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Approvals:

Site	**Sponsor**
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Table of Contents

A Feasibility Study of Focused Ultrasound to Perform Bilateral Medial Thalamotomy for the Treatment of Chronic Trigeminal Neuropathic Pain

The goal of this prospective, randomized, sham-controlled, crossover study is to generate data to evaluate the safety and feasibility of ExAblate 4000 treatment of chronic trigeminal neuropathic pain.

Indication of Use: Bilateral ablation of medial thalamic nuclei for treatment of trigeminal neuropathic pain.

1.0 PRECIS

Focused ultrasound has proven effective for deep brain lesioning through the intact skull, and MRI can be utilized for stereotactic targeting and continuous temperature monitoring. Recently, focused ultrasound was used to successfully perform ventrolateral thalamotomy to alleviate essential tremor – an event paving the way for the first FDA approval in brain.

Historically, medial thalamotomy, the termination of the primary pain pathway from the spinal cord, has suggested efficacy for the treatment of various pains. Neurosurgical interventions for pain have been plagued, however, by open label studies confounded by heterogeneous pain conditions and imperfect outcome measures.

This pilot study will investigate the feasibility of focused ultrasound to safely perform a bilateral medial thalamotomy and the potential to relieve neuropathic pain (NP). The neuropathic pain from trigeminal neuropathies and other craniofacial pain syndromes represent a relatively homogenous condition that is disabling and notoriously refractory to medical treatment. This study is rigorously designed as a randomized, sham-controlled trial where the ten patients and their assessors are blinded to the treatment assignment. Validated pain scales and functional measures of pain and quality of life will be assessed by a multidisciplinary team. Objective measures of treatment effect will be determined by functional brain imaging.

2.0 BACKGROUND

2.1 The problem of neuropathic pain

Neuropathic pain, defined by the International Association for the Study of Pain as "pain initiated or caused by a primary lesion of dysfunction of the nervous system," is a disabling and chronic pain with limited effective treatments. Surveys of primary care patients estimate the incidence of neuropathic pain in communities to approximate 10%. [1,2] This pain is difficult to treat despite multimodal therapies with ~50% patients achieving only partial relief.[3]

Pain remains a major societal problem and has resulted in an opioid epidemic. Approximately 20% of patients presenting to physician offices with pain receive an opioid prescription.[4] In 2012, clinicians wrote 259 million prescriptions for opioids for pain, enough for every adult in the United States to have a bottle.[5] Opioid pain medication use presents serious risks, including overdose and opioid use disorder.[6] From 1999 to 2014, over 165,000 persons died in the U.S. from overdose related to opioid pain medication.[7] Prescriptions for opioids have increased in parallel with opioid-related overdose deaths.[8] The Drug Abuse Warning Network estimated that 420,000 emergency department visits in 2011 were related to the misuse or abuse of narcotic pain relievers.[9]

2.2 Neuropathic pain syndromes of the head and neck

With damage to the peripheral nervous system, sensory symptoms develop including numbness, tingling, allodynia, paresthesia and neuropathic pain. Neuropathic pain is the prominent and most disabling manifestation of most peripheral neuropathies. This is similarly observed with cranial nerves and nerves of the head and neck region. Craniofacial neuropathic pain occurs from a variety of etiologies and can manifest as a severe, disabling and difficult to treat pain syndrome.
Trigeminal neuralgia is perhaps the most commonly recognized craniofacial pain syndrome, and perceived as one of the most severe pain conditions afflicting humans. As a rule, trigeminal sensation is preserved, and the disease solely manifests as pain. Fortunately, there are several medical and surgical therapies which can be effective. While the disease may not be cured, it can be managed effectively.

Trigeminal neuropathy, on the other hand, is a similarly painful condition where the nerve is damaged with resulting associated sensory deficits. The pain of trigeminal neuropathy is notoriously refractory to medical and surgical treatments. Because of the differential response to therapy, the diagnostic distinction between trigeminal neuralgia and trigeminal neuropathy is imperative. There are a variety of etiologies for trigeminal neuropathic pain. The condition usually results from axonal damage, but can be associated with demyelination. Some common disorders resulting in trigeminal neuropathy include: trauma, infection, tumors, and iatrogenic. Burchiel proposed a classification for common facial/trigeminal pains[10]:

	Diagnosis	History
Spontaneous onset	Trigeminal neuralgia, type 1	>50% episodic pain
	Trigeminal neuralgia, type 2	<50% episodic pain
Trigeminal injury	Trigeminal neuropathic pain	*Unintentional* injury, trauma, MS, tumor
	Trigeminal deafferentation pain	*Intentional* deafferentation
	Postherpetic neuralgia	Herpes zoster, shingles
	Atypical facial pain	Somatoform pain disorder

There are other cranial neuralgias besides trigeminal that can affect the head, neck, and face region. These cranial neuralgias can be successfully treated with surgery and medicine, although the surgical options are limited, and there are minimal choices for those that are refractory to the traditional approaches. Geniculate and glossopharyngeal neuralgia similarly respond to microvascular decompression, but when the surgery is unsuccessful or associated with cranial neuropathy morbidity, severe medically refractory pain conditions result.

Craniofacial neuropathic pain shares many similarities in that the pain conditions can be rather similar in their severity, disability, and refractoriness to intervention. Craniofacial pain syndromes are one of the most severely debilitating pain conditions of the peripheral or central nervous system. They can result in anxiety and mood disorders and loss of work.

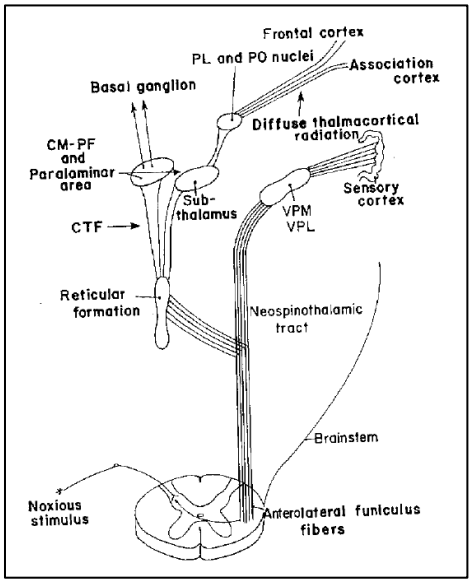
An overview of craniofacial pain syndromes is included below. This study is proposed to investigate a cohort of patients with treatment-resistant pain from trigeminal and other cranial neuropathies. These subjects will be refractory to at least 3 trials of medication therapy and failed interventional or surgical procedures. We intend to exclude trigeminal neuralgia where neural function is preserved and may represent a different pathophysiology than the other neuropathies included. Similarly, craniofacial pains from malignancy will be excluded as many of these manifest a nocioceptive component, and the primary investigation here is for neuropathic pain.

Craniofacial Pain Syndromes to be included in this trial
Trigeminal neuropathic pain • Trauma (*facial fractures, sinus surgery*) • Tumors (*cavernous sinus meningioma*) • Infection (*Tolosa Hunt*) • Multiple sclerosis
Trigeminal deafferentation, *anesthesia dolorosa*
Postherpetic neuralgia

Other Craniofacial pain syndromes not to be included in this study
Trigeminal neuralgia, *idiopathic (type 1)*
Trigeminal neuralgia, *atypical (type 2)*
Craniofacial pain of malignancy
Atypical facial pain
Migraine
Headache syndromes
Temporomandibular joint syndrome

2.3 The origins of stereotactic surgery to treat pain

The evolution of neurosurgical procedures to treat pain conditions is based on the anatomy of pain transmission to the thalamus and a history of targeting these discrete pathways. First described and illustrated in 1906, the spinothalamic tract is recognized as the primary pathway conveying nocioceptive information from the spinal cord to the brain.[11] Nocioceptive information is conveyed primarily through the anterior quadrant of the spinal cord as the spinothalamic or spinoreticular tracts with much smaller components to parabrachial, mesencephalic, and hypothalamic areas. There are certainly other projections of the spinothalamic tract as only 10% of the axons reach thalamic terminals.[12] The spinothalamic tract terminates laterally to the ventral posterolateral, somatosensory thalamus and likely conveys the discriminative components of pain with a strong somatotopic organization. The most posterior and inferior region of the lateral thalamic group (VMpo) contains neurons that are nocioceptive-specific and produce sensations of pain or cold during microstimulation in humans with a distinct architecture and histology.[13] The predominant nocioceptive projection to the medial thalamus derives from the spinoreticular tract terminating at the pontomedullary reticular formation. Medial spinothalamic projections are primarily to the central lateral nucleus (CL) [14-16] but also to centromedian (CM) and parafasicular (Pf) nuclei.[15]



Neurons of the medial pain system have larger receptive fields that are poorly localizing and more likely involved in the affective aspects of pain like arousal, attention, and emotion.[17,18] Nocioceptive-responsive neurons responding to pin prick or heat have been identified in human CM-Pf.[19-21] Intralaminar neurons that are nocioception-responsive are more likely to process the intensity rather than location of the stimulus.[22] While both lateral and medial thalamic regions project to somatosensory cortex, the latter also projects to the anterior cingulate and insula and thus has been implicated in the emotional aspects of pain. In fact, nocioceptive stimulation has been shown by functional imaging to activate both somatosensory and limbic regions of the cortex.[23-29]

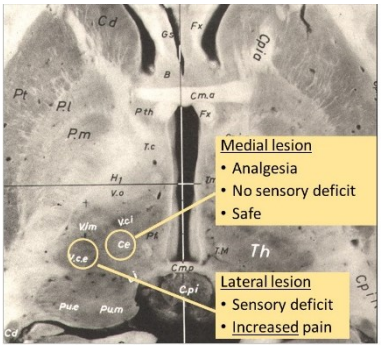
Surgical sectioning of the spinothalamic tract in the anterolateral quadrant of the spinal cord proved effective for pain conditions, especially those originating from malignancy.[30,31] Pain relief could be achieved without loss of sensation. The tract was later targeted at the level of the mesencephalon to treat pain conditions of the upper extremities and head which are less effectively treated by spinal cordotomy.[32,33] But early, 'open' mesencephalotomy procedures required sectioning of the overlying medial lemniscus, resulting in numbness and often dysesthesia. 'Stereotactic'mesencephalotomy allowed for more discrete lesioning without lemniscal damage.[34,35] Nashold refined the procedure with functional stimulation mapping, confirming that dysesthesia likely resulted from medial lemniscus damage and that the emotional aspects of pain could also be treated by including the medial reticular formation.[36-38] Stereotactic (extralemniscal) mesencephalotomy was 76-85% effective for pain relief, but failed acceptance because of morbidity including dysesthesia and extraocular deficits as well as a risk of mortality.[39-43]

The termination of the spinothalamic tract at the ventral posterolateral and posteromedial nucleus was targeted as a lateral thalamotomy. The sensory representation of these nuclei had been well established with primate studies.[44] But lesions of the lateral sensory thalamus resulted in a high incidence of numbness and deafferentation pain. Spiegel & Wycis had demonstrated in the laboratory and in patients that the spinoreticular tract was involved in pain transmission.[45,46] Thus the medial thalamus, recipient of both ascending spinothalamic and spinoreticular projections, was proposed as a more favorable thalamotomy for pain alleviation.[47]

2.4 Rationale for medial thalamotomy

There were several events leading to the development of bilateral medial thalamotomy for pain alleviation. First, anatomic evidence shows a significant proportion of nocioceptive fibers in the anterolateral quadrant of the spinal cord project to the medial thalamus and its intralaminar nuclei. It is been estimated that 80% of these fibers represent spinoreticular tract[48], and spinothalamic fibers also project medially: most densely to the CL but also to the CM and Pf nuclei.[49] The <u>lateral pain system</u> ('neo-spinothalamic'), which consists primarily of spinothalamic projections to ventrolateral thalamus, is involved in the discrimination of pain. The <u>medial pain system</u> ('paleo-spinothalamic') is conveyed by spinoreticular to the intralaminar nuclei and is implicated in the affective aspects of pain.

Secondly, mesencephalotomy is effective in lesioning ascending pain pathways with significant rates of pain relief.[32,34,36-41,50] Bilateral medial thalamotomy may relieve pain to a lesser degree than mesencephalotomy, but procedural morbidity is dramatically reduced.[50] Third, thalamotomy of the ventral posterolateral thalamus, the primary terminus of the spinothalamic tract, is associated with significant risk of worsening deafferentation pain and numbness. In a prospective DBS study for pain, medial thalamic stimulation of the CM-Pf complex proved more effective than VPL/VPM.[51,52]



2.5 Results of medial thalamotomy

The medial thalamic nuclei have been stereotactically targeted with electrophysiologic mapping[53] and also with MRI guidance.[54-56] Physiologic localization of nocioceptive regions is imperfect because many of the intralaminar nuclei elicit a recruiting response[57] as originally described during identification of the dorsomedian nucleus in epilepsy[58] that may be nonspecific. Importantly, while nocioceptive-responsive neurons have been identified in the medial thalamus with microelectrode recordings, the vast majority of cells are unresponsive.[53]

The most common bilateral medial thalamotomy performed for pain has targeted the CM-Pf complex and is performed bilaterally, even in the setting of unilateral pain. Bilateral medial thalamotomy procedures have not been associated with higher rates of morbidity than unilateral procedures. Numerous series of medial thalamotomy exist documenting initially favorable rates of pain relief.[42,59-62] CM lesions result in pain relief without sensory loss.[61] Two large reviews of the literature have assimilated the results of numerous studies over several decades. Lenz and Dougherty reported 73% of 913 patients with initial, partial relief of pain, and the outcomes diminished with time as expected for lesional procedures and clinical trials of pain.[63] The recurrence rate was ~25% and occurred more commonly for neuropathic than noicioceptive/cancer pains. In his review, Tasker also noted a difference between patients with nocioceptive (N=175) and neuropathic (N=47) pain with relief from medial thalamotomy at 46% and 29%, respectively.[62]

All series consistently report relatively low morbidity from these procedures that is most commonly reported as transient cognitive disturbance and sensory deficits if the lesions extends laterally to the ventrolateral nuclear groups.[60] Symptomatic hemorrhagic complications likely occur at the same rate (<1%) as other stereotactic electrode procedures.[64]

