Version Date	**December 2, 2013**
Amendment No.	**1**
Protocol Number	**PD001**
IDE Number	**G120017**
Protocol Title	A Feasibility Study to Evaluate Safety and Initial Effectiveness of ExAblate Transcranial MR Guided Focused Ultrasound for Unilateral Thalamotomy in the Treatment of Medication-Refractory Tremor Dominant Idiopathic Parkinson's Disease

Approvals:

Site	**Sponsor**
_____ Principal Investigator Date Signature	_____ Nadir Alikacem, PhD, Date VP Global Regulatory Affairs and CRO InSightec

A Feasibility Study to Evaluate Safety and Initial Effectiveness of ExAblate Transcranial MR Guided Focused Ultrasound for Unilateral Thalamotomy in the Treatment of Medication-Refractory Tremor Dominant Idiopathic Parkinson's Disease.

The goal of this prospective, randomized, double-arm with sham procedure, single site, feasibility study is to develop data to evaluate the safety and initial effectiveness of unilateral focused ultrasound thalamotomy using this ExAblate Transcranial System in the treatment of medication-refractory tremor resulting from idiopathic Parkinson's disease.

The Indications for Use claim for this system is: treatment of medication-refractory tremor in subjects with idiopathic Parkinson's disease.

Protocol Number: PD001, Amendment 1

TABLE OF CONTENTS

1 Background and Significance

1.1. ExAblate MR Guided Focused Ultrasound Treatments

The ExAblate, using Magnetic Resonance Guided Focused Ultrasound (MRgFUS), is an attractive modality for non-invasive, thermal ablation of soft tissue and brain. The technology utilizes the combination of the diagnostic imaging benefits of high-resolution MRI and MR thermometry with the therapeutic potency of high-intensity focused ultrasound to deliver a precise ablation with many potential clinical applications.

The treatment begins by acquiring a series of MR images of the target tissue. The physician then reviews the images on the ExAblate system workstation, identifies a target volume on the MRI, delineates the treatment contours on the images, and reviews the treatment plan. Therapy planning software calculates the parameters required to effectively treat the defined region with high intensity, focused ultrasound. During the treatment, an ultrasound transducer generates a point of focused ultrasound energy, called a *sonication*. The sonication raises the tissue temperature within a defined region, causing a thermal coagulation effect. MR images acquired during sonication provide a quantitative, real-time temperature map of the entire field-of-view around the target area to confirm the location and intensity of treatment. The sonication process can be repeated at multiple adjacent points and with increased energy to cover a prescribed treatment volume such that a coagulated region of tissue results.

The ExAblate system consists of two units capable of delivering treatment to the body and to the brain. The ExAblate Body system is being investigated in clinical trials for soft tissue tumors, [1-6], including breast cancer, prostate cancer, and for the palliation of pain from metastatic bone tumors. It has been approved by the FDA for the treatment of uterine fibroids.

The ExAblate Transcranial system has been investigated in the treatment of brain tumors[7, 8], neuropathic pain[9], and more recently for the treatment of medication-refractory essential tremor. This latter, phase 1 clinical trial of unilateral ExAblate Transcranial thalamotomy to treat essential tremor (IDE#G100169) has demonstrated safety and efficacy in the initial 15 subjects treated (study still not final, and the data of the first 13 subjects is presented below). The proposed study intends to build upon this concept by utilizing the ExAblate to deliver a unilateral lesion within the ventralis intermedius (Vim) nucleus of the thalamus for the treatment of tremor associated with idiopathic PD.

1.2. Idiopathic Parkinson’s disease

Idiopathic Parkinson's disease (PD) is a common, progressive, incurable neurodegenerative disease that results in severe disability and eventually, death.[10, 11] PD affects adults of all races, and the incidence tends to increase with age, with estimated lifetime risk estimated at 8.5% and 7.7% for men and women, respectively.[12, 13] In PD, the initial pathology is a progressive loss of dopaminergic neurons within the substantia nigra in the brainstem. The classic motor

impairments of PD (tremor, bradykinesia, rigidity and gait impairment) appear when ~50-70% of nigral dopaminergic cells are lost.[14, 15] Early in the course of the disease, medical therapy with dopamine replacement is effective at minimizing symptoms like tremor and bradykinesia to preserve quality of life. But as the disease progresses, many subjects develop medication-refractory PD symptoms, motor fluctuations, and medication-induced dyskinesias.[16] Within 10 years, an estimated 59-100% of subjects suffer from medication-related side effects.[17-19] Furthermore, some aspects of PD, like tremor, can be less responsive to medical therapy than other motor symptoms. Even with optimization of medical therapy, the amount of time spent with good motor control declines in late-stage PD, and it is at this point that subjects typically consider surgical options.[20, 21].

