Clinical Protocol - Appendix NCT02289560

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Protocol Title	**A Long-term Observational Follow-up Study of Medication Refractory Essential Tremor Subjects Treated with ExAblate Neuro Thalamotomy under P150038**

Approvals:

Site	**Sponsor**
Principal Investigator Signature Date	Nadir Alikacem, PhD, VP Global Regulatory Affairs and CRO InSightec Date 10/16/17

A Long-term Observational Follow-up Study of Medication Refractory Essential Tremor Subjects Treated with ExAblate Neuro Thalamotomy in Clinical Trials

The Objective of this observational follow-up study is to collect long-term information regarding the Safety and Efficacy of medication-refractory Essential Tremor subjects treated with the ExAblate Neuro System under P150038 (original IDE# G120246).

The Indications for Use claim for this system is as follows:

> 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.

Protocol Number: ET002-LTF

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1. BACKGROUND and SIGNIFICANCE

1.1 Movement Disorder in Essential Disorders Patients

Essential tremor is the most common movement disorder with an estimated prevalence between 0.3% and 5.6% [1-5]. Recent epidemiological reports[1] indicate that prevalence across 19 countries (pooled) was 0.9%, but increased to 4.6% among those 65 years and as high as 21.7% in those aged 95 and older. The condition is a genetically inherited disorder with a child of an ET person having a 50% chance of inheriting a gene causing the condition. Approximately 50-70% of people diagnosed with ET have a positive family history for the condition. Caucasians are 5 times more likely to report physician diagnoses of ET than are African Americans; Hispanics have a rate between them. Gender predisposition as reported in various articles is variable depending upon the author's population.

ET is a slowly progressive neurological disorder characterized by a tremor of the arms or hands that occurs during voluntary movements (intention tremor), such as eating/drinking and writing. The tremor may also present in the head (neck) and jaw and may affect voice. The disease may present in the teens or in the 40-50 age range. Generally, tremor begins in the arms and then spreads to these other regions in selected patients. Other types of tremor may also present, including postural tremor of the outstretched arms, and intentional tremor (below 5 Hz) and rest tremor of the arms. The amplitude of an intention tremor increases as an extremity approaches the endpoint of deliberate and visually guided movement (hence the name intention tremor). An intention tremor is usually perpendicular to the direction of movement. An intention tremor causes the person to overshoot or undershoot their target (dysmetria).

1.2 ExAblate Neuro System.

The non-invasive high-intensity focused ultrasound has been coupled with high resolution MRI to provide precise, consistent treatments that can be monitored in real-time. The development of phased array transducers allows for tightly focused treatment volumes and for the ability to compensate for distortions by tissue heterogeneity [6-8]. The landmark advance in the ExAblate transcranial MR guided focused ultrasound for neurosurgeons occurred as the ability to sonicate through the intact cranium was achieved with phased array transducers and acoustic modeling using CT reconstructions of the skull [6-10]. By coupling focused ultrasound technology with MRI, the ExAblate system allows detailed treatment plans to be performed and real time intra-procedure monitoring [11]. Standard MR sequences have been shown to reliably predict tissue damage during thermal lesioning with ultrasound [11, 12]. We anticipate that the ExAblate Neuro non-invasive thermal lesioning is safe and will provide several years of benefit through

[1] http://www.medmerits.com/index.php/article/epidemiology_of_movement_disorders/P4

reduction of contralateral motor symptoms and potential medication side effects in ET subjects.

2 OBJECTIVES

The objective of this clinical trial is to follow, observationally, the medication-refractory Essential Tremor subjects who underwent ExAblate Neuro thalamotomy under IDE# G120246 to capture long-term safety and effectiveness out to Year 5.

> **Safety**: To evaluate long-term incidence and severity of adverse events (AE/AEs) associated with ExAblate Neuro treatment of medication-refractory ET
>
> **Effectiveness**: To collect long term effectiveness and quality of life of the ExAblate Neuro treatment of medication-refractory Essential Tremor (ET).

This study is designed as a long-term prospective, observational clinical trial to follow device related safety, and long term effectiveness (CRST) and quality of life (QUEST) for subjects previously treated with ExAblate Neuro under IDE#120246.

The purpose of this protocol is to set the follow-up schedule for all IDE #G120246 subjects out to Year 5 in compliance with the post approval conditions.