More contemporary series have utilized stereotactic radiosurgery to perform bilateral medial thalamic lesioning.[55,56] Leksell's original intention for developing stereotactic radiosurgery and the Gamma Knife was for the noninvasive treatment of intractable pain.[65,66] Central pain from a thalamic infarction has been successfully treated with stereotactic radiosurgery targeting the CM nucleus.[55] Young et al treated 20 intractable pain patients with 140-180 Gy to the lateral MD and CM-Pf region.[56] Sixty-five percent who were followed for longer than 3 months reported over 50% relief, but one patient developed an atypical large lesion with hemiparesis and another developed fatal radiation necrosis by 14 months. There are certainly theoretical benefits of thermal lesioning over ionizing radiation including lesion consistency.[67,68]

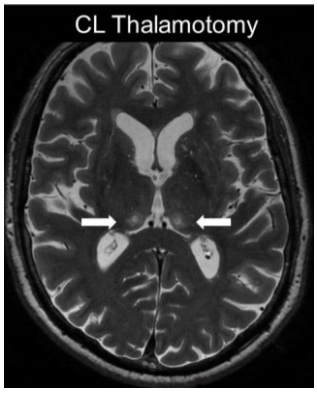
2.6 Central lateral thalamotomy: refinement of the medial thalamotomy

Stereotactic medial thalamotomy for pain syndromes has been refined over a couple decades by Jeanmonod and colleagues to target the central lateral nucleus (CL) based on anatomic, physiologic, and clinical studies.[69] The medial ascending fibers of the spinothalamic tract project to intrathalamic regions with the CL nucleus receiving the most dense spinothalamic

innervation.[14,15,70] Hirai and Jones described clusters of cells in the posterior region of CL (CLp) that stain richly for acetylcholinesterase, encephalin, and substance P.[71] During the development of her stereotactic atlas of the human basal ganglia and thalamus[72], Morel noted that these neurons of the CLp also express calbindin and calretinin.[73]

During extensive single cell microelectrode mapping during medial thalamotomy surgeries, Jeanmonod *et al* identified bursting cells correlating to this region of CLp.[60,74] These low threshold calcium spike bursts had previously been described by Lenz in neuropathic and deafferented human VPL thalamus.[75] There is controversy whether these bursting neuronal patterns are pathologic or a physiologic response to neurogenic pain.[59] Jeanmonod and Llinas have proposed a unifying concept of thalamocortical dysrhythmia syndrome based on the observation of the bursting cells in a variety of neurologic conditions.[74,76]

2.7 Stereotactic radiofrequency CL thalamotomy



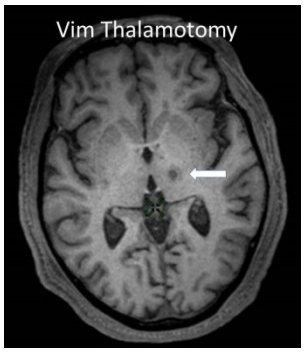
Stereotactic radiofrequency CL thalamotomy localized with micro-electrode recordings was reported in 96 patients with a variety of chronic therapy-resistant peripheral and central neuropathic pain syndromes.[77] Fifty three percent of the patients were deemed responders (at least 50% pain relief) and complete pain relief was achieved in nearly 19% of the study. Reduced drug requirement was noted for 32%. The mean follow-up was 3 years and 9 months. There was no correlation between pain relief and duration or prior procedure, and a slight trend was noted for improvement with peripheral compared to central conditions. Morbidity primarily resulted from hemorrhagic events identified in six of eleven patients and one of these resulted in a significant neurologic injury. These events occurred early in the series and may have been attributed to electrode design and extensive electrode mappings of the CL target.[69] The other five complications involved reversible somatosensory deficits, which were attributed to explorations of the lateral portion of the nucleus early in the study.[77] In a recent report utilizing comprehensive measures of cognition and mood from neuropsychologists, there were no effects on these measures following CL thalamotomy in eight patients treated for chronic neuropathic pain conditions.[78]

2.8 Stereotactic focused ultrasound CL thalamotomy

More recently, Jeanmonod *et al*. achieved bilateral central lateral thalamotomy ablations with submillimeter precision[79] for therapy resistant neuropathic pain syndromes using focused ultrasound.[54] Mean pain relief using a visual analog scale was reported as 49% at 3 months, and 57% at one year. There was a single thalamic hemorrhage resulting in neurologic morbidity, and this complication led to the universal adoption of cavitation detectors in the technology.[80]

2.9 Rationale for this study: focused ultrasound medial thalamotomy for the trigeminal and other craniofacial neuropathic pain syndromes

Contemporary MR guided focused ultrasound is capable of delivering high intensity energy through the intact human skull with precision to deep brain targets. Thalamic lesions have been created within 1-2 millimeters of accuracy [79,81] and temperature monitoring of the focus and surrounding brain is possible with a resolution of ~1^0 Celsius.[82-87] A recent international, randomized, controlled trial in 76 patients resulted in FDA approval of the ExAblate Neuro in July 2016.[88] Please see Appendix B for a list of prior investigations using ExAblate Neuro.



Medial thalamotomy for pain should represent an iterative advance in the use of MR-guided FUS where the medial thalamic (CL) target is less associated with eloquent structures than the ventrolateral thalamus. This cohort of treatment-resistent craniofacial neuropathic pain is intended to represent a severe pain condition with few treatment options. The etiologies may be diverse but the pathophysiology for the development of neuropathic pain is more homogenous and results from peripheral injury/ neuropathy to cranial nerves or those of the head and neck.

We intend to exclude trigeminal neuralgia where neural function is preserved and may represent a different pathophysiology than the other neuropathies included. Similarly, craniofacial pains from malignancy will be excluded as many of these manifest a nocioceptive component, and the primary investigation here is for neuropathic pain.

This proposed pilot study has several innovative aspects:

1. Painful, trigeminal neuropathy and other craniofacial pain syndromes are ideal conditions for investigation of pain relief because:
   - A relatively homogenous disorder resulting from injury or pathophysiology of a cranial nerve.
   - Associated neuropathic pain is notoriously refractory to medical therapies
   - Surgical options are quite limited and not amenable to common neuromodulation therapies like spinal cord stimulation or intrathecal narcotics
   - Severely affects functional status and quality of life
2. Focused ultrasound has been demonstrated to be a precise stereotactic lesioning modality, and the technique can be performed without incisions or craniotomy.
3. Medial thalamotomy for the alleviation of nocioceptive and neuropathic pains is safe and historical studies have suggested efficacy.
4. Rigorous evidence of neurosurgical interventions for pain relief is lacking, and traditional clinical studies have been confounded by heterogeneous patient populations and uncontrolled studies.

5. The technology is ideal for using sham procedures as a control, and the symptom of pain is extremely susceptible to placebo effects during treatment. Thus a randomized, controlled study is appropriate even at this early stage of investigation.

2.10 Outcome reporting in neuropathic pain:

The Numeric Pain Rating Scale (NPRS) has been shown to be clinically significant when at least a two point change occurs.[96] Farrar et al suggested this 30% change was clinically meaningful based on its relationship to global assessments of change in multiple studies of chronic pain. The association of the NPRS and the PGIC is highly consistent over multiple trials regardless of the disease, treatment, trial outcome, or patient demographic factors.[96]

The PROMIS inventory (Patient-Reported Outcomes Measurement Information Systems) was developed by the NIH over a decade as a precise set of tools to measure various aspects of health status across patients with varying conditions and especially chronic diseases. From the over 70 domains assessed, pain represents a key component with items addressing: Intensity, Neuropathic and Nocioceptive Quality, Behavior and Interference.

3.0 OBJECTIVES

This proposed pilot study will investigate the safety and initial effectiveness of focused ultrasound lesioning of the bilateral medial thalamus for severe, treatment-refractory chronic trigeminal neuropathic pain.

Safety: To evaluate the incidence and severity of adverse events associated with ExAblate lesioning of the bilateral medial thalamus for painful neuropathies of the face and head that are severe and treatment-refractory.

Efficacy: To determine the level of efficacy of the treatment of medication-refractory painful PN using validated numeric pain scales and patient-reported measures of pain.

3.1 Safety

The safety of Exablate lesioning of the bilateral medial thalamus using the ExAblate device will be determined by an evaluation of the incidence and severity of device- and procedure-related complications from the first / treatment day visit through the post–treatment visits. Safety analysis will also include monitoring for any worsening of pain related to painful PN. Events that are neither device- nor procedure-related will be captured and recorded but will not be considered reportable device events unless caused by the device. Relative Safety will be evaluated using a common description of Significant Clinical Complications for patients treated in this study.

3.2 Efficacy

Outcome assessments will primarily be made at baseline, one, and three months post procedure for patients receiving either the active treatment or sham procedure. Clinical assessments of pain will be made at the all clinic visits.

Primary outcome: **safety** as assessed from adverse event reporting and MRI evaluation

Primary efficacy outcome measure will compare the change of **WORST** pain experienced in 24 hours before and at 3 months following bilateral FUS medial thalamotomy versus sham procedures as determined from the 11-point numeric pain rating scale.

Secondary outcome measures will include other patient-reported outcomes including the Global Impression of Change and the Pain Domain from the PROMIS Inventory including items for intensity, quality, behavior and interference.

Imaging assessments will be obtained before and after treatment. The location and precision of the treatment, as well as the volume of the lesion, will be determined from pre- and posttreatment MRI at baseline, 1 day, 1 week, 1 month and 3 months. Functional imaging assessments with Dynamic 2-[^{18}F] fluoro-2-deoxy-D-glucose Positron Emission Tomography (FDG PET) will be obtained at baseline and three months for each patient. Functional imaging will serve as an objective measure to correlate with clinical pain assessment.

A summary of outcome measures is listed:

Primary (efficacy) outcome: 11-point numeric pain rating scale NPRS ("**worst**" NPRS score over 24 hours). The change in pain rating from baseline to 3 months posttreatment will be determined and compared between treatment and control cohorts.

Secondary outcomes:
Patient-reported outcome measures:

- PROMIS scale v1.0 – Pain Intensity 3a
- PROMIS scale v2.0 – Neuropathic Pain Quality 5a
- PROMIS scale v2.0 – Nocioceptive Pain Quality 5a
- PROMIS scale v1.0 – Pain Behavior 7a
- PROMIS scale v1.0 – Pain Interference 8a
- Patient Global Impression of Change, 7 point

Functional imaging assessments:

- Dynamic FDG PET

4.0 HYPOTHESIS

Study hypothesis: For patients with treatment-refractory chronic trigeminal neuropathic pain, ExAblate Neuro can safely create lesions in the bilateral thalamic nuclei to reduce pain and provide functional benefits in daily activities.

4.1 The Hypotheses Tested

- For patients with treatment-refractory chronic trigeminal neuropathic pain, MR guided focused ultrasound can safely create lesions, bilaterally, in thalamic nuclei to reduce pain and provide functional benefits in daily activities.
- FUS under MRI-guidance and MRI-based thermometry can be safely delivered through an intact human skull with a low risk of transient adverse effects as evaluated during blinded follow-up of up to 3 months and an additional 3 months follow-up in open-label setting for those subjects who were initially randomized to Sham treatment.
- Pre-defined medial thalamic target volumes inside the brain can be precisely ablated, as demonstrated on post-treatment MRI.

4.2 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.

5.0 DESCRIPTION OF PATIENT POPULATION

Subject Selection

The cohort of subjects with chronic trigeminal neuropathic pain should represent a relatively homogenous pain condition that can be quantitatively diagnosed and treated with a minimal number of confounding factors (e.g. mood disorders, secondary gain, and additional interventions). Subjects diagnosed with a painful cranial neuropathy that is deemed treatment-resistant will be eligible for this study. The principal investigator has a clinical practice of surgery for medication-refractory cranial neuralgias and neuropathies, and he has experience in the classification and diagnosis of these chronic trigeminal neuropathic pain syndromes.[98]

Subjects will first be consented in the study, and then will receive the standard clinical, psychological, and imaging work-up as part of their study baseline requirements. A total of ten (10) subjects will be recruited from University of Virginia Health System in this feasibility study.

5.1 Subject Enrollment

a) Subjects will be referred primarily from the Neurosurgery or Pain Management clinics at the University of Virginia. Information concerning preliminary eligibility for the study will initially be taken from the subject's case history. Subjects who appear to be eligible will be asked if they would like to participate in this study.

b) Written informed consent will be obtained from each participating subject prior to collecting a subject history or other testing. The subject will be counseled concerning the research nature of this study, and the risks and possible benefits to participation. Participation is fully voluntary.

5.2 Inclusion Criteria

1. Men and women, between 18 and 75 years, inclusive
2. Subjects who are able and willing to give consent and able to attend all study visits
3. Severe chronic, trigeminal neuropathic pain of ≥6 months duration.
4. Severity is defined as: Worst NPRS score of ≥ 5 out of 10 at current visit and the subject reports having a similar level of pain for at least the past two months.
5. Pain is medication-refractory to adequate trials of at least 3 prescription medications commonly used for symptomatic relief of neuropathic pain with current adjunctive use of at least one medication. An adequate medication trial is defined as a therapeutic dose of each medication without sufficient effect.
6. Pain is treatment-resistant to at least one interventional therapies including injections, procedures, neuromodulation, and surgery. The interventions trialed depend on the disease and are more specifically defined below:

    - Trigeminal neuropathic pain: failed peripheral injection, percutaneous RF ablation, transcutaneous stimulation, peripheral nerve stimulation, caudalis DREZ lesioning, trigeminal tractotomy, motor cortex stimulation, intraventricular or intrathecal medication infusions, or deep brain stimulation
    - Trigeminal deafferentation pain: pain has resulted from failed trigeminal procedures including percutaneous RF rhizotomy, percutaneous chemical rhizotomy, percutaneous balloon compression rhizotomy, stereotactic radiosurgery, microvascular decompression , or intracranial partial sensory rhizotomy
    - Postherpetic neuralgia of the trigeminal nerve: failed peripheral injection, percutaneous RF ablation, transcutaneous stimulation, peripheral nerve stimulation, caudalis DREZ lesioning, trigeminal tractotomy, motor cortex stimulation, intraventricular or intrathecal medication infusions, or deep brain stimulation

7. Central lateral nucleus of thalamus can be targeted by the ExAblate device. The CL region of the thalamus must be apparent on MRI such that indirect targeting can be performed by measurement from a line connecting the anterior and posterior commissures of the brain.
8. Able to communicate sensations during the focused ultrasound treatment

9. Stable prescribed doses of all symptomatic pain medications for 30 days prior to study entry and for the duration of the 3-month blinded phase of the study.
10.