1.2.1. Surgical treatments for the motor symptoms of PD

The earliest surgical interventions for involuntary movements were developed in an effort to treat the large number of cases of postencephalic Parkinsonism resulting from the 1920s epidemic of influenza. These procedures, aimed toward the motor system and specifically the motor cortex, reduced hyperkinetic symptoms like tremor and chorea, but did little for the bradykinesia typically prominent in idiopathic PD. Excision of the precentral (primary motor) cortex effectively alleviated some involuntary movements, but was associated with significant morbidity and loss of limb function. Subtemporal lesioning of the cerebral peduncle (pedunculotomy) was developed in order to avoid the epileptic convulsions that accompanied cortical resection surgery.

Lesioning of subcortical structures like the pallidum and thalamus evolved from the famous surgical accident of Cooper who inadvertently ligated the anterior choroidal artery during a cerebral pedunculotomy procedure, causing a therapeutic pallidal infarction.[22, 23] Soon thereafter, precise stereotactic techniques were applied to pallidotomy procedures to create more consistent and reproducible lesioning.[24-26] Stereotactic pallidotomy became recognized as a viable treatment for PD with alleviation of bradykinesia and tremor, and the modification of the target to the posteroventral pallidum by Leksell was observed to better treat bradykinesia. [27] Similarly, ventrolateral thalamotomy, the primary outflow target of the pallidum, was observed to improve parkinsonian features and especially tremor. [27-29] In the 1960s, dopamine replacement became available for symptomatic therapy of PD, and surgical procedures essentially disappeared for decades. [30] It was Laitinen who "rediscovered" posteroventral pallidotomy decades later as an effective treatment for severe PD symptoms and especially for the dyskinetic side effects associated with chronic dopamine replacement. [31]

Stereotactic radiofrequency lesioning of the thalamus (see Section 1.2.3 below) and the pallidum have proven effective for the motor symptoms of PD. Numerous retrospective case series of posteroventral pallidotomy with over six months followup have documented 20-30% improvement in PD motor function on the nonmedicated UPDRS.[32-43] Randomized, prospective clinical trials of unilateral pallidotomy as compared to best medical therapy have confirmed these results [31, 43, 44] with sustained benefits observed over five and ten years. [34, 45] Unilateral pallidotomy is safe, effective, and recognized as an excellent treatment option for a subject suffering from PD. [46] PD is rarely unilateral, however, and contralateral lesioning is discouraged because of a lesser beneficial effect of the contralateral lesion [47] paired with a higher risk of dysphonia, dysarthria, and cognitive dysfunction. [47-49] This results

in decreased use of pallidotomy, as disease progression and medication-related side effects eventually involve both sides of the body and warrant bilateral treatment.

Electrical stimulation in basal ganglia targets was welcomed in the late 1980s because of a need for improving the safety and reducing side effects of bilateral stereotactic treatments for movement disorders. High frequency electrical stimulation has long been used for acute target localization during stereotactic surgery, and chronic stimulation of the sensory thalamus was utilized therapeutically to treat neuropathic pain. [50] In the early 1990's, Siegfried *et. al*. and Benabid *et. al*., recognized that chronic thalamic stimulation could be used effectively and permanently to suppress tremor, and yet the effects were reversible when the stimulation was stopped. [51, 52] Thus, deep brain stimulation was embraced as a reversible therapy that could be titrated toward symptom relief while minimizing negative side effects. Theoretically, DBS would be safer than irreversible, stereotactic ablations. DBS was soon applied to the pallidum in the treatment of Parkinson's disease [52], and the efficacy of chronic bilateral pallidal DBS was observed as comparable to pallidal lesioning. [38, 52, 53] Like the internal segment of the globus pallidum, the subthalamic nucleus (STN) was recognized in experimental models of Parkinson's disease to be hyperactive.[54-56] STN lesions in nonhuman MPTP primates alleviated parkinsonian signs, thus paving the way to explore the subthalamus as a potential stereotactic target for Parkinson's disease.[54, 55, 57-60] In the 1990's, bilateral STN DBS in human subjects improved PD symptoms in a manner similar to pallidal DBS or pallidal lesioning [15, 61-63]. Rigorous trials of STN versus globus pallidus interna (GPi) DBS include three randomized, double-blind, controlled trials documenting similar motor improvements as tested using UPDRS in the nonmedicated state.[64-66]. The only consistent difference between targeting the STN and GPi for DBS involves substantial reductions in levodopa medications and more cognitive and psychological sequelae with STN DBS. [15, 64, 65, 67, 68].