2.1 Primary Endpoints

2.1.1 Safety

> *Safety of ExAblate will be determined by an evaluation of the incidence and severity of device / treatment related complications from the treatment day visit through ALL study follow ups through Year 5. Adverse events (type, frequency, severity) are expected to be similar to those of previous studies using ExAblate Neuro for Thalamotomy*

Recorded adverse events will be reported and categorized by investigators as definitely, probably, possibly, or unrelated to the device or procedure. Events which are not considered to be possibly or probably caused by the device are not required to be reported here.

2.1.2 Effectiveness

Primary effectiveness will be assessed using the CRST as scored by the site neurologist.

Secondary effectiveness will be followed using the QUEST quality of life patient outcomes questionnaire.

2.1.2.1 Efficacy Assessments

Tremor symptom severity will be assessed using the CRST as scored by the site neurologist at each follow-up visit. The CRST is a validated clinical instrument used to assess tremor symptom severity.

Quality of life will be evaluated using the QUEST assessment to assess durability (as measured by QUEST upper arm extremity questions) of the procedure. The QUEST is an ET specific assessment of quality of life changes associated with ET. Tröster *et al*., 2005, developed QUEST as a clinical tool for correlating changes in 30 aspects of tremor severity, social and personal disability, and perception of health. An independent validation study of the QUEST performed by Martinez-Martin *et al*. concluded that most of the psychometric parameters were found to be satisfactory in their ability to assess the impact of ET on the patients' quality of life.

2.2 Study Hypothesis

The purpose of this study is to continue to follow the ExAblate-treated medication-refractory ET subjects for long-term safety and effectiveness of MRI-guided focused ultrasound thalamatomy out through 5 years.

2.3 Case Report Form Data

The study data will be collected electronically. This electronic data capture (EDC) system complies with the current guidance of 21 CFR Part 11, Electronic Records and Signatures.

3 DESCRIPTION OF PATIENT POPULATION

3.1 Patient Selection

3.1.1 Inclusion Criteria

1. Subjects who have been treated with ExAblate thalamotomy for medication-refractory ET under previous clinical trials.

3.1.2 Exclusion Criteria

1. Subjects who have had a subsequent intervention for ET on their treated side.

4 INVESTIGATIONAL PLAN

The IRBs will be notified of the Post-Approval condition to follow these subjects and the study will be converted from IDE#120046 to a Post-Approval Study status under P150038. The study data will be collected electronically.

4.1 LTF Follow Up Periods Years 2 – 5 Post Treatment

The treatment long term safety and effectiveness follow up will be completed annually from Year 2 through Year 5 post treatment under this protocol. It should be noted that at these visits, the CRST assessments will be performed and scored by the site neurologist.

The following evaluations should be performed at Year 2, Year 3, Year 4 and Year 5:

- Review of medications
- Physical exam
- CRST – Assessed by site evaluator
- QUEST questionnaire should be completed by the subject
- Adverse events

4.2 Exit from the study for reason of alternative treatment

In this study, subjects who opt for alternative treatments for Essential Tremor (not including medication change) at any point in the follow-up period will be exited from the study after completing the required study examinations. The last set of evaluations prior to alternative therapy is considered the last study visit. The reason(s) for study exit will be noted on the Case Report Forms. No analyses of post alternative treatment changes are planned.

4.3 Study Requirements and Visit Schedule

All subjects who were part of the original IDE, IDE # G120246 in either the ET002 pivotal trial, or the ET002CA (Note: inclusive of all patients treated under the original Pivotal Study, those treated under the Continued Access approval, and those treated as part of the 1.5T Coil cohort) will be rolled into this PAS study at whatever stage of follow-up is coming due. Follow-up will be continuous from the time of treatment to the Year 5 visit.

Subjects who have not attained Month 12 will continue their schedule of visits as (originally scheduled):

1 Week ± 3 days

1 Month ± 7 days,

3 Month ± 14 days

6 Months ± 21 days

12 Months ± 4 month

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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	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
Forms "UB-04 (In Patient subjects) or CMS-1500 (Out Patient subjects)		X	X	X	X	X	X	X	X
Exit Form									X

The table below summarizes the long-term study visit schedule and procedures.

The study visits are as follows:

Year 2 ± 4 Month;

Year 3 ± 4 Month,

Year 4 ± 4 Month,

Year 5 ± 4 Month.