5.3 Exclusion Criteria

1. Craniofacial pain syndromes related to malignancy of the head and neck
2. Idiopathic trigeminal neuralgia
3. Headache syndromes like migraine, cluster headache
4. Temporomandibular joint syndrome
5. Atypical facial pain or pain related to a somatoform disorder
6. Subjects deemed poor candidates by a licensed psychologist with expertise in screening for pain procedures as evidences by:
    a. Significant clinician concern about reliability of subject-reported information, such as subject in active process of seeking disability for neuropathic pain
    b. Subjects exhibiting any behavior(s) consistent with ethanol or substance abuse as defined by the criteria outlined in the DSM-V as manifested by one (or more) of the following occurring within a 12 month period: Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household). Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use)
    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).
7. Subjects with active psychiatric illness will be excluded. For the purpose of this study, active psychiatric illness includes:
    a. Exhibiting current suicide ideation and/or a history of suicide attempt within past 2 years
    b. been hospitalized for the treatment of a psychiatric illness within the past 2 years
    c. received transcranial magnetic stimulation for depression treatment
    d. received electroconvulsive therapy for depression
8. Any presence or history of psychosis will be excluded.
9. 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

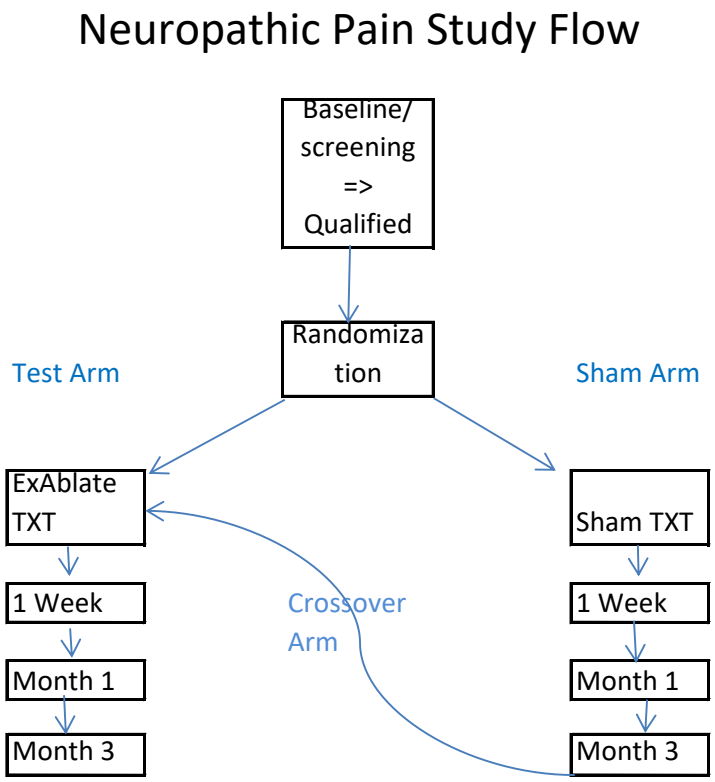
10. Severe hypertension (diastolic BP > 100 on medication)
11. Subjects with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc.
12. On medications that increase the bleeding risk, we are following the published guidelines which are currently recognized by the American Society of Regional Anesthesia and Pain Medicine, American Academy of Pain Medicine and the North American Neuromodulation Society (Reg Anesth Pain Med 2015;40: 182–212); specifically:
    a. Aspirin or another antiplatelet medication (clopidogrel, prasugrel, ticlopidine, abiciximab) for the last 7 days prior to treatment.
    b. Oral, subcutaneous or intravenous anticoagulant medications, such as oral vitamin K inhibitors for the last 7 days, non-vitamin K inhibitor oral anticoagulant (dabigatran, apixaban, rivaroxaban) for the last 72 hours.
    c. Intravenous or subcutaneous heparin-derived compounds for the last 48 hours.
13. Individuals who are not able or willing to tolerate the required prolonged stationary supine position during treatment (can be up to 4 hours of total table time.)
14. Subjects participating or have participated in another clinical trial in the last 30 days
15. Presence of systemic neurological disease or dysfunction
16. Known life-threatening systemic disease
17. Subjects with risk factors for intraoperative or postoperative bleeding from a documented coagulopathy or if their serum coagulation studies (platelet count, PT, PTT, and INR) exceed the institutional laboratory limits.
18. Subjects with brain tumors or any significant intracranial mass. *Trigeminal or cavernous sinus tumors causing neuropathic pain are <u>not</u> excluded.*
19. Any illness that in the investigator's opinion preclude participation in this study
20. Pregnancy or lactation
21. Legal incapacity or limited legal capacity
22. Subjects with a deep brain stimulation implant or with a prior stereotactic thalamic ablation
23. Skull density ratio, calculated from the baseline noncontrasted head CT, is less than 0.4
24. History of hemorrhagic stroke or cerebrovascular event within the past year of treatment exhibiting incomplete resolution
25. History of seizures within past year of treatment
26. Severe kidney disease or on dialysis

27. Subjects who are unable to tolerate medications due to intolerable side effects.
28. Subjects whose primary pain is other than craniofacial neuropathic pain**.**

6.0 INVESTIGATIONAL PLAN

6.1 Study Design

This study is designed as a prospective, double-blinded, randomized trial in 10 subjects with sham procedures serving as the control. A rigorous clinical trial design is required for the subjective measurement of pain and clinical outcome where a placebo effect is anticipated. Primary safety and efficacy assessments will be made before and after treatment through the 3 month blinded phase. After 3 months, subjects in the sham arm will be offered a focused ultrasound bilateral thalamotomy as an open label extension of the study. All subjects receiving treatment, either during the primary blinded analysis or open-label extension phase, will be followed for at least 3 months post-thalamotomy.



6.2 Sham Study Design

The randomized, control arm subjects will undergo a sham procedure that is identical to the treatment except the energy output will be disabled. These control subjects will then be followed up for 3-months post-sham procedure to assess study endpoints; study follow-up: 1 day, 1 week, 1 and 3 month visits.

At the 3-Month time point, all subjects will be unblinded and offered crossover to the actual treatment. All these crossover subjects will be followed again according to the same schedule as the treatment through the Month 3 post treatment study visit.

6.3 Pre-Treatment Procedures

1. PRE-SCREENING: Subjects with medication-refractory, trigeminal or other craniofacial neuropathic pains may be eligible for the study. The diagnosis will be confirmed by the neurosurgeon from the patient's medical history and physical examination.
2. CONSENT: Those who meet the preliminary criteria for the study based on pre-screening of available information will be offered an Informed Consent to sign prior to further evaluation (see Appendix-B for an Informed Consent template). Those who accept will be assigned a subject study number. No study specific tests or procedures will be done until the subject has signed consent.
3. SCREENING and ENROLLMENT:
    a. All current medications will be documented in the medical record and any changes over the past two months will be noted. Record prescribed and PRN medication usage.
    b. The investigator will review and document any medical history that pertains to study eligibility.
    c. Subjects will complete screening questionnaires
        - Worst 24 Hr NPRS assessment, including report of pain levels over past two months (for eligibility)
        - PROMIS (patient reported outcomes of pain)
            a. Intensity
            b. Neuropathic pain quality
            c. Nocioceptive pain quality
            d. Behavior
            e. Interference
    d. Focused neuro-exam by neurosurgeon including:
        - Cranial nerve examination
        - Sensory examination
        - Gait
    e. Screening blood tests: Blood will be drawn by venipuncture for PT, PTT, Metabolic panel, and CBC including platelets
    f. Women of childbearing age will undergo a urinary or serum Beta-hCG test for pregnancy. If the test is positive, the subject will be excluded from the study. If the test is negative, she must agree to maintain a suitable form of birth control throughout study. This includes the screening period until study completion.

g. A comprehensive assessment of pain symptoms, functional limitations, and comorbid mood issues will be made by licensed pain psychologist. The evaluation consists of a clinical interview, as well as questionnaires/assessment tools that address mood and identify potential biopsychosocial factors that may contribute to the patient's pain experience. The Patient Health Questionnaire (PHQ-9) identifies potential depressive symptoms and the Generalized Anxiety Disorder 7-Item Scale (GAD-7) addresses anxiety. Additionally, the Pain Catastrophizing Scale (PCS) is helpful in recognizing a patient's tendency toward catastrophic thinking that is likely to negatively impact surgical or other invasive interventions' outcomes. Lastly, the Brief Battery for Health Improvement 2 (BBHI-2) is a psychometrically sound instrument that is normed on patients with pain and provides objective information related to underlying pain-related issues that are biopsychosocially related. Standard screening for pain procedures includes assessments of anxiety and mood:

   - GAD-7
   - PHQ-9
   - PCS
   - BBHI-2

h. Evaluation by a pain management physician.

i. CT Imaging: For the purpose of this study, the CT Exam should be an Axial scan with bone filter, an image resolution of 512x512, and image thickness of 1mm with zero (0) spacing

j. MR Imaging: For the purpose of this study, unenhanced MR Exams will be performed and include: volumetric MPRAGE, axial and coronal T2-weighted sequences, and axial and coronal diffusion-tensor imaging (DTI)

k. Once all items required for eligibility are completed, the principal investigator will review and sign eligibility or document the screen-failure. If at this point it is determined that the subject ***does not*** meet all Inclusion and Exclusion criteria and cannot be treated, the subject will be removed from the study. These subjects will be considered screening failures, and will not be included in any of the safety or efficacy endpoint analyses.

l. If the subject is deemed eligible for the study based on the screening criteria, then the following will be scheduled:

   - Presurgical evaluation by the anesthesiology team
   - Baseline assessments including Dynamic FDG PET imaging using the following process
      a. Placement of IV catheter

b. Slow injection with ~10 mCi of the FDG tracer via the catheter

c. Imaged using the PET/CT scanner for 60 minutes starting at injection

d. The final 10-15 minutes of the 60 minute scan will consist of a static FDG PET scan.

- Procedure (sham or treatment).

4. BASELINE ASSESSMENTS:

During the week prior to the procedure, the subject will be provided with time to complete all questionnaires per the schedule of events. These will establish the baseline measures for these particular data points. Baseline assessments include:

- NPRS
- PROMIS measures of pain
- History and physical exam
- Concomitant medications
- Dynamic FDG PET

6.4 Randomization

Randomization occurs at the start of the focused ultrasound procedure, immediately prior to the first sonication. Subjects will be randomized in a 1:1 fashion to receive either a sham procedure, where the acoustic power is disengaged, or a bilateral medial thalamotomy. The treatment team (neurosurgeon and clinical research coordinator) will be aware of the treatment assignment. The assessment team (pain management specialist, pain psychologist, and nuclear medicine radiologist who interprets PET) and the subjects will be blinded throughout the three month study period. Subjects are unblinded at the end of the three month visit and sham subjects will be offered cross-over to treatment arm at that time.

6.5 Treatment Procedures

On the day of the treatment, the following clinical team members should be present:

Neurosurgeon: leads the planning and guidance of the treatment. They will also monitor the neurological performance and clinical status of the subject. They will be responsible for the overall management of the subject. The neurosurgeon will evaluate the subject's comfort level and direct sufficient sedation to maintain this comfort. Feedback of symptom relief is not expected to be necessary for this procedure.

The anesthesiologist or nurse anesthetist: they will monitor vital signs and provide necessary medications to keep the subject comfortable.

The overall treatment procedure steps will be performed as follows:

1. Subjects will be reminded to not take any anticoagulant (e.g. warfarin) or antiplatelet (e.g. aspirin) therapy in the week prior to and in the week after the focused ultrasound procedure.
2. The subject will be instructed not to eat or drink after midnight prior to the MRgFUS procedure, in order to permit the use of immediate general anesthesia in case of a treatment complication that may require emergency intervention.
    -
3. Medications will be reviewed to confirm regimen is unchanged since study enrollment. Record prescribed and PRN medication usage.
4. An IV line will be positioned for the delivery of fluids and any medications required during the procedure. Some of the subjects may require a urinary catheter to keep the bladder empty during treatment. Noninvasive monitoring of heart rate, blood pressure, systemic oxygen saturation, electrocardiogram, and end-tidal CO2 will be maintained throughout the procedure using standard MR-compatible monitoring devices.
    - The anesthesiologist or nurse anesthetist will administer appropriate medications for subject management if necessary. Since the medial thalamotomy procedure is image-guided and does not rely on intraprocedural feedback for targeting, intravenous sedation may be used as necessary for comfort. Subjects will not be intubated.
5. The subject's head will be carefully shaved and examined for pre-existing scalp scars or any other scalp lesions.
6. Graduated compression stockings will be worn to prevent deep venous thrombosis in the lower limbs.
7. The subject's head will be placed in the immobilization unit (similar to those used in stereotactic radiotherapy head fixation).
8. Subject will be positioned supine and headfirst on the MRgFUS therapy table.
9. The half-spherical helmet containing the elements of MRgFUS transducer will be positioned around the subject's head in the treatment position. This should be done according to measurements taken from the pre-operative/imaging session(s).
10. A rubber diaphragm will be attached to the subject's head and to the transducer to create the acoustic coupling system between the ultrasound transducer and the scalp.
11. The immobilization system will be secured over the subject head to maintain a constant relationship between the target and the transducer.

12. A localizer scan (quick T1) and a non-contrast T2-FSE MR scan will be obtained to allow further refinement of the position the MRgFUS transducer focal point with respect to the targeted zone.

13. The interface within the rubber diaphragm will then be filled with degassed water. This volume will be completely filled with care to avoid air bubbles between the face of the transducer and the scalp. Through active circulation and cooling system, the water will be maintained chilled throughout the procedure to avoid undesired heating of the scalp and skull.