1.2.2. Tremor in PD

Tremor is the most recognizable of the cardinal signs of idiopathic PD, and was the basis of the original description of the "Shaking Palsy" by James Parkinson in 1819. We now know that parkinsonian tremor is, in fact, very common with the condition, likely occurring 75-100% of the time at some point during the course of the disease.[69, 70] The classic tremor of PD is reported as a resting tremor of 4-7 Hertz that abolishes with volitional movement.[71] PD tremor can also include a postural or action component, but the combination of a pathological resting tremor with bradykinesia qualifies as a necessary criteria for the clinical diagnosis of idiopathic PD.[72]

Even though tremor may frequently represent the initial manifestation of PD, its occurrence during the course of the disease varies, and it has been demonstrated to occur independently of the other cardinal motor symptoms.[73] Such a variation in symptomatology has led to the proposal of clinical subtypes of the disease with "tremor dominance" representing one of the major categories [74]. Tremor-dominant PD (TDPD) is now recognized as a distinct clinical subtype from the akinesia/rigidity (AR) or postural instability/gait disorder (PIGD) subtypes. [75]

Tremor-dominant PD tends to present at a younger age and progresses more slowly to the disabling stages [76] or to dementia.. [77] Conversely, limb tremor severity tends to decline or

disappear in later stages of the disease, although jaw and mouth tremors may remain. [78] Rajput *et al* observed 166 cases of PD over a 39 year time period and reported an 8% incidence of tremor-dominant subtype as compared to 26% AR and 66% with mixed features. [76] It has been demonstrated by several groups that lower amounts of striatal dopamine lead to akinesia/rigidity symptoms and worsened disease severity, but this does not correlate with the presence or severity of tremor [75, 79-83], suggesting a different pathophysiologic mechanism for PD tremor.

1.2.3. Contemporary surgical treatments for PD tremor

PD tremor usually improves with dopamine replacement, but often to a lesser extent than bradykinesia and rigidity.[84] Thus, many individuals with PD may be well-treated for their bradykinesia and rigidity, but display continued disabling medication-resistant tremor. Since higher doses of dopaminergic therapy are associated with drug-induced side effects such as drowsiness, nausea, dyskinesias, hallucinations, and orthostatic hypotension, subjects may also be unable to tolerate the doses required to control their tremor symptoms. It has long been known that stereotactic lesioning of the thalamus controls tremor, but the location of the optimal targets were controversial. [85] Improved imaging with MRI and refined electrophysiological localization over the past two decades have revealed that the Vim nucleus of the thalamus is an effective target, integrating the inflow of cerebellothalamic projections with proprioceptive and kinesthetic sensory information. Furthermore, an abundance of tremor cells which fire synchronously with the limb tremor can be recorded in this region.[86] With electrophysiological confirmation and identification of these cells, only small volumes of Vim (~40 mm^3) are required to be targeted for effective treatment.[87]

Both stereotactic radiofrequency thalamotomy and DBS targeted to the Vim have proven effective for the treatment of PD tremor and other tremors. [88] Numerous studies of Vim ablation and stimulation have demonstrated dramatic improvements of appendicular tremors in PD and ET, and prospective and retrospective comparisons of the two report similar control rates of tremor with 69-90% improvement in appendicular symptoms.[89, 90] Qualitative and quantitative measures have been used to depict the benefits of thalamic stimulation in the upper extremities. [91]. Axial tremors also improve with Vim stimulation [92, 93] including vocal tremors. [94]. Most importantly, quality of life for subjects with tremor, whether due to ET or PD, improves with both unilateral and bilateral therapies targeted to the Vim.[95-97]

A long term study of RF-thalamotomy, however, revealed that nearly 12% of treated subjects experienced tremor recurrence when followed for a mean of 8.6 years.[98] DBS is now much more widely accepted because the therapy is reversible and adjustable. Thalamic DBS is associated with long term tremor benefits [99], but tolerance to thalamic stimulation can occur in up to 30% of cases. [99-102] Furthermore, DBS has its own inherent hardware-related complications, infection, expense, maintenance demands and other risks mentioned above.