Table 4.2—2 Summary of Study Schedules and Evaluations				
	Year 2 4 Month	**Year 3** ± 4 Month	**Year 4** ± 4 Month	**Year 5** ± 4 Month
Physical Exam	**X**	**X**	**X**	**X**
CRST	**X**	**X**	**X**	**X**
QOL (QUEST)	**X**	**X**	**X**	**X**
ET medications	**X**	**X**	**X**	**X**
Adverse Events	**X**	**X**	**X**	**X**
Exit Form	**X**	**X**	**X**	**X**

Note:

1. To enable subject(s) retention in the Long Term Follow-up study as well as to ensure patient welfare and safety (in full compliance with all applicable patient consent regulation(s) and their corresponding IRB approvals), all participating sites should make every effort to maintain frequent contact with subjects (at least 3 to 4 times a year)to encourage visit compliance and keep them engaged for patient retention.

In the event a patient miss their scheduled visit to complete the study visit requirements, sites should at the very least inquire with subject to provide an overall assessment of their safety and of their tremor in full compliance with all applicable patient consent regulations and rights, and or schedule another clinical visit even if it is outside the visit window.

5 DATA ANALYSIS PLAN

5.1 Safety

Adverse events will be recorded and categorized according to severity, relationship to procedure and relationship to device. All AEs will be assessed for their relationship to the study device or procedure. Standard Code of Federal Regulation definitions for Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs) will be used in assessment of AEs.

It is the responsibility of the investigator to document all AE's occurring during the course of the study. At each visit, the investigator will evaluate AE's. AE's not previously documented in the study will be recorded on the Adverse Event Log within the CRF. The nature of each event, date and time (when appropriate) of onset, outcome, frequency, maximum intensity, action taken, expectedness, and causal relationship will

be recorded. AEs already documented in the CRF (i.e., at a previous assessment) and designated as 'ongoing', should be reviewed at subsequent visits as necessary. If these have resolved, the documentation in the CRF should be completed including an end date for the event.

Standard Code of Federal Regulation (CFR) definitions for Serious Adverse Events (SAEs) will be used for evaluation of adverse events.

> ***SAE*** *[§803.3(aa)(1)] is an injury or illness that:*
>
> - *causes death*
> - *is life threatening, even if temporary in nature;*
> - *results in permanent impairment of a body function or permanent damage to a body structure; or*
> - *necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.*

All AEs (related or unrelated) meeting the criteria for an SAE require notification of the sponsor and the reviewing IRB as soon as possible, with subsequent completion of additional paperwork provided by the sponsor fully documenting the course of the event, all treatments, and final outcome. Initial reporting of an SAE should be made to the sponsor no later than two (2) working days after the PI learns of the incident. AE's that do not affect the safety or overall well-being of the subject, are mild/moderate in nature, are estimated to be temporary in duration even though the exact end date may not be determined *a priori* (e.g., eye twitch increased from baseline) may be presented and discussed with DSMB to determine their final classification status as a serious or non-serious adverse event.

Standard Code of Federal Regulation (CFR) definitions for Unanticipated Adverse Device Effects (UADEs) will be used for evaluation of this type of adverse event.

> ***UADE*** *[§812.3(s)] means any serious adverse event on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.*

Any UADEs will be reported to the Sponsor and to the reviewing IRB as soon as possible. However, in no event must this report be made later than two (2) working days after the PI learns of the incident.

5.2 Data Safety Monitoring Board

A Data Safety Monitoring Board will be used to review all AE's on the study. Their role is to evaluate all AE's that occur throughout the study and determine if they are in fact related to the ExAblate, or some other cause. Investigators will monitor all treatments for any AE's, and consider the following questions for AEs in the Test Arm:

- Was the adverse event serious?

- Was the adverse event life-threatening, caused a disability, required or prolonged hospitalization, or caused death?

- Was the adverse event device related?

- Was the adverse event unexpected?

- Is there an unreasonable risk in continuing the trial?

Adverse Events meeting all the above conditions would require reporting to the FDA, stopping the study pending the results of further investigation, and FDA approval to re-start the study.

All adverse events will be assessed for their relationship to the study device or procedure. Standard Code of Federal Regulation (CFR) definitions for SAEs and UADEs will be used in assessment of adverse events.

5.3 Efficacy

Primary effectiveness will be evaluated using the CRST scored by the site assessor based upon patients where unilateral ExAblate thalamotomy was performed. Secondary efficacy will be collected using the QUEST.

5.4 Subject Health Status

The results from the physical exams will be recorded in the CRFs and will be presented.