14. A series of MR images will be acquired to identify the target area, and plan the actual treatment
    - T2 Weighted imaging exam along at least 2 axes: Axial and Coronal
    - Other MR imaging series may also be acquired
15. The pre-therapy MRI and CT image datasets will be registered to the T2 weighted MR images that were just acquired. This image fusion of pre-operative MR assists in the accurate delineation of the target area and determination of a safe sonication pathway
    - The fusion of the CT data is required for the computation of phase correction values to correct for skull aberration, and identification of intracranial calcifications
    - Scars of the scalp will be designated to ensure the ultrasound beam avoids these specific areas

16. The treatment volume and plan will be defined by the neurosurgeon. The MRgFUS system will automatically compute the number of sonications, and the (per sonication spot) phase and amplitude corrections necessary for the system to produce a focal spot at each of the desired locations.

17. An intravenous line will be maintained throughout the procedure. Noninvasive blood pressure, systemic arterial oxygen saturation, electrocardiogram, and end-tidal carbon dioxide will be monitored throughout the MRgFUS treatment using standard MRI-compatible monitoring devices.

NOTE: All procedures for both arms are the same to this point. Below is the description of treatment for ExAblate Arm. The Sham will be identical except that the energy will be turned to 0.

18. A central point in the targeted area will be targeted with a low dose, sub-lethal energy level sonication to confirm the targeting accuracy on the MR images. Focal point position and/or transducer location will be adjusted as necessary. The bilateral lesioning will be planned and executed as follows:

a. Stereotactic planning of both (left and right) medial thalamic targets will be performed on the ExAblate Neuro workstation in the pre-planning phase. The central lateral thalamic nucleus CLT nucleus will be targeted by stereotactic coordinates in reference to the midcommissural point of the ACPC line.
b. If the pain symptoms are asymmetric or unilateral, the CLT nucleus contralateral to the most symptomatic side will be treated first. The acoustic energy will be escalated in a series of incremental sonications until a therapeutic ablation of temperature of 60-65^{0}C is reached by peak voxel, MR thermometry. The second, ipsilateral CLT target will then be treated with the same protocol.

c. If the pain symptoms are symmetric, the nondominant CLT will be treated first. The dominant side CLT will be treated as the second target.

19. To enhance the procedure safety and mitigate some of the inherent risks of thermal lesioning of brain tissue:
    a. The thalamotomy treatment will be performed as a series of sonications with small increments in power within the designated target volume.
    b. The subject will be examined periodically by the clinical team for neurologic signs and symptoms.
    c. Sonication will start with low energy prior to permanent thermal ablation. This is to ensure the planned sonication to be centered on the CL nucleus of the Thalamus. Low energy sonication will non-destructively warm the target. The warming will be captured by the MR thermometry and the MR thermal images will be displayed in real time to the treating physician. The physician will then verify that the warming is centered on the anatomic target. This will allow the centering of the eventual permanent thermal lesion in the correct location, in the center of the CL nucleus of the Thalamus.
    d. The titration of escalating focal sonications will continue up to 60ºC within a 5 mm diameter centered on CL, or until potential side effects are reported by the subject or observed by the clinical team.
    e. The MRgFUS system is equipped with Stop Sonication Buttons: one for the subject to utilize, one for the nurse/anesthesiologist, and one for the treating physician to use. Hence, in the event of discomfort or pain, the subject will have the ability to abort the sonication at any time by activating the Stop Sonication Button. Once this button is activated, the system will instantly stop the energy delivery. The same thing will happen in the event the treating physician or the nurse activates their button. After addressing the subject concerns or discomfort, the procedure may continue without further delay. All adverse events that may be caused by these potential activation(s) of the Stop Sonication Button will be captured on the CRFs.

20. The physician may decide to terminate the sonication procedure at any time. For example for any of the following reasons:
    a. the subject's wish to terminate due to pain, severe discomfort, or any other reason,
    b. development of focal neurological deficits,
    c. occurrence of seizures,
    d. MRI signs of intracranial bleeding or significant brain swelling
    e. targeting difficulties, due to subject motion,
    f. inability to observe the focal point during sonication,
    g. inability to communicate with the subject
    h. any other medically indicated reason
21. After the procedure, an initial series of T1 or T2 weighted MR images will be acquired along two planes to assess the early treatment effects. Comprehensive MR imaging is obtained the following day with a head coil to optimally characterize the lesion. This will include: T1, T2, SWI, DWI, and DTI.

    In the event of new neurological deficits or seizures are observed, other imaging modalities (including CT) should be performed immediately in addition to neurological and physical examinations.
22. The subject will be removed from the ExAblate table and taken to the hospital for recovery and neurological observation until the next morning. The neurosurgeon will evaluate the subject's neurological status and make a decision whether or not to discharge the subject. Subjects who are found to be neurologically unstable will remain in the hospital until the neurosurgeon determines it is medically indicated to discharge.
23. Subject will be asked the "Patient Blinding Question" to determine whether or not they believe they had a sham or real procedure.

6.6 Sham Procedures

For all subjects randomized to a sham procedure, all activities will occur including I.V. lines, planning MRI's, etc, and an identical procedure will be performed with the energy output disabled. The treating physician will determine a sonication (treatment) time for sham subjects to be similar to that which is occurring in the treatment arm to maintain consistency between arms. It should be noted that all treatment times of study arms will be captured in the study CRF.

6.7 Follow-up

Subject follow-up will be completed at Day 1, Day 7, Month 1, and Month 3 for all subjects who underwent CL lesioning/ablation using ExAblate system. Subject follow-up will be similar for those who underwent sham treatment. At 3 months, subjects who had sham treatment will be unblinded and offered MRgFUS.

Subjects will be evaluated at all follow-up visits for general health, neurological changes and efficacy measurements as well as for device/procedure related adverse events that may have occurred during the follow-up period. Medication regimen and PRN usage will be recorded at each follow-up along with the following assessments:

6.7.1 Day 1

- Evaluation of general health and neurological changes
- NPRS (Worst pain in 24 hrs)
- PROMIS
- Assess patient blind
- Assess safety and update adverse events as needed
- Review medications and record any changes
- MRI

6.7.2 Day 7

- Evaluation of general health and neurological changes
- NPRS (Worst pain in 24 hrs)
- PROMIS
- PGIC
- Assess patient blind
- Assess safety and update adverse events as needed
- Review medications and record any changes
- MRI

6.7.3 Month 1

- Evaluation of general health and neurological changes
- NPRS (Worst pain in 24 hrs)
- PROMIS
- PGIC
- Assess patient blind
- Assess safety and update adverse events as needed
- Review medications and record any changes
- MRI

6.7.4 Month 3

- Evaluation of general health and neurological changes
- NPRS (Worst pain in 24 hrs)
- PROMIS
- PGIC
- Assess patient blind
- Neuropsychological Pain Assessment
- GAD-7
- PHQ-9
- PCS
- BBHI-2
- MRI

- Dynamic FDG PET
- Assess safety and update adverse events as needed
- Review medications and record any changes
- Evaluation by a pain management physician

All pre-treatment and post treatment MR images will be de-personified (i.e.: subject identifiers made anonymous), archived and sent to InSightec. These analyses will also include full radiological assessments from baseline through all follow up visits.

In this study, subjects who use alternative treatments (not including medication change) during the 3-month follow-up period will be exited from the study, after completing required study examinations. The reason(s) for study exit will be noted on the Case Report Forms.

7.0 STUDY REQUIREMENTS AND VISIT SCHEDULE

The table below summarizes the study visit schedule and procedures.

Table 1 Schedule of Events

Procedures	Screening	Baseline (within 1 week of day 0)	Day 0 (Procedure)	Day 1	Day 7 (±3 days)	Months 1 (±7 days)	Month 3 (±14 days)[1]
Written Consent	X						
Check Eligibility	X						
Demographics	X						
History and Physical Exam		X					
Screening Labs	X						
CT Scan	X						
MRI	X			X	X	X	X
Dynamic PET		X					X
NPRS and PROMIS Pain Questionnaires[2]	X	X		X	X	X	X
PGIC					X	X	X
Neurological Exam	X			X	X	X	X
Pain Psychological Exam[3]	X						X
Pain Management Exam	X						X
MRgFUS Treatment or Sham Procedure			X				
Assessment of patient blind			X	X	X	X	X
Concomitant Medications (prescribed and PRN)	X	X	X	X	X	X	X
Adverse Events			X	X	X	X	X

[1] Subjects will be un-blinded to randomization arm at the completion of month 3 visit. Subjects who initially were randomized to the sham arm may go back to day 0 in schedule of events and receive an unblinded MRgFUS thalamotomy.

[2] Five PROMIS fixed length short forms to be completed on paper at each indicated timepoint. PROMIS scale v1.0: Pain Intensity 3a, Pain Behavior 7a, Pain Interference 8a. PROMIS scale v2.0: Neuropathic Pain Quality 5a, Nociceptive Pain Quality 5a.

[3] To include: GAD-7, PHQ-9, PCS, BBHI-2

8.0 DATA ANALYSIS PLAN

A statistical analysis is not proposed. For this study, the Safety and Effectiveness assessment will be descriptive with no statistical endpoints. The results will be examined and analyzed and used as a basis for determining the nature of future studies.

8.1 Safety

All adverse events will be recorded and categorized according to severity, relationship to procedure and relationship to device. Any subject who receives at least one sonication will be considered Intent to Treat (ITT) for safety assessments. 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.

8.2 Efficacy

The primary efficacy outcome is the change in worst NPRS score from baseline to 3 months compared between medial thalamotomy and sham procedures with no change or increase in baseline pain medications. A mean change of 2 points has been shown to be clinically significant.[99] Responder analysis (e.g. number of subjects who have 3-point or better improvement in worst NPRS pain score at 1 and 3 months) will also be performed. Data analyses will also be performed on all PROMIS measures and other subject-reported measures, including PET.

If there is a significant symptomatic pain medication change following MRgFUS treatment, the subject's data will not be used in the Efficacy analysis but the aspects of their procedure will still be included in the Safety analysis.

8.3 Subject Health Status

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

8.4 Statistical Considerations and Sample Size

This is a feasibility study of ten (10) subjects who will be randomized in 1:1 fashion to receive either bilateral FUS medial thalamotomy or a sham procedure. A statistical analysis is not proposed. Nevertheless, reported adverse events will be examined and analyzed and used as a basis for determining the nature and extent of future studies.

8.5 Subject Confidentiality

Subject confidentiality will be maintained throughout this study, including all publications. Data collected and entered into the CRFs are the property of Insightec as the study sponsor. Representatives from the study sponsor or authorized sponsor representatives, the Institutional

Review Board Ethics Committee or other regulatory bodies may receive copies of the study records and may review medical records related to the study.

9.0 RISK MITIGATION

Worldwide, over 12,500 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). This data has been re-examined by InSightec 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 that is completely different from the body system. This system is referred to internally as the Exablate Neuro system. However, in principle, the body and brain systems have the same purpose namely to coagulate soft tissue within the body by means of MR guided high intensity focused ultrasound. The potential risks described below will be explained to the subject in the informed consent process.

9.1 General Device Related Risks

Risk of Magnetic Resonance Scanners:

MRI has no known deleterious biological effects in subjects with no contraindications. The incidence of claustrophobia during MRI examinations is approximately 10-15%, although it is expected to be less frequent in the study population due to the use of sedation.

Risk of Intravenous (IV) Catheter:

There is a potential risk from the IV catheter used during the ablation. Participants can expect a small amount of pain and/or bleeding/bruising at the IV site. There is a small risk of infection. This procedure will follow the 'standard of care' at the study sites.

Risks related to Dynamic FDG PET imaging:

PET Scan: This imaging study involves radiation exposure from a Positron Emission Tomography (PET) scan combined with a Computed Tomography (CT) scan using the radiopharmaceutical F-18 FDG. Using the standard way of describing radiation dose, from participating in this study, the wall of your bladder, heart, and pancreas will receive the most radiation from this study. All other organs will receive smaller amounts of radiation. Although each organ will receive a different dose, the total effective radiation dose you will receive from one procedure is approximately 10 mSv. You will have 2 of these scans. For comparison, this dose is roughly 40% the annual radiation dose safely allowed for a radiation worker such as the person performing your scan.

This radiation exposure is not necessary for your medical care but is necessary to obtain the research information desired. This radiation dose is what you will receive from this study only and does not include any exposure you may have received or will receive from other tests. If you

are pregnant or breastfeeding, you may not participate in this research study. It is best to avoid radiation exposure to unborn or nursing children since they are more sensitive to radiation than adults.

9.2 Risk of Contrast Agent

This study does not intend to use MRI or CT contrast agents.

9.3 Risks incidental to the MRgFUS treatment

- There is a potential risk of conscious sedation, which includes reaction to the drugs or over-sedation.
- There is a potential risk from the intravenous catheter used during the treatment. Subjects can expect a small amount of pain and/or bleeding/bruising at the IV site. There is a small risk of infection. This procedure will follow the 'standard of care' at the Study Sites.
- There is a potential risk to the subject of deep venous thrombosis from lying stationary for 3 to 4 hours. The risk to the subject from lying still for this treatment should be no greater than that of lying still for any other reason. Subjects will be provided compression stockings, as described above (Section 4.3), to use during treatment. All subjects will be screened for DVT prior and post-ablation procedure. This will further reduce the risk to subjects by screening out all those with DVT risk prior to ablation.
- There is a risk that the subject may experience a sore neck or discomfort from lying in the same position for a long time during the treatment.
- There is a potential risk from a urinary catheter if used during the procedure. Participant may expect varying levels of Urinary Tract Infection due to the use of the urinary catheter. In a different study for the MRgFUS treatment of uterine fibroid (Pivotal study under IDE G020001 that lead to PMA approval under PMA # P040003), the incidence of this risk was found not to exceed 3.7%. This procedure will follow the "standard of care" at the study sites.

