTER 5: POST MARKETING SURVEILLANCE - ACCUMULATED LESSONS LEARNED

INSIGHTEC is committed to collect reports regarding safety events from commercial treatments done with the MRgFUS system. As part of this data collection process, several factors were identified with potential effect on the treatment safety profile (the applicable ones included in chapter 2):

- Determination of target location – target determination is a critical task for treatment success and for avoiding side effects. Therefore, this task should be done by a qualified physician with the required knowledge and experience and based on the local neurosurgical standard of care. In addition, it is important to monitor real time feedback from the patient and the system throughout treatment, in order to confirm the target location and adjust it, if needed.
- Thermal spot shape – thermal heat should be confined to the target location. The Exablate phased array transducer uses a dedicated algorithm to correct for thermal heat distortion, caused by the skull. In some cases, skull and tissue variability may still affect spot shape. Therefore, it is required to carefully examine the real time thermal images during treatment and identify changes in the thermal spot shape, such as elongation. If needed, the operator should apply available tools to confine the spot shape within the target location.
- Thermal spot alignment – correct alignment of the transducer is critical for proper tissue targeting. The geometrical verification process must be performed at the beginning of the treatment (with sublethal energy levels) to ensure proper alignment in all 3 axes. In case the thermal spot deviates from the desired location, adjustment of thermal spot should be performed.
- Patient fixation during treatment – target determination is done on MR anatomical images taken at the beginning of the treatment. Therefore, it is important that from this point on, patient's head will be immobilized throughout the treatment. This is accomplished by attachment of head frame to the patient's head by the treating team and their confirmation that frame is fixated in place and by connecting the head frame to the treatment table and assuring its locking (see section 2.3). In addition, an automatic image-based movement detection feature alerts in case of patient movement, prior to each energy transmission; in

such cases, the treating team should examine the available information and if needed operate according to use instruction. Moreover, in each sonication, it is important to visually check the real time images and compare them to the planning images to capture patient movement events.

- Symptomatic Edema – as in other clinical interventions, it is possible to have tissue reaction to ablation that involves induced edema. Edema of surrounding tissue can be associated with neurological deficits and usually causes transient and mild to moderate symptoms. In order to minimize the adverse effect, the treating team needs to follow the hospital/ clinic standard of care in such events, which may also include steroids administration in the days following the procedure.
- Rarely, an abnormal reaction of patient to the treatment might occur, leading to anticipated transient or permanent neurological deficits. Such rare events cannot be explained by any of the above factors and might be related to patient anatomy or physiology. To minimize such risk, it is important to evaluate the medical history and condition of the patient, and to constantly monitor patient inputs throughout the treatment.

In order to reach a durable and full effect of tremor suppression, in some cases the treatment approach may be skewed towards efficacy over safety, based on physician clinical judgement. Such cases may end up with infliction of mild side effect. The treating team is required to have clear understanding of possible risks and complications when performing the treatment, set up the patient expectations, and give adequate follow up and care.

## CHAPTER 6: REFERENCES

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