5.5 Statistical Considerations and Sample Size

There is no statistical consideration or sample size for this study. All ExAblate treated subjects who were treated under ET002 or ET002-CA will be included in this study, starting at the next scheduled study visit date; ET002-CA was FDA approved under IDE Supplement G120246/S07.

5.6 Missing Data

Analyses will be performed on both observed and data with missing values imputed per the method of last observation carried forward (LOCF) where data for missing visits is assigned the value of the previous visit.

NOTE:

All Demographic, Screening, Baseline, Treatment and some amount of Follow-up data are collected under ET002 or ET002-CA and these data will be used in coordination with that collected under this protocol.

5.7 Statistical Analysis Plan.

The analysis will be performed based upon the Statistical Analysis Plan ("SAP") procedures as defined for the pivotal study (FDA Approval of SAP under IDE Supplement G120246/S06). Please note, however, that for the PAS, all analyses will be performed using the site assessor data only.

5.8 Subject Confidentiality

Subject confidentiality will be maintained throughout this study, including all publications. Data collected and entered into the CRFs are the property of the study sponsor. Representatives from the study sponsor or authorized sponsor representatives, the Institutional Review Board, Data Safety Monitoring Board, Ethics Committee or other regulatory bodies may receive copies of the study records and may review medical records related to the study.

6 PMA P150038 Specific Questions

What serious or unexpected adverse events may occur in the long-term (up to 5 years) after receiving treatment for the proposed indication?

No known device-related SAEs/UADEs are expected over the follow-up of subjects through Year 5 based on historical literature on thalamotomies as published in the literature. The ExAblate procedure is a one-time procedure. However, per this study protocol, safety data will be collected through Year-5 as planned. The full safety data will be reported to the Agency as required.

In the long-term (5 years), will favorable Composite Tremor/Motor Function scores compared to the baseline be sustainable among the patients who have received the treatment?

Based on historical outcomes as published in the literature, it is reasonable to believe that the Composite Tremor/Motor Function improvement will be maintained through follow-up. However, because this cohort of subjects is the first group of subjects to be treated using the ExAblate 4000 device and for many investigators, this was the first hands-on experience in using the device, it is reasonable to anticipate that there may be some patients who do not sustain their improvement over the duration of this study. With the accumulation of user expertise in using the ExAblate 4000, it is expected that the composite Tremor/Motor score outcomes will be sustainable over long durations. It is the purpose of this long-term follow-up protocol to capture the very long term data of the composite Tremor/Motor scores for this cohort of subjects.

7 RISK ANALYSIS

Worldwide, over 12,7000 treatments have been performed to date with the MR guided FUS ExAblate body system. Risk analysis for InSightec ExAblate systems/clinical investigations has been conducted as part of previously approved FDA IDE submissions (G930140, G990151, G990184, G990201, G000203, G010225, G020001, G020182, G050177, and G060023, G070022, G080009, G080206, G100108, G100127, G100169, G120246, G120017, G140018, G140082, G160021, P040003 and subsequent supplements, P110039 and P150038). This data has been re-examined by the study sponsor and it has been concluded that this risk analysis has limited applicability to the proposed clinical investigation. The key consideration here is the fact that this proposed study is conducted with an ExAblate Neuro system that is completely different from the body system. This is system is referred to internally as the Neuro system. However, in principle, the body and neuro systems have the same purpose, namely to coagulate soft tissue within the body by means of MR guided high intensity focused ultrasound.

There are no additional new risks anticipated under this study. All the risks were described under the original treatment protocol and are still active for this protocol. No new treatments are performed here as this is strictly a long-term observational study.

7.1 Criteria for Removal from the Study

The investigator may withdraw subjects from the study as is deemed necessary or deemed to be in the best interests of the subject, such as,

- continued noncompliance with the protocol or study visits,
- severe illness or disability during the study for non-study issues,
- pursuit of subsequent alternative treatment for the same condition, or
- development of intolerable side effects where continued follow-up becomes too burdensome.

In addition, a subject may also chose to exit the study at any time, but will be strongly encouraged to participate in the follow-up visits for safety reasons (continued monitoring of subject safety). Sites should make every effort to contact all subjects for study follow-up to encourage visit compliance. Sites should keep a log of dates of attempted contact and results. After 3 unsuccessful attempts at contact (e.g., by telephone or email) and sending 1 certified letter to solicit their visit compliance a subject may be considered lost to follow-up.