9.4 Risks Associated with the MRgFUS Treatment

- There is a potential risk of hemorrhage during MRgFUS treatment. In MRgFUS thermal ablation, the high temperature at the focal point results in immediate protein denaturation and coagulative necrosis. This should be expected to rapidly stop any bleeding that might occur in the capillary bed and within small vessels. At the end of the MRgFUS procedure an unenhanced MR scan is performed to assess the treated area and adjacent tissues.
- There is a risk of discomfort to the subject caused by heating of tissue. Focused ultrasound therapy involves precisely controlled pulses of thermal energy resulting in tissue coagulation (typically 55-65°C for several seconds) in small tissue volumes. This induces thermal coagulation of the targeted soft tissue. The energy intensity at the level

of the skin is quite low, and there should be no local heating, hence no sensation of pain at the scalp. The rise in temperature in the skull should be kept to below pain level by active cooling of the water within the rubber diaphragm. Because the focal point of the beam will be > 2.5 cm from the dura and there are no pain receptors in the brain, there should be no pain associated with ablation. The subject will be in verbal contact with the physician and appropriate action can be taken in the event that a subject does experience discomfort. Remedies could involve lowering energy levels, increasing the time interval between consecutive treatment pulses, or increasing the level of sedation and/or analgesia. The subject also has the ability to abort the sonication at any time by activating a handheld cut off circuit (i.e., stop switch).

- There is a risk of imprecise targeting of the focal point, and ablation of an area of tissue outside the planned treatment volume. If this occurred it is possible that serious neurological deficit or even death could result. To limit the risk of this occurring, the treatment process includes a mandatory verification step that requires the operator to first check the alignment of the subject anatomy, the focal point of the transducer and the MR imaging system. This procedure, done while the subject is in position for treatment, uses a very low energy sonication to confirm of the alignment of the focal point and the targeted treatment point in all three axes. For each sonication delivered during treatment, the operator gets continuous feedback on the position of the intended treatment point superimposed on the thermal dosimetry image and can make corrections where required. At any point in the treatment process this low-power verification of the localization may be repeated prior to full power sonication.
- There is the risk that the tissue along the path to the target (scalp, skull, dura, brain, etc) could become heated to the point where tissue-damage or a burn might occur. This heating could be caused by direct improper treatment targeting, irregularities on the skin surface (e.g.: scars), treatment of a volume of tissue too close to the skin or bone, energy absorption by the bone, or the conduction of sufficient heat to cause a burn at the surface. In the case of a first or second degree burn of the scalp, the skin should heal without a scar. In the case of a 3^{o} burn, a scar, or loss of sensation in the area of the burn could result.
- Although skin burn is a risk associated with both the ExAblate Neuro and body systems, there have been no cases of skin burn in all ExAblate Neuro treatments; over 400 subjects have been treated with the ExAblate Neuro system to date. However, over the last decade, there have been four reports of skin burns in breast treatments and two reports of skin burns in uterine fibroid treatments. These subjects were treated with the ExAblate body system. The circumstances of these events are not applicable to the ExAblate Neuro system. However, the heating in the energy pass zone is always monitored and an additional cooling time can be administered when elevated temperatures are detected. Because the issue of energy absorption and overheating of the skull and scalp is so critical in the brain application, this system includes an active cooling sub-system that circulates the water in the space between the face of the transducer and the scalp. This will help keep the scalp within a safe temperature range and reduce the risk of overheating. If non-superficial tissue along the path to the target

were to become heated to the point that damage occurs, there is the possibility that it would result in significant neurological damage or even death. To reduce the possibility that this could occur, several measures will be taken:

- First, the procedure is performed in the MR scanner. During the treatment MR images will be acquired. Using specific scanning sequences and a rapid post-processing program, changes in temperature can be detected, and a thermal map of the brain generated. This thermal map will reveal any potentially dangerous elevations in temperature.
- Third, MR-compatible pulse oximeter, blood pressure cuff, and EKG monitor will be monitored throughout the procedure. This information will permit detection of tissue damage, edema, or bleeding, if brain or blood vessels along the beam paths are injured by heat.
- Finally, the subject and the neurosurgeon will each have a stop switch that can instantaneously interrupt the energy delivery at any time. The subject is given a stop switch in case aberrant tissue heating causes any compromise to speech, word finding, or other communication difficulties. The subject will be instructed prior to the proceeding that they should use the stop switch any time they feel excessive pain, discomfort, disorientation or any other unusual sensation. The neurosurgeon has a stop switch so that if there is any sign of neurological change, the energy delivery can be immediately stopped and the subject carefully evaluated. Temporary interruption of energy delivery will in no way compromise the potential for therapeutic benefit to the subject. Following subject evaluation treatment can resume without delay.

- There is a risk associated with subject motion during a sonication or between sonications. This could cause a movement of the tissue relative to the planned treatment volume on the system, and in extreme cases could result in the treatment of a point outside the planned treatment volume. Also, because the skull functions as a defocusing lens, the phase correction map computed for the target spot will become ineffective if the subject moves. To prevent or minimize this risk, there are several precautions taken to prevent motion, and to detect it, if it occurs:
- The system is equipped with a movement detection algorithm. Prior to each sonication, a brief MRI assessment is made of fiducials in the transducer. If any of the fiducials are misaligned within the voxel coordinate system of the MRI, the system will not proceed. The movement detection algorithm is set to trigger with alterations of >2mm.
- During subject positioning every effort will be made to make the subject comfortable and the subject will be educated as to the importance of maintaining their position during the treatment.
- The subject will be managed with conscious sedation. This will enable them remain still during the procedure.

- The subject will be placed in a head immobilization unit based on a stereotactic frame. This technology has been effective in preventing movement in stereotactic neurosurgery, and has been adapted and modified to the specification of MR-guided FUS.
- One or more members of the medical team will be in the room throughout the sonication to monitor the subjects' medical status and comfort. Hence, subject motion will also be monitored.
- There is a risk of cavitation in the tissue at the focal point. Cavitation is the collapse of rapidly developed gas bubbles at the focal point due an extreme intensity of ultrasound excitation. This rapid collapse could cause high pressure, shock waves, and high temperatures. All systems are now equipped with cavitation detectors.
- There is a risk of blood brain barrier (BBB) disruption, edema, swelling, hemorrhage outside and remote to the targeted area. These events may theoretically occur due to heating effects (ie secondary hot spots) and or to the pressure wave of the ultrasound beam. The secondary hot spots risks are discussed below. To address the risks due to pressure waves of the ultrasound beam path, the system has been designed to be well below the "pressure wave threshold" that may trigger events of this nature. In all cases, thermal and regular imaging will be continuously assessed during the procedure. Finally, the subject(s) is continuously monitored by the anaesthesiologist (or nurse anaesthetist) during the ablation procedure for any change in the subject condition.

9.5 Risks related to bilateral lesioning of central lateral thalamic nucleus

We perceive the following primary risks of bilateral FUS medial thalamotomy based on our review of the historical literature of medial thalamotomy, the extensive experience of CL thalamotomy by our colleague Jeanmonod, and our experience with FUS Vim thalamotomy for ET:

1. Somatosensory deficit & increase pain – from lateral extension of the lesion to VPL
2. Transient cognitive disturbance or confusion
3. Hemorrhagic morbidity – from thermal ablation
4. Cavitation – from focused ultrasound

Somatosensory deficit & increased pain.

Medial thalamic lesions target the intralaminar nuclei and do not result in discriminative somatosensory deficits. Historical lesion of the lateral thalamus (VPM/VPL) often resulted in somatosensory deficits and increased pain due to deafferentation. In order to mitigate this risk, medial thalamic lesions will be confined to the CL nucleus and will not extend laterally to the VPM. The laterality of the coordinates for medial thalamic lesions will be maintained less than 10 mm.

The thermal lesioning process with focused ultrasound could cause **neurological effects** for several reasons. Any effects outside of the treatment area could result in neurologic signs or symptoms. These could occur from the thermal lesioning process that is 'off-target' or

associated infarction, hemorrhage or edema. Subjects will be observed and monitored during the treatment for signs of neurologic side effects. They will also be observed overnight on the neurosurgical ward. Most neurologic side effects would manifest within minutes to hours. Those related to cerebral edema will be transient and expected to resolve within 2-3 weeks.

Perioperative confusion has infrequently been observed with medial thalamotomy procedures. Jeanmonod reported one case of somnolence from 96 Radio Frequency (RF) CL thalamotomies[100] and no occurrences when the lesions performed with FUS.[54] The risk of this almost certainly increases with older age. In order to mitigate the risks of perioperative confusion or cognitive decline, subjects will undergo preoperative psychological assessment to gauge their cognitive reserve exclude those with significant cognitive impairment. The precise delivery of acoustic energy with MR-guidance will ensure that lesions are not delivered outside of the targeted CL nuclei – a technology that much less susceptible to confounding features like brain shift or stereotactic inaccuracies. MRgFUS has been shown consistently with submillimeter precision.[79,81]

Symptomatic intracerebral hemorrhage with stereotactic procedures has been consistently estimated to range from 1 to 2%, and may be slightly higher with pallidotomy procedures which have been reported in large series to almost 4%. Intracerebral hemorrhage from stereotactic RF lesions likely occurs in a slightly higher fashion than stereotactic FUS lesioning because electrode penetration of the brain is required. In order to mitigate the risk for intracerebral bleeding from FUS, subjects with severe hypertension and coagulopathy will be excluded from trial participation, and normotension will be maintained throughout all procedures.

In the RF ablation experience of the PI, out of a series of 94 radiofrequency lesioning procedures for movement disorders, a single 10-mm thalamic hemorrhage was noted in a subject undergoing thalamotomy at a probe tip temperature of 70ºC. (unpublished data) It is difficult to translate the probe tip temperature in an RF lesion to the target volume temperature of an MRgFUS lesion, but it may be postulated that thermal lesioning at higher temperatures could increase the risks of hemorrhage. In order to minimize such risk, we propose to perform permanent ultrasound lesioning bilaterally with a measured temperature of 65ºC at the target. This temperature is sufficient for thermal coagulation of the target but well below the peak temperature observed in the case cited above. The experience of the ExAblate TcMRgFUS thalamotomy in the treatment of subjects with neuropathic pain and Essential tremor entailed treatment to 65ºC at target without any observed neurologic or hemorrhagic consequences.

Cavitation. More recently, Jeanmonod et al. achieved central lateral thalamotomy ablations with submillimeter precision[79] for therapy resistant neuropathic pain syndromes using focused ultrasound. There was a single thalamic hemorrhage resulting in neurologic morbidity which possibly occurred from cavitary effects. This complication led to the universal adoption of cavitation detectors in the ExAblate technology. [54]

D**elayed ischemic infarction** has been rarely observed with stereotactic RF lesioning of the basal ganglia. The occurrence of this complication has been only reported in 3 of 50 cases of RF pallidotomy, and these cases occurred in subjects with a significant history of vasculopathy

identified either clinically or radiographically. [101] These ischemic events occurred in a delayed fashion at 10, 51, and 117 days following the procedure. One of 89 subjects undergoing subthalamotomy presented with a delayed onset of involuntary movements at one week and imaging suggested a thalamic/subthalamic infarction[102] It is postulated that these delayed infarctions results from damage to the perforating of vessels of the basal ganglia. Lenticulostriate perforating vessels are much less prevalent in the medial thalamus. Subjects at risk for bleeding (low clotting factors or anticoagulants) are excluded. In addition, heating should seal vessels.

Infection has been rarely observed with stereotactic lesioning and certainly with less frequency than occurs with implanted devices from DBS procedures. We anticipate a negligible risk for meningitis or brain abscess with ExAblate thalamotomy as this is not an open brain procedure requiring incisions or burr holes through the skull.

Mortality. There have been no mortalities in over 400 ExAblate Neuro ablations performed worldwide. The mortality rate with surgical radiofrequency thalamotomy, a much more common procedure that has been employed for decades, has not been reported and likely occurs in much less than 1% of cases. At the University of Virginia, over 100 radiofrequency thalamotomies have been performed without mortality.

9.6 Risks Related to the Sonication Pathway

Skin: The treatment set-up process includes filling the gap between the ultrasound transducer and the skull with a water-filled membrane to provide acoustic coupling. There is a possibility of small air bubbles remaining attached to the skin. These could cause a small focal hot spot and cause local pain or a burn to the scalp. The active cooling mechanism unique to this system is designed to reduce the risk of skin burns and improve subject comfort. In previous studies, MRgFUS treatments have caused burns of the skin (see analysis above). To minimize this risk, the scalp will be carefully shaved, and scars or other irregularities (e.g. eczema) will be kept outside the treatment pathway. Subjects with remarkable atrophy and poor healing capacity of the scalp (> 30% of the skull area traversed by the sonication pathway) will be excluded from this study.

Skull and air-filled spaces: In the treatment planning, air-filled spaces (frontal, ethmoid, sphenoid sinus, mastoid) inside the skull are identified in bone window CT images and kept outside the pathway. Other irregularities of the skull, which might scatter the acoustic energy, are compensated for in the system. Skull may become heated by absorbing more acoustic energy than normal soft tissue. The skull cannot sense pain but the overlying soft tissues may sense pain if the bone becomes heated. MRI thermometry at 1.5 T is able to detect changes of ±3 Celsius in soft tissues [103]. Possible heat transfer from the skull bone to the brain by successive sonications is monitored by MRI thermometry of the cortex and white matter. The sonication duration and energy levels, and the cooling times between the sonications are adjusted so that the focus in the target tissue is heated while allowing other tissue to cool down between sonications. Local bone damage is very unlikely because the active cooling mechanism system is designed to keep the bone temperature below a temperature that can damage it. Based on the data acquired to date and reviewed by FDA under G020182/S04, the average temperature rise at the skull level ranges

between 1 to 5 Celsius. Hence, this active cooling strategy should continue to provide the safety needed.

Dura, meningeal arteries and venous sinuses: The dura adjacent the skull may absorb heat if the bone becomes heated. Dura itself may sense pain and the main branches of the arteries are sensitive to heat. The meningeal arteries can generally be avoided in the treatment planning as their grooves in the skull are visible in 3D-CT. Local necrosis of the dura is unlikely, and were it to happen, it would not cause cerebrospinal fluid leakage. The venous sinuses between the two leaves of the dura, the sagittal sinus, the straight sinus and the transverse sinus may be in the sonication pathway. Their heating will be avoided by the active cooling sub system. The sigmoid sinus and the cavernous sinus will be kept outside the pathway due to their proximity to the skull base and cranial nerves, respectively.