Gamma knife thalamotomy is a potentially attractive, noninvasive approach for controlling tremors, and has in fact been associated with significant rates of tremor control. Unfortunately, the treatment has not achieved widespread acceptance because of its latent effects (inconsistent lesion sizes) and the lack of intraoperative testing to confirm the target.

With the ExAblate system, non-invasive high-intensity focused ultrasound has been coupled with high resolution MRI to provide precise, consistent treatments that can be monitored in real-time. The development of phased array transducers allows for tightly focused treatment volumes and for the ability to compensate for distortions by tissue inhomogeneities.[103-105] The landmark advance making the ExAblate Transcranial system possible for neurosurgeons occurred when the ability to sonicate precisely through the intact cranium was achieved with phased array transducers and acoustic modeling using CT reconstructions of the skull [100, 103-106] By coupling high intensity focused ultrasound with MRI, detailed treatment plans can be generated and intra-procedural real-time monitoring is available. [5] Standard MR sequences have been shown to reliably predict tissue damage during thermal lesioning with ultrasound.[5, 107] The precision of the technology has already been demonstrated in animal models [108] and is currently being investigated in humans with brain tumors [7, 8], neuropathic pain syndromes [9], and essential tremor (IDE#100169). Unlike stereotactic radiosurgery, the treatment can be monitored continuously in real-time with MRI and MR-thermography.[4, 109-114] Furthermore, clinical testing can be performed during low intensity sonication to potentially test the target prior to permanent lesioning. Similarly to the Essential Tremor study under IDE # 100169, we anticipate that an ExAblate thermal lesion has a similar safety profile as compared to invasive radiofrequency lesioning and will provide years of benefit through reduction of contralateral Parkinsonian tremor.

1.3. ExAblate Transcranial System

Ultrasound energy was shown to propagate through intact skull. Transcranial ultrasound has been used in pediatric subjects to detect midline shift of the brain.[116] In adults, blood velocity in the basal arteries may be monitored through the intact temporal bone using the Doppler effect. [117] In fact, since the 1950's, the ability of focused ultrasound to produce focal thermal lesions deep in the brain has been shown in several studies. Animal studies and early clinical studies provided encouraging results, showing well-defined tissue coagulation at the focal zone [118-121]. Fry *et al*. showed that a low frequency (around 0.5 MHz) beam could be focused through the skull [122, 123]. Their work produced thermal lesions in animal brains through a piece of skull immersed in water (bone temperature was not monitored).

However, ultrasound is strongly attenuated by bone [124]. For this reason, a consensus was reached that therapeutic ultrasound cannot be delivered through an intact skull because the deflecting effect of the bone; the variable thickness of the skull affects the wave propagation so much that the focal spot is lost.

- High temperatures that are generated in the bone, due to energy absorption, could damage the scalp, bone and adjacent brain tissue. [125]

For these reasons, previous focused ultrasound treatments of the brain have involved removal of the skull for the sonication pathway [119, 126], resulting in an invasive procedure with additional risk and costs.

The device used in this study, namely the ExAblate Transcranial system addresses the above limitations by combining a large phased array, active water-cooling, acoustic aberration

correction algorithm, and CT data of the skull thickness registration (see component descriptions below).

Large Phased Array Transducer. The system utilizes a large phased array transducer that is composed of numerous transducer elements (current system has more than 1000 elements). It has been shown that large hemispherical phased arrays can deliver adequate energy through human skulls to coagulate brain tissue in vivo without excessive temperature elevation on the skull surface [127, 128] (see **Sections 1.6.2.1** for clinical experience with ExAblate transcranial system).

Active water-cooling. The interface between the subject head and the transducer is filled with water, which provides the acoustic path. The system includes a chiller (refrigerating unit) that keeps the water chilled at constant temperature so that the skull-bone temperature remains within safety limits.