7.2 Data Safety Monitoring Board

A Data Safety Monitoring Board will be used to review all recorded AEs on the study. Note that only ET-disease, device and procedure-related adverse events will be recorded Their role is to evaluate all recorded AEs that occur throughout the study and determine if they are in fact related to the original ExAblate procedure, or some other cause.

Investigators will capture all adverse events, and consider the following questions:

- *Was the adverse event serious?*

- *Was the adverse event life-threatening, caused a disability, required or prolonged hospitalization, or caused death?*

- *Was the adverse event device related?*

- *Was the adverse event unexpected?*

- *Is there an unreasonable risk in continuing the trial?*

Adverse Events meeting all the above conditions would require reporting to the FDA, stopping the study pending the results of further investigation, and FDA approval to re-start the study. Following the DSMB review of the event, and if in the opinion of the DSMB, a modification of the study protocol were necessary to provide adequate protection to future study participants, the modification would be implemented prior to reinitiating the investigation. Any such amendment would be reported to the IRB and FDA for their respective approvals to re-start the study as it is required by the applicable regulations.

All recorded adverse events will be assessed for their relationship to the study device or procedure. Standard Code of Federal Regulation (CFR) definitions for SAEs and UADEs will be used in assessment of adverse events.

8 POTENTIAL BENEFITS

The pivotal trial cohort of subjects being followed in this study demonstrated a powerful, robust result at Month 3 with the ExAblate group experiencing a highly significant improvement in the PE and all secondary confirmatory endpoints (See table). The outcomes were essentially unchanged and still favorable by Month 12.

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

The safety profile for the pivotal trial cohort demonstrated a rather benign and favorable profile in relation to benefit. Many events were considered Transient and Unrelated and most resolved. The remaining events were Procedure or Thalamotomy related events. All but one were Mild / Moderate in severity. Only 1 serious, related event occurred of

Moderate Numbness/Tingling of the thumb which interfered with the subject's ability to hold a pen and write at work.

This PAS is simply an observational study to collect longer-term safety and durability of treatment effect in the IDE study population all the way out to 5 years.

9 MONITORING PLAN

Clinical Monitoring for this study will be managed by InSightec. The Clinical Monitor is qualified by training and experience to oversee the conduct of this study. The Clinical Monitor's responsibilities include maintaining regular contact with each investigational site through telephone contact and on-site visits, to ensure that:

- The trial is conducted according to FDA and GCP requirements;
- The trial is conducted according to InSightec internal SOPs
- The Investigational Plan is followed;
- Complete, timely, and accurate data are submitted;
- Problems with inconsistent or incomplete data are addressed;
- Complications and unanticipated adverse effects are reported to the Sponsor and the IRB;
- The site facilities will be monitored to stay adequate to meet the requirements of the study.

Sites should make every effort to contact all subjects for study follow-up to encourage visit compliance. Sites should keep a log of dates of attempted contact and results. After 3 unsuccessful attempts at contact (e.g., by telephone or email) and sending 1 certified letter to solicit their visit compliance a subject may be considered lost to follow-up.

The Clinical Monitor will continue to perform on-site monitoring visits as frequently as deemed necessary. At this visit and all monitoring visits, the Clinical Monitor will compare the data entered onto the CRFs with the hospital or clinical records (source documents). Source documentation must be available to substantiate adherence to protocol procedures, adequate reporting and follow-up of AEs, and verification of all clinical data captured at the visit. Findings from the review of CRFs and source documents during a monitoring visit will be discussed with the PI. Completed paper or electronic CRFs will be reviewed prior to data closure. The dates of the monitoring visits will be recorded in a Log to be kept at the clinical site. During monitoring visits, the Sponsor expects that the study coordinator and the PI will be available, the source documentation will be available, and a suitable environment will be provided for review of Study related documents.

Monitoring procedures will follow the Sponsor SOPs.

9.1 Electronic Data Capture (EDC)

Electronic CRFs (eCRFs) will be to capture protocol-specific information during the conduct of this study. This electronic data capture of the eCRFs is based on the Oracle Software system, and is designed, run and hosted by Sponsor (Haifa, Israel).

10 INVESTIGATOR RESPONSIBILITIES

The Principal Investigator will be required to sign the Investigator Agreement. All investigators will undergo extensive training on the protocol and operation of the ExAblate system, and provide documentation of their specialized training.

11 REFERENCES

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