Subarachnoid space: Cerebrospinal fluid in the thin subarachnoid space between the dura and the cortex could possibly transfer heat from bone to the cortex. There is no specific risk to the CSF itself becoming heated. Because it can flow within the subarachnoid space, this can serve as another mechanism to prevent local hot spots next to the skull.

Cortex: In prior studies of ExAblate lesioning of thalamus for tremor, nearly one hundred subjects have been treated without any neurological or imaging evidence of cortical effects. All subjects have been assessed posttreatment with MRI, and there have not been detectable changes outside of the treatment area.

Brain, cranial nerves and cerebral arteries: In this study the treatment path will avoid cranial nerves and major cerebral arteries (ICA, MCA, ACA, BA).

Micro-calcification: The subject population of this study may have some level of micro-calcification present in the brain tissue. Given calcium's higher absorption of ultrasound energy, its presence may create additional heating effect along the beam path. This risk is mitigated by utilizing the CT data (to localized the calcified areas) and the various tools of the ExAblate system to delineate these areas so that the beam is blocked from passing through these calcified areas.

Secondary Hot Spots: theoretically speaking, there is a potential risk due to secondary hot spots that may occur along the beam path outside the focus. This has been reported in the literature for different types of transducer configurations using similar frequencies. The ExAblate system, with its unique, highly focused transducer configuration, was tested extensively using advanced simulations. The results of this work showed no evidence of significant hot spots away from the focal area. In any case, the real time thermal imaging feedback samples the entire field of view around the targeted tumor. These thermal images are displayed during the course of the energy delivery and therefore if there is evidence of any secondary hot spot is observed, the treating physician will be able to utilize the other specific feature of the ExAblate system that is "real-time" stop sonication button that instantaneously halts energy delivery. Hence, if this risk exists, the system is well equipped to handle it in real time and prior to incurring any tissue damage.

9.7 Neurological Risks

The thermal lesioning process with focused ultrasound could cause neurological effects for several reasons. Any effects outside of the treatment area could result in neurologic signs or symptoms. These could occur from the thermal lesioning process that is 'off-target' or

associated infarction, hemorrhage or edema. Subjects will be observed and monitored during the treatment for signs of neurologic side effects. They will also be observed overnight on the neurosurgical ward. Most neurologic side effects would manifest within minutes to hours. Those related to cerebral edema will be transient and expected to resolve within 2-3 weeks.

9.8 Anticipated Treatment Side Effects from MRgFUS

All adverse events will be reported in the Case Report Forms (CRFs) and analyzed for their relation to the ExAblate device as well as other causes (Expected procedure findings, Drug/Contrast media reactions, Medical conditions, and Unrelated to device or procedure). Adverse events related to the device or procedure occur during or shortly after the procedure (within 30 days) since the effect is a one-time, focal treatment. Based on existing treatment experience in the brain using the ExAblate Neuro Type 1.0 (650 KHz), the following anticipated side effects have been identified as possibly occurring during/following the ExAblate procedure.

9.8.1 Procedure-related events include:

- Claustrophobia. Medications may be useful in controlling symptoms, but may also result in nausea/vomiting.
- Pain/discomfort:
    - Sonication-related headache or head/face flushing or warmth. Usually these are transient, but are coincident with a sonication. Headache may occasionally last for several days.
    - Headache may related to the headframe or fasting status. The brain has no pain sensors, but the scalp, dura and bone tissues do.
    - Position-related pain related to being uncomfortable in the scanner (e.g., sore neck, back pain, muscle or joint pain.
- Hypertension/hypotension, and bradycardia/tachycardia may be related to pre-procedure nervousness or comorbid conditions / missed medication dose pre-procedure as an NPO requirement. Medications can be administered peri-procedure to control them.
- Neurological deficits may result from damage to nearby structures in the brain and thus is specifically related to the target location. To date, the following has been reported:
    - vestibular with or without vegetative manifestations
    - paresthesias
    - dysesthesias/pain.

9.8.2 Events which are Unrelated to the ExAblate device include:

- Events associated with the headframe, such as pin site pain, pin site or scalp/facial edema, pin site burning or bleeding.
- Events associated with the urinary catheter, such as urinary tract infection.

- Events associated with the intravenous line used to administer medications, such as infection and/or bruising.
- Events that are associated with comorbid conditions or unforeseen circumstances.

9.8.3 Drug reactions include:

- Nausea or vomiting
- Dizziness
- Overdose or mis-dosing in error

9.8.4 Events related to malfunction or mis-use of the device include:

- Mis-alignment, mis-targeting or reflection of the ExAblate beam.
- Heating of structures in the FUS backbeam or forebeam
- Additionally, the following side effects are thought to be improbable but their relative risks remain to be defined:

Scalp in the sonication pathway: ● Skin burns (>2º) with ulceration of the skin ● Scar formation ● Loss of sensation ● Atrophy *Bone in the sonication pathway:* ● Bone necrosis	*Dura, venous sinuses, and cortical veins* ● Subdural bleeding ● Vein thrombosis ● Cortex heating ● Seizures ● Symptoms from disturbances of eloquent cortical areas (motor, sensory, auditory, visual, speech)
Other brain tissue ● Necrosis of normal tissue due to incorrect targeting ● Thermal damage to adjacent functional brain tissue (e.g.: optical tract) ● Bleeding in the treated area ● Cerebral infarction ● Moderate or severe increase in cerebral edema as shown by MRI scans ● Symptomatic increase of intracranial pressure ● Death	*Cerebral arteries* ● Bleeding ● Coagulation thrombosis ● Vasospasm ● Death

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.

Focused Ultrasound thalamotomy has previously been described for essential tremor. These thalamotomies for tremor were performed unilateral to the ventral intermediate nucleus, which is located adjacent to the internal capsule and ventral posterolateral somatosensory nucleus of the thalamus. The medial thalamic target for this study will serve as a central lateral thalamus, and immediately positioned intralaminar nucleus that should not incur risks for sensory, motor, or

cerebellar disturbance. This nocioceptive region of the thalamus will be targeted bilaterally. Acoustic energy will be titrated until peak voxel temperatures at the target reach 55 to 65 degrees Celsius. Intraoperative feedback is less important for this target than for tremor monitoring, so subjects can undergo intravenous sedation for comfort without losing localizing clinical feedback. The postoperative care of medial, CL thalamotomy will be the same as those for Vim thalamotomy with a one day hospital stay.

9.9 Adverse Reactions and Precautions

The subjects will be educated as to what to expect during the procedure and the importance of immediately communicating any problems, unusual symptoms, or discomfort, to the investigator during the treatment and throughout the follow-up period. Subjects will also be educated as to what sensations or perceptions could indicate that neurological damage may be starting to occur. They will be told to use their handheld stop sonication button if they felt anything unusual may be happening so that they can be neurologically assessed. All adverse reactions occurring in this study will be recorded in the Case Report Forms. Each will be assessed for its probable cause (unrelated to the treatment, device related, procedure related, etc) as described below.

9.10 Criteria for Removal from the Study

Subjects can be exited from the study at any time if in the opinion of the principal investigator it is not in the best interest of the subject to carry on as planned. In addition, subjects may also choose 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).

9.11 Criteria for Stopping the Study

The study will be stopped for evaluation should:

1. any death occur, or
2. if two or more subjects experience
    a. a cerebrovascular hemorrhage
    b. or serious related neurological adverse event
    c. or a 50% increase in pain from Baseline following two consecutive visits starting from 7-days post treatment visit.

10.0 Adverse Event Reporting

It is the responsibility of the investigator to document all treatment related and device related Adverse Events (AE's), which occur 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 subject's CRF. The nature of each event, date and time (when appropriate) of onset, outcome, frequency, maximum intensity, action taken, and attribution 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.

If an AE increases in frequency or severity during a study period, a new record of the event will be started.

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.

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 InSightec through the eCRF 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.

Other common non-study or non-device related, minor health complaints will not be collected as AEs (for example: colds, sprains, headaches). Subjects who have a progression of their primary disease or symptoms that lead to an alternative treatment will not be reported as an AE.

10.1 Adverse Events Analysis

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. We would closely monitor all treatments for any AE's, and consider the following questions for AEs in the Test Arm:

- Was the adverse event serious?

- life-threatening, caused a disability: required or prolonged hospitalization: caused death.

- *Was the adverse event device related?*
- *Was the adverse event unexpected?*
- *Is there an unreasonable risk in continuing the trial?*

If in fact it is determined that an ExAblate-treated subject experienced an AE that met all of the above criteria, we would stop the trial pending further investigation. 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 as required by the applicable regulations.

11.0 POTENTIAL BENEFITS

There may or may not be any benefit to participating in this study. This technique is still being investigated. It may provide some therapeutic value for subjects with few or no other options. The symptoms may decrease and/or the quality of life of the subject may improve due to relief of symptoms. However, there is no guarantee that this procedure will reduce, eliminate symptoms, or otherwise treat the underlying disorder. Other subjects may benefit from this procedure in the future, if further trials prove it to be a safe and effective therapy.

12.0 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 the investigational site through telephone contact and on-site visits, to ensure that:

- The trial is conducted according to FDA and ICH-GCP requirements;
- The trial is conducted according to InSightec internal SOP's
- 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.

The Clinical Monitor will initiate the Study during an on-site visit and will continue to perform on-site monitoring visits as frequently as deemed necessary. The first monitoring visit will usually be made as soon as possible after enrollment has been initiated. 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 proper informed consent procedures, adherence to protocol procedures, adequate reporting and follow-up of AEs, and device procedure information. 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 at each visit. 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.

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.

Monitoring procedures will follow the Sponsor SOPs.

12.1 Electronic Data Capture (EDC)

Electronic CRFs (eCRFs) will be used 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 InSightec.

13.0 INVESTIGATOR RESPONSIBILITIES

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

14.0 APPENDICES

Appendix – A: Copy of Publication of ExAblate Neuro Treatment of Neuropathic Pain

Appendix – B: Prior Investigations using ExAblate Neuro (ExAblate Model 4000 Type 1)

15.0 REFERENCES

1. Yawn BP, Wollan PC, Weingarten TN, Watson JC, Hooten WM, Melton LJ, 3rd. The prevalence of neuropathic pain: clinical evaluation compared with screening tools in a community population. Pain medicine 2009;10:586-93.
2. Torrance N, Smith BH, Bennett MI, Lee AJ. The epidemiology of chronic pain of predominantly neuropathic origin. Results from a general population survey. The journal of pain : official journal of the American Pain Society 2006;7:281-9.
3. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132:237-51.
4. Daubresse M, Chang HY, Yu Y, et al. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. Medical care 2013;51:870-8.
5. Paulozzi LJ, Mack KA, Hockenberry JM, Division of Unintentional Injury Prevention NCfIP, Control CDC. Vital signs: variation among States in prescribing of opioid pain relievers and benzodiazepines - United States, 2012. MMWR Morbidity and mortality weekly report 2014;63:563-8.
6. Dowell D, Haegerich TM, Chou R. CDC Guideline for Prescribing Opioids for Chronic Pain--United States, 2016. Jama 2016;315:1624-45.
7. Control CfD. Multiple cause of death data on CDC WONDER. Atlanta: US Department of Health Services; 2016.
8. Centers for Disease C, Prevention. Vital signs: overdoses of prescription opioid pain relievers---United States, 1999--2008. MMWR Morbidity and mortality weekly report 2011;60:1487-92.
9. Crane EH. Highlights of the 2011 Drug Abuse Warning Network (DAWN) Findings on Drug-Related Emergency Department Visits. The CBHSQ Report. Rockville (MD)2013.
10. Burchiel KJ. A new classification for facial pain. Neurosurgery 2003;53:1164-6; discussion 6-7.
11. WP M. The afferent path. The conduction of painful impulses in the spinal cord. Brain : a journal of neurology 1906.
12. Glees P, Bailey RA. The course and relations of the spino-thalamic tract in man. Acta psychiatrica et neurologica Scandinavica Supplementum 1951;74:199-206.
13. Blomqvist A, Zhang ET, Craig AD. Cytoarchitectonic and immunohistochemical characterization of a specific pain and temperature relay, the posterior portion of the ventral medial nucleus, in the human thalamus. Brain : a journal of neurology 2000;123 Pt 3:601-19.
14. Bowsher D. Termination of the central pain pathway in man: the conscious appreciation of pain. Brain : a journal of neurology 1957;80:606-22.
15. MR M. The anatomy of the so-called “pain tract” in man: an analysis of the course and distribution of the ascending fibers of the fasciculus anterolateralis. Basic research in paraplegia 1962;26:55.
16. Mehler WR. Some neurological species differences-a posteriori. Annals of the New York Academy of Sciences 1969;167:424-68.
17. Haber LH, Moore BD, Willis WD. Electrophysiological response properties of spinoreticular neurons in the monkey. The Journal of comparative neurology 1982;207:75-84.
18. Kinomura S, Larsson J, Gulyas B, Roland PE. Activation by attention of the human reticular formation and thalamic intralaminar nuclei. Science 1996;271:512-5.