Acoustic aberration correction algorithm. Acoustic aberration is created mostly by the variations in the bony structure of the skull. The degree of compensation necessary for each transducer element is based on predicting the aberration along the acoustic path from that element to the target and calculating the relative phase and amplitude correction necessary for that element. The result of this compensation is that the acoustic energy contribution from each element will arrive at the focal point in phase.

CT data analysis. The phase/amplitude correction algorithm, based on ray acoustics methods, relies on an input that provides the bone density profile along one or more rays between each acoustic element and the target point. This information is extracted from a three dimensional CT image of the skull [106].

Preliminary clinical data using the ExAblate Transcranial system is now available. These data demonstrate the feasibility of the ExAblate Transcranial thalamotomy procedure as well as the initial safety and efficacy in terms of ability to ablate a targeted brain tissue (**see Sections 1.6.2.1.2 & 1.6.2.1.3**) **.**

The ExAblate Transcranial system combines a focused ultrasound surgery delivery system and a conventional diagnostic 1.5 T or 3T MRI scanner. This ExAblate transcranial system provides real-time therapy planning algorithm, thermal dosimetry, and closed-loop therapy control. The latter is achieved by utilizing the unique interactive MRI scan control features of the GE MRI system.

The treatment process concept of this ExAblate Transcranial system is not different from the ExAblate body system which is currently in clinical use for some soft tissue applications (see Section 1.4). The treatment begins with a series of standard diagnostic MR images to identify the location and shape of the target volume to be treated. The ExAblate computer uses the physician's designation of the target volume to plan the best way to cover the target volume with small spots called "sonications". The size of these cylindrical lesions depends on sonication power and duration. During the treatment, a specific MR scan, which can be processed to identify changes in tissue temperature, provides a thermal map of the treatment volume to confirm the therapeutic effect [129]. The thermal map is used to monitor the treatment in

progress, and confirm that the ablation is proceeding according to plan, thus closing the therapy loop.

The ExAblate Transcranial system operates a helmet-shaped transducer (currently utilizing 1000+-element phased array transducer) positioned above the subject head. The ExAblate Transcranial system also includes means to immobilize the subject's head, cool the interface water, and software for CT analysis and phase correction computation.

1.3.1. Rationale for ExAblate Transcranial System Thalamotomy for the Treatment of Medication-Refractory, Tremor-Dominant PD

Both stereotactic radiofrequency (RF) lesions and deep brain stimulation (DBS) targeted to the Vim have proven effective for the treatment of ET, PD tremor, and other tremors.[88] Ablation and stimulation have demonstrated equivalent dramatic improvements of tremors, with prospective and retrospective comparisons reporting 69-90% improvement in appendicular tremors.[89, 90] Stereotactic radiosurgery using the gamma knife (GK) is a third technique directed to the Vim thalamus to control tremor. GK thalamotomy does not require an incision nor burr hole, and has been reported to have efficacy equal to other lesion methods. Unlike the former two stereotactic techniques, the effects of the GK thalamotomy procedure has a latent onset of action with up to 6 months being required for maturation of the lesion.

Niranjan *et al*. [130] compared results of 15 gamma knife thalamotomies, 13 RF thalamotomies, and 11 thalamic DBS implants. They reported all three to be safe and effective, with each approach having advantages and disadvantages.

1.3.2. Risks associated with the current standard of practice in stereotactic brain surgery/therapies.

1.3.2.1. Hemorrhagic surgical complications

Stereotaxy uses modern, computer-assisted, volumetric imaging techniques to identify targets deep in brain in order to advance an electrode to the target. These stereotactic procedures require a scalp incision, a bur hole drilled through the skull, and then penetration of the brain with an electrode to reach the target location. In any open stereotactic procedure, there is a risk of hemorrhage associated with insertion of the electrode. The overall risk of hemorrhagic complications is about 2% per electrode insertion, with a risk of permanent neurologic deficit of about 1%. Intraventricular hemorrhages occur in 5% of cases when the electrode traverses the lateral ventricular system. Typically in a stereotactic procedure, the majority of surgical complications are associated with traversal of overlying structures such as the cortex or cerebral ventricles [131].