19. Ishijima B, Yoshimasu N, Fukushima T, Hori T, Sekino H, Sano K. Nociceptive neurons in the human thalamus. Confinia neurologica 1975;37:99-106.
20. Rinaldi PC, Young RF, Albe-Fessard D, Chodakiewitz J. Spontaneous neuronal hyperactivity in the medial and intralaminar thalamic nuclei of patients with deafferentation pain. Journal of neurosurgery 1991;74:415-21.
21. Tsubokawa T, Moriyasu N. Follow-up results of centre median thalamotomy for relief of intractable pain. A method of evaluating the effectiveness during operation. Confinia neurologica 1975;37:280-4.
22. Bushnell MC, Duncan GH. Sensory and affective aspects of pain perception: is medial thalamus restricted to emotional issues? Experimental brain research 1989;78:415-8.
23. Davis KD, Kwan CL, Crawley AP, Mikulis DJ. Functional MRI study of thalamic and cortical activations evoked by cutaneous heat, cold, and tactile stimuli. Journal of neurophysiology 1998;80:1533-46.
24. Derbyshire SW, Jones AK. Cerebral responses to a continual tonic pain stimulus measured using positron emission tomography. Pain 1998;76:127-35.
25. Jones AK, Brown WD, Friston KJ, Qi LY, Frackowiak RS. Cortical and subcortical localization of response to pain in man using positron emission tomography. Proceedings Biological sciences / The Royal Society 1991;244:39-44.
26. Porro CA, Cettolo V, Francescato MP, Baraldi P. Temporal and intensity coding of pain in human cortex. Journal of neurophysiology 1998;80:3312-20.
27. Talbot JD, Marrett S, Evans AC, Meyer E, Bushnell MC, Duncan GH. Multiple representations of pain in human cerebral cortex. Science 1991;251:1355-8.
28. Treede RD, Kenshalo DR, Gracely RH, Jones AK. The cortical representation of pain. Pain 1999;79:105-11.
29. Vogt BA, Derbyshire S, Jones AK. Pain processing in four regions of human cingulate cortex localized with co-registered PET and MR imaging. The European journal of neuroscience 1996;8:1461-73.
30. Spiller WG ME. THE TREATMENT OF PERSISTENT PAIN OF ORGANIC ORIGIN IN THE LOWER PART OF THE BODY BY DIVISION OF THE ANTEROLATERAL COLUMN OF THE SPINAL CORD Jama 1912;58:1489-90.
31. WG S. The location within the Spinal Cord of the Fibers for Temperature and Pain Sensations. The Journal of Nervous and Mental Disease 1905;32:318-20.
32. Walker A. RElief of pain by mesencephalic tractotomy. Archives of Neurology & Psychiatry 1942;48:865-83.
33. Dogliotti M. First Surgical Sections, In Man, of the Lemniscus Lateralis (Pain-Temperature Path) at the Brain Stem, for the Treatment of Diffused Rebellious Pain.*. Anesthesia & Analgesia 1938;17:143-5.
34. Spiegel EA, Wycis HT. Mesencephalotomy in treatment of intractable facial pain. AMA archives of neurology and psychiatry 1953;69:1-13.
35. Spiegel EA, Wycis HT. Present status of stereoencephalotomies for pain relief. Confinia neurologica 1966;27:7-17.
36. Nashold BS, Jr., Wilson WP. Central pain. Observations in man with chronic implanted electrodes in the midbrain tegmentum. Confinia neurologica 1966;27:30-44.
37. Nashold BS, Jr., Wilson WP, Slaughter DG. Stereotaxic midbrain lesions for central dysesthesia and phantom pain. Preliminary report. Journal of neurosurgery 1969;30:116-26.
38. Nashold BS, Jr., Wilson WP, Slaughter DG. Sensations evoked by stimulation in the midbrain of man. Journal of neurosurgery 1969;30:14-24.
39. Amano K, Kawamura H, Tanikawa T, et al. Long-term follow-up study of rostral mesencephalic reticulotomy for pain relief--report of 34 cases. Applied neurophysiology 1986;49:105-11.
40. Shieff C, Nashold BS, Jr. Stereotactic mesencephalic tractotomy for the relief of thalamic pain. British journal of neurosurgery 1987;1:305-10.

41. Shieff C, Nashold BS, Jr. Stereotactic mesencephalotomy. Neurosurgery clinics of North America 1990;1:825-39.
42. Gybels J, Sweet W. Neurosurgical Treatment of Persistent Pain. Physiological and Pathological Mechanisms of Human Pain. Vol 11. Basel, Switzerland: Karger; 1989.
43. Gybels JM, Sweet WH. Neurosurgical treatment of persistent pain. Physiological and pathological mechanisms of human pain. Pain and headache 1989;11:1-402.
44. Walker AE. The primate thalamus: University of Chicago Press; 1938.
45. Spiegel EA, Kletzkin M, Szekely EG. Pain reactions upon stimulation of the tectum mesencephali. Journal of neuropathology and experimental neurology 1954;13:212-20.
46. Spiegel EA, Kletzkin M, Szekely EG, Wycis HT. Role of hypothalamic mechanisms in thalamic pain. Neurology 1954;4:739-51.
47. Mark VH, Ervin FR, Yakovlev PI. Correlation of pain relief, sensory loss, and anatomical lesion sites in pain patients treated with stereotactic thalamotomy. Transactions of the American Neurological Association 1961;86:86-90.
48. Richardson DE. Single unit responses in the neospinothalamic system of the cat. The Journal of surgical research 1973;14:472-7.
49. Willis WD CR. Sensory Mechanisms of the Spinal Cord. . 3rd ed. New York: Plenum press; 2004.
50. Frank F, Fabrizi AP, Gaist G, Weigel K, Mundinger F. Stereotactic mesencephalotomy versus multiple thalamotomies in the treatment of chronic cancer pain syndromes. Applied neurophysiology 1987;50:314-8.
51. Krauss JK, Pohle T, Weigel R, Burgunder JM. Deep brain stimulation of the centre median-parafascicular complex in patients with movement disorders. Journal of neurology, neurosurgery, and psychiatry 2002;72:546-8.
52. Weigel R, Krauss JK. Center median-parafascicular complex and pain control. Review from a neurosurgical perspective. Stereotactic and functional neurosurgery 2004;82:115-26.
53. Jeanmonod D, Magnin M, Morel A. A thalamic concept of neurogenic pain. Proceedings of the 7th World Congress on Pain Progress in pain research and management; 1994. p. 767-87.
54. Martin E, Jeanmonod D, Morel A, Zadicario E, Werner B. High-intensity focused ultrasound for noninvasive functional neurosurgery. Annals of neurology 2009;66:858-61.
55. Keep MF, Mastrofrancesco L, Craig AD, Ashby LS. Gamma Knife surgery targeting the centromedian nucleus of the thalamus for the palliative management of thalamic pain: durable response in stroke-induced thalamic pain syndrome. Journal of neurosurgery 2006;105 Suppl:222-8.
56. Young RF, Vermeulen SS, Grimm P, et al. Gamma Knife thalamotomy for the treatment of persistent pain. Stereotactic and functional neurosurgery 1995;64 Suppl 1:172-81.
57. Jasper H. Diffuse projection systems: the integrative action of the thalamic reticular system. Electroencephalography and clinical neurophysiology 1949;1:405-20.
58. Dempsey EW, Morison RS. The production of rhythmically recurrent cortical potentials after localized thalamic stimulation. American Journal of Physiology--Legacy Content 1941;135:293-300.
59. Dougherty PM LJ, Dimitiou T, Lenz FA. Medial thalamotomy. In: KJ B, ed. Surgical Managament of Pain. New York: Pain Surgery. Thieme; 2002:795-804.
60. Jeanmonod D, Magnin M, Morel A. Thalamus and neurogenic pain: physiological, anatomical and clinical data. Neuroreport 1993;4:475-8.
61. Richardson DE. Thalamotomy for intractable pain. Confinia neurologica 1967;29:139-45.
62. Tasker R. Thalamotomy. Neurosurgery clinics of North America 1990;1:841-64.
63. Lenz F, Dougherty P. Pain processing in the human thalamus. Thalamus 1997;2:617-52.
64. Sansur CA, Frysinger RC, Pouratian N, et al. Incidence of symptomatic hemorrhage after stereotactic electrode placement. J Neurosurg 2007;107:998-1003.
65. Leksell L. Cerebral radiosurgery. I. Gammathalanotomy in two cases of intractable pain. Acta chirurgica Scandinavica 1968;134:585-95.

66. Steiner L, Forster D, Leksell L, Meyerson BA, Boethius J. Gammathalamotomy in intractable pain. Acta neurochirurgica 1980;52:173-84.
67. Elias WJ. Editorial: tremor. Journal of neurosurgery 2013;118:711-2; discussion 2.
68. Elias WJ, Khaled M, Hilliard JD, et al. A magnetic resonance imaging, histological, and dose modeling comparison of focused ultrasound, radiofrequency, and Gamma Knife radiosurgery lesions in swine thalamus. Journal of neurosurgery 2013;119:307-17.
69. Jeanmonod D MA. The CL thalamotomy for neuropathic pain. In: Lozano AM GP, Tasker RR, ed. Textbook of stereotactic and functional neurosurgery: Springer Science & Business Media; 2009:2081-96.
70. Mehler WR. The posterior thalamic region in man. Confinia neurologica 1966;27:18-29.
71. Hirai T, Jones EG. Distribution of tachykinin- and enkephalin-immunoreactive fibers in the human thalamus. Brain research Brain research reviews 1989;14:35-52.
72. Morel A. Stereotactic atlas of the human thalamus and basal ganglia: CRC Press; 2007.
73. Morel A, Magnin M, Jeanmonod D. Multiarchitectonic and stereotactic atlas of the human thalamus. The Journal of comparative neurology 1997;387:588-630.
74. Jeanmonod D, Magnin M, Morel A. Low-threshold calcium spike bursts in the human thalamus. Common physiopathology for sensory, motor and limbic positive symptoms. Brain : a journal of neurology 1996;119 (Pt 2):363-75.
75. Lenz FA, Kwan HC, Dostrovsky JO, Tasker RR. Characteristics of the bursting pattern of action potentials that occurs in the thalamus of patients with central pain. Brain research 1989;496:357-60.
76. Llinas RR, Ribary U, Jeanmonod D, Kronberg E, Mitra PP. Thalamocortical dysrhythmia: A neurological and neuropsychiatric syndrome characterized by magnetoencephalography. Proceedings of the National Academy of Sciences of the United States of America 1999;96:15222-7.
77. Jeanmonod D. MM, Morel A, Siegemund M. Surgical control of the human thalamocortical dysrhythmia: Central lateral thalamotomy in neurogenic pain. Thalamus and Related Systems 2001;1:71-9.
78. Pirrotta R, Jeanmonod D, McAleese S, et al. Cognitive functioning, emotional processing, mood, and personality variables before and after stereotactic surgery: a study of 8 cases with chronic neuropathic pain. Neurosurgery 2013;73:121-8.
79. Moser D, Zadicario E, Schiff G, Jeanmonod D. Measurement of targeting accuracy in focused ultrasound functional neurosurgery. Neurosurgical focus 2012;32:E2.
80. Jeanmonod D, Werner B, Morel A, et al. Transcranial magnetic resonance imaging-guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain. Neurosurgical focus 2012;32:E1.
81. Elias WJ, Huss D, Voss T, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. The New England journal of medicine 2013;369:640-8.
82. Jolesz FA, Blumenfeld SM. Interventional use of magnetic resonance imaging. Magn Reson Q 1994;10:85-96.
83. Jolesz FA, McDannold N. Current status and future potential of MRI-guided focused ultrasound surgery. J Magn Reson Imaging 2008;27:391-9.
84. Cline HE, Schenck JF, Watkins RD, Hynynen K, Jolesz FA. Magnetic resonance-guided thermal surgery. Magnetic resonance in medicine 1993;30:98-106.
85. De Poorter J, De Wagter C, De Deene Y, Thomsen C, Stahlberg F, Achten E. Noninvasive MRI thermometry with the proton resonance frequency (PRF) method: in vivo results in human muscle. Magnetic resonance in medicine 1995;33:74-81.
86. Chang WS, Jung HH, Kweon EJ, Zadicario E, Rachmilevitch I, Chang JW. Unilateral magnetic resonance guided focused ultrasound thalamotomy for essential tremor: practices and clinicoradiological outcomes. J Neurol Neurosurg Psychiatry 2015;86:257-64.
87. Lipsman N, Schwartz ML, Huang Y, et al. MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. The Lancet Neurology 2013;12:462-8.

88. Elias WJ, Lipsman N, Ondo WG, et al. A Randomized Trial of Focused Ultrasound Thalamotomy for Essential Tremor. The New England journal of medicine 2016;375:730-9.
89. Gwathmey KG, Conaway MR, Sadjadi R, et al. Construction and validation of the chronic acquired polyneuropathy patient-reported index (CAP-PRI): A disease-specific, health-related quality-of-life instrument. Muscle & nerve 2016;54:9-17.
90. Burns TM. The best of both worlds: Using patient-reported plus physician-scored measures during the evaluation of myasthenia gravis. Muscle & nerve 2016;53:3-4.
91. Burns TM. Using disease-specific, patient-reported measures in everyday clinic. Neurology 2016;87:858-9.
92. Burns TM, Conaway M, Sanders DB, Composite MG, Group M-QS. The MG Composite: A valid and reliable outcome measure for myasthenia gravis. Neurology 2010;74:1434-40.
93. Burns TM, Conaway MR, Cutter GR, Sanders DB, Muscle Study G. Less is more, or almost as much: a 15-item quality-of-life instrument for myasthenia gravis. Muscle & nerve 2008;38:957-63.
94. Burns TM, Grouse CK, Conaway MR, Sanders DB, mg c, mg-qol15 study g. Construct and concurrent validation of the MG-QOL15 in the practice setting. Muscle & nerve 2010;41:219-26.
95. Burns TM, Grouse CK, Wolfe GI, et al. The MG-QOL15 for following the health-related quality of life of patients with myasthenia gravis. Muscle & nerve 2011;43:14-8.
96. Burns TM, Mauermann ML. The evaluation of polyneuropathies. Neurology 2011;76:S6-13.
97. Sadjadi R, Reilly MM, Shy ME, et al. Psychometrics evaluation of Charcot-Marie-Tooth Neuropathy Score (CMTNSv2) second version, using Rasch analysis. Journal of the peripheral nervous system : JPNS 2014;19:192-6.
98. Elias WJ, Burchiel KJ. Trigeminal neuralgia and other neuropathic pain syndromes of the head and face. Current pain and headache reports 2002;6:115-24.
99. Farrar JT, Young JP, Jr., LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain 2001;94:149-58.
100. D Jeanmonod, M Magnin, A Morel, M Siegemund. Surgical control of the human thalamocortical dysrhythmia:: I. Central lateral thalamotomy in neurogenic pain. Thalamus & Related Systems 2001;1:71-9.
101. Lim JY, De Salles AA, Bronstein J, Masterman DL, Saver JL. Delayed internal capsule infarctions following radiofrequency pallidotomy. Report of three cases. J Neurosurg 1997;87:955-60.
102. Alvarez L, Macias R, Pavon N, et al. Therapeutic efficacy of unilateral subthalamotomy in Parkinson's disease: results in 89 patients followed for up to 36 months. J Neurol Neurosurg Psychiatry 2009;80:979-85.
103. McDannold, Hynynen K, Wolf D, Wolf G, Jolesz F. MRI evaluation of thermal ablation of tumors with focused ultrasound. J Magn Reson Imaging 1998;8:91-100.
104. McDannold N, Clement GT, Black P, Jolesz F, Hynynen K. Transcranial magnetic resonance imaging- guided focused ultrasound surgery of brain tumors: initial findings in 3 patients. Neurosurgery 2010;66:323-32; discussion 32.
105. Ram Z, Cohen ZR, Harnof S, et al. Magnetic resonance imaging-guided, high-intensity focused ultrasound for brain tumor therapy. Neurosurgery 2006;59:949-55; discussion 55-6.
106. Elias WJ, Huss D, Voss T, et al. A pilot study of focused ultrasound thalamotomy for essential tremor. N Engl J Med;369:640-8.
107. Lipsman N, Schwartz ML, Huang Y, et al. MR-guided focused ultrasound thalamotomy for essential tremor: a proof-of-concept study. Lancet Neurol;12:462-8.

Appendix A

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Transcranial magnetic resonance imaging–guided focused ultrasound: noninvasive central lateral thalamotomy for chronic neuropathic pain

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Object. Recent technological developments open the field of therapeutic application of focused ultrasound to the brain through the intact cranium. The goal of this study was to apply the new transcranial magnetic resonance imaging–guided focused ultrasound (tcMRgFUS) technology to perform noninvasive central lateral thalamotomies (CLTs) as a treatment for chronic neuropathic pain.

Methods. In 12 patients suffering from chronic therapy-resistant neuropathic pain, tcMRgFUS CLT was proposed. In 11 patients, precisely localized thermal ablations of 3–4 mm in diameter were produced in the posterior part of the central lateral thalamic nucleus at peak temperatures between 51°C and 64°C with the aid of real-time patient monitoring and MR imaging and MR thermometry guidance. The treated neuropathic pain syndromes had peripheral (5 patients) or central (6 patients) origins and covered all body parts (face, arm, leg, trunk, and hemibody).

Results. Patients experienced mean pain relief of 49% at the 3-month follow-up (9 patients) and 57% at the 1-year follow-up (8 patients). Mean improvement according to the visual analog scale amounted to 42% at 3 months and 41% at 1 year. Six patients experienced immediate and persisting somatosensory improvements. Somatosensory and vestibular clinical manifestations were always observed during sonication time because of ultrasound-based neuronal activation and/or initial therapeutic effects. Quantitative electroencephalography (EEG) showed a significant reduction in EEG spectral overactivities. Thermal ablation sites showed sharply delineated ellipsoidal thermolesions surrounded by short-lived vasogenic edema. Lesion reconstructions (18 lesions in 9 patients) demonstrated targeting precision within a millimeter for all 3 coordinates. There was 1 complication, a bleed in the target with ischemia in the motor thalamus, which led to the introduction of 2 safety measures, that is, the detection of a potential cavitation by a cavitation detector and the maintenance of sonication temperatures below 60°C.

Conclusions. The authors assert that tcMRgFUS represents a noninvasive, precise, and radiation-free neurosurgical technique for the treatment of neuropathic pain. The procedure avoids mechanical brain tissue shift and eliminates the risk of infection. The possibility of applying sonication thermal spots free from trajectory restrictions should allow one to optimize target coverage. The real-time continuous MR imaging and MR thermometry monitoring of targeting accuracy and thermal effects are major factors in optimizing precision, safety, and efficacy in an outpatient context.
(http://thejns.org/doi/abs/10.3171/2011.10.FOCUS11248)

Key Words • central lateral thalamotomy • neuropathic or neurogenic pain • transcranial magnetic resonance imaging–guided focused ultrasound

Considering the inherent risks related to neurosurgical procedures, such as infections and hemorrhages, there is an obvious demand for less invasive alternative procedures. Following extensive preclinical investigations,[4–8,10,11,13,15,24,25,31,32] a clinically relevant prototype of a tcMRgFUS device for thermal ablation was developed.[9,12,14] Because of its noninvasiveness, focused ultrasound technology eliminates the risk of infection, reduces the risk of bleeding, and limits collateral damage to nontargeted tissue. Magnetic resonance imaging allows precise intraprocedural localization of the ablation target, definition and verification of safety margins for the ultrasound treatment, real-time monitoring of thermal ablation dynamics, and intra- and posttreatment assessment of intervention results.[2,3,21] The tcMRgFUS technique involves the transformation of sonic into thermal energy and the production of a thermolesion. The possibility of

Abbreviations used in this paper: CLp = posterior part of the thalamic central lateral nucleus; CLT = central lateral thalamotomy; DT = diffusion tensor; EEG = electroencephalography; tcMRgFUS = transcranial magnetic resonance imaging–guided focused ultrasound; VAS = visual analog scale; VLp = posterior part of the thalamic motor ventral lateral nucleus.

Appendix B

The ExAblate Neuro system Type 1.0 that is approved for Essential Tremor (P#150246) is also being investigated for the treatment of Parkinson's Disease, Brain Tumor and Epilepsy subjects (under IDE # G020182, G120017, G140018, G140082, G160021). The transducer helmet for the Type 1.0 system is 650 KHz and is used for ablation of deep brain targets and includes ALL clinical features and tools of the current FDA ET IDE approved version, subject interface and coupling, etc. There is no change to the thermal modeling, energy delivery, beam forming, nor treatment parameters and guidelines, and mitigating steps. Furthermore, the manufacturing process, device risk analysis, SW and HW verification and validation have also remained unchanged.

Pivotal Study for Essential Tremor IDE - G120246 - ExAblate 4000 Type-1

This global, multi-center, randomized, sham-controlled pivotal study evaluated the safety and efficacy of ExAblate Neuro unilateral thalamotomy for treating medication-refractory Essential Tremor. A total of 76 subjects were recruited for this study and followed for 12 months which is the basis for the PMA submission to the FDA under PMA # P150039 and was approved July 2016. Regulatory submissions were also submitted to the following regulatory agencies in other countries to gain commercial approval for this indication:

- Korea MFDS - Approved November 2015 –for the following indication of use:
  ExAblate Model 4000 MR guided focused ultrasound system intended for thermal ablation of normal brain structure targets in the Basal Ganglia and Limbic System of the brain for the treatment of movement, pain and behavioral disorders by heat induced focusing using ultrasound energy under full MR planning and thermal imaging control.
- Health Canada - Approved by Health Canada License #96969 on May 17, 2016 for the following indication of use

  The ExAblate Neuro is intended for use in the unilateral Thalamotomy treatment of idiopathic Essential Tremor subjects with medication-refractory tremor. Subjects 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.

- U.S. FDA – Approved July 2016 for the following indication of use:
  The Exablate Neuro is intended for use in the unilateral Thalamotomy treatment of idiopathic Essential Tremor subjects with medication-refractory tremor. Subjects 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.

- Japan MHLW PMDA – Approved December 2016 for the following indication of use:
  ExAblate Neuro for the non-invasive treatment of essential tremor in subjects who have not responded to medication

CE Approval of the ExAblate Neuro MRgFUS System

In December-2012, InSightec received CE Mark of Conformity approval for the ExAblate Model 4000 Type 1 for the following Indication of Use:

Intended use	ExAblate 4000 transcranial MR guided focused ultrasound (TcMRgFUS) system (type 1) intended for thermal ablation of targets in the thalamus, sub thalamus and Pallidum regions of the brain.
Indication for use	ExAblate 4000 transcranial MR guided focused ultrasound (TcMRgFUS) can be used for the treatments of neurological disorders (Essential Tremors, Tremor Dominant Idiopathic Parkinson's Disease – Unilateral) and Neuropathic pain in the brain by heat induced focusing using ultrasound energy under full MR planning and thermal imaging control.

Open FDA IDEs	Open HealthCanada ITAs
Movement Disorders	
9.11.1.1.1 Feasibility Study for Brain Tumor IDE # G020182 – ExAblate Model 4000 Type-1 In 2002, the FDA approved an IDE for a feasibility clinical study for the ExAblate Neuro system in the treatment of brain tumors.[104,105] The purpose of this study was to evaluate the safety of MRI-guided focused ultrasound ***thermal ablation*** of brain tumors performed through intact human skull using the ExAblate system. The study is on-going.	***Feasibility Study for Brain Tumor*** . ITA# 165868 ***– ExAblate Model 4000 Type-***1 The purpose of this study was to evaluate the safety of MRI-guided focused ultrasound thermal ablation of brain tumors performed through intact human skull using the ExAblate system. The study is on-going.
Feasibility Study for Tremor Dominant Parkinson's Disease IDE - G120017 - **ExAblate 4000 Type-1 Neuro System** This is a multi-center, randomized, sham-controlled feasibility study to evaluate the safety and efficacy of ExAblate Neuro unilateral thalamotomy for treating medication-refractory Tremor Dominant Parkinson's Disease. A total of 30 subjects were to be recruited for this study. To date, 27 subjects have been treated. The study was closed to enrollment as the 20th subject randomized to ExAblate was treated. All follow-up is now complete and the final clinical study report in progress.	***Feasibility Study for Unilateral Pallidotomy for the Treatment Dyskinesia (LID) of Parkinson's Disease – Health Canada ITA # 222434 - ExAblate 4000 Type-1 Neuro System*** This is a, single-center feasibility study to evaluate the safety and efficacy of ExAblate Neuro unilateral pallidotomy for treating medication-refractory LID Parkinson's Disease to be performed at Sunnybrook. A total of 6 subjects will be recruited for this study. This study has been approved by Health Canada, and the first subject has been treated.
Feasibility Study for Unilateral Subthalamotomy ("STN") Treatment of Dyskinesia of Parkinson's Disease with ExAblate 4000 Type-1 Neuro System – FDA IDE # G140018. In April 2014, InSightec received the FDA approval to conduct a feasibility study for	***A Feasibility Clinical Trial of the Magnetic Resonance Guided Focused Ultrasound (MRgFUS) for the Management of Treatment-Refractory Movement Disorders - Health Canada Application # 228826***

ExAblate Neuro in the STN treatment of dyskinesia in subjects with Parkinson's disease. Three subjects have now been treated.	This multicenter (2) study is designed to treat (thalamotomy or pallidotomy) any one of several movement disorders in a total of 40 subjects. Currently, 29 subjects have been treated. Enrollment is on-going.
Feasibility study for Unilateral Pallidotomy for the Treatment Dyskinesia Parkinson's Disease with ExAblate 4000 Type-1 Neuro System – FDA IDE # G140082. In June-2014, InSightec received the FDA approval to conduct a feasibility study for ExAblate Neuro in the GPi treatment of dyskinesia in subjects with Parkinson's disease. The study is on-going.	***Feasibility Study for Unilateral Pallidotomy for the Treatment Dyskinesia (LID) of Parkinson's Disease – Health Canada ITA # 222434.*** This is a, single-center feasibility study to evaluate the safety and efficacy of ExAblate Neuro unilateral pallidotomy for treating medication-refractory LID Parkinson's Disease to be performed at Sunnybrook. A total of 6 subjects will be recruited for this study. This study has been approved by Health Canada, and one subject has been treated.
Epilepsy	Brain Tumor
Feasibility study for Treatment of Subcortical Lesional Epilepsy with ExAblate 4000 Type-1 Neuro System – FDA IDE #G160021 In February 2016, InSightec received FDA approval to conduct a feasibility study for the treatment of subcortical lesions that induce epilepsy in 15 adult subjects. This is a multi-center, prospective, open-label study that is just starting up.	***Feasibility Safety Study Using the ExAblate 4000 System in the Management of Benign Centrally-Located Intracranial Tumors Which Require Clinical Intervention in Pediatric and Young Adult Subjects.*** In 2016, InSightec received FDA approval to conduct a feasibility study on benign brain tumors. This is a single center, prospective, open-label, descending age cohort designed study

Closed Studies using ExAblate 4000, Type I	
Feasibility Study for Neuropathic Pain Outside the US - ExAblate 4000 Type-1 Neuro System An investigator initiated and sponsored study in the treatment of neuropathic pain was conducted at the University Hospital Zurich (Zurich Switzerland) using the InSightec ExAblate Neuro (650 KHz) system. The study was approved by and performed according to the guidelines of the ethics committee of the University and the State of Zurich. Nineteen (19) subjects with chronic, medication-resistant neuropathic pain underwent selective central lateral thalamotomy (CLT) using the ExAblate Neuro treatment. Therapy-resistance was defined as occurring when the subject's pain was not effectively treated with medication.	**Feasibility Study for Essential Tremor IDE - G100169 - ExAblate 4000 Type-1** InSightec received FDA approval for a feasibility trial of ExAblate Neuro System for unilateral thalamotomy in the treatment of Essential Tremor under IDE # G100169. Total of 15 subjects were enrolled and treated at one site. This study has been completed and the full results of this study were published in the *New England Journal of Medicine.* [106] Based on the investigator and the subject's feedback, subjects have shown a great level of acceptance of the procedure. Furthermore, subjects have shown a significant improvement in their Essential Tremor disease following their unilateral treatment with the ExAblate Neuro device. Subjects who completed the study requirements have shown stability of the tremor suppression all the way to the end of the study.

For all subjects, the treatment was well tolerated and did not result in any side effects or neurological deficits. The only significant event reported to date from this study is an event of neurological deficit, i.e. "dysmetria (dyscoordination) of the right hand, dysarthria, motor neglect and gait disorder". This event was reported immediately following the last sonication. All subjects experienced some level of pain relief during the procedure, and at 48 hours after the treatment, subjects reported pain relief ranging from 30 to 100% (mean = 68%).[80] Partial results of this study were published in the *Annals of Neurology Journal*.[54]	**Feasibility Study for Essential Tremor ITA# 166556- ExAblate 4000 Type-1** A similar feasibility study in 6 subjects was also conducted at Sunnybrook, Toronto under Health Canada Application # 166556 and published in Neurotherapeutics.[107]