1.3.2.2. Placement error

Target identification in stereotaxy is derived from preoperative CT or MR scans taken with the subject in a supine position [132]. The stereotactic surgery is often performed with the subject in a semi-recumbent position to minimize the loss of cerebrospinal fluid. Problems can arise under some circumstances [133] such that the brain moves relative to the preoperative scan and the

calculated coordinates. This represents a potential source of error in electrode placement. Any deviation in the mechanical geometry of the electrode or the stereotactic apparatus will also contribute error which can have a considerable impact on the safety and efficacy of the treatment. Location of the electrode is verified by electrophysiological signal pattern recognition, but it cannot be determined whether the electrode is located in the center of the nucleus, or in the periphery.

1.3.2.3. Risk from RF ablation

The electrode used for RF ablations has an RF heated tip. The peak temperature and the time it is maintained define the ultimate size of the lesion. Temperature drops off smoothly with distance from the heated tip, and there is a fairly wide zone of thermal injury that extends for several mm around the necrotic core of the lesion. The damaged tissue will rapidly produce edema which can produce local mechanical stress. The risk of perioperative hemorrhage after RF ablation may be higher than after DBS implant [134]. This may be the result of damage to blood vessels within the perimeter of the lesion, in areas hot enough to damage the vessel but not hot enough to coagulate it. Mechanical strains on the damaged vessel can develop as the necrotic tissue contracts and injured tissue swells, leading to a rupture and intracranial hemorrhage. The ability to produce very sharp temperature gradients at the margins of the planned lesion would provide a more homogenous lesion and reduce the extent of potentially dangerous perilesional edematous regions.

1.3.2.4. Risk from DBS

DBS therapy has a lower risk of acute perioperative complications than does RF ablation [134]. It is also adjustable and able to adapt to some degree to symptom progression. However, DBS requires the permanent implantation of at least one multi-contact electrode, a lead extension and an implanted pulse generator (IPG). The implanted DBS hardware is likely permanent for the life of the subject. This means the subject will require surveillance and maintenance of the device with replacement of the IPG every 3 to 5 years. Furthermore, DBS devices produce electromagnetic interference and are sensitive to high energy electrical fields which can switch them off or even cause a "factory reset" of the device.

As an implantable device, the DBS hardware problems are not uncommon. Some reports suggest that upwards of 10% of DBS subjects experience some form of hardware failure including infection, skin erosion, lead fracture or migration. Hardware failures can lead to a precipitous, unexpected loss of efficacy and invariably requires urgent surgical intervention to replace one or more components.

Implanted DBS hardware is associated with higher risks of infection and skin complications than lesioning procedures. The rate of postoperative infection with DBS surgery has been estimated between 3-10%, and such infections typically lead to device explantation if the infection cannot be cleared with antibiotics. Such a scenario leaves the subject without treatment. Wound dehiscence can also occur over the implanted hardware leading to infection as well.

Even though the DBS technology continues to gain acceptability, its technology remains very expensive. A bilateral Vim implant will incur an institutional cost nearing $100,000 for

hardware and hospitalization. Additionally, expensive pulse generator replacements are required every three to five years.

An intervention to inactivate the Vim thalamus without requiring the use of implanted hardware would be more cost-effective and would avoid the inherent risks associated with chronic implants.

1.3.2.5. Risk from gamma knife thalamotomy

The GK uses ionizing radiation to denature cellular DNA and ultimately cause cell death within the area defined by the 50% isodose margins around the target. It requires a long time (median several months) [135-137], for the lesion to develop. This means that the procedure is performed without confirmation of efficacy or lack of associated side effects until months following the procedure. In fact, it has been reported that the lesions eventually observed on MR after 3 months are variable in volume and distribution, although the clinical effects seem consistent [137].

Because of a lack of intraoperative feedback and a small risk of radiation-induced neoplasia, GK thalamotomy remains very uncommon, restricted to subjects with advanced age or medical conditions (e.g. anticoagulant therapy) perceived to be high risk for open stereotactic surgery such as DBS or RF lesioning. Because "*delayed complications have been reported, and clinical improvement may take weeks to months to occur*," the American Academy of Neurology concluded in 2005 that *"There is insufficient evidence to make recommendations regarding the use of gamma knife thalamotomy in the treatment of "essential" tremor* (Level U)" [138]. This recommendation may also be applicable for PD tremor treatment.

1.4. History of and Rationale for ExAblate for Brain Surgery

High-intensity focused ultrasound has been used to destroy soft tissue such as neoplasms for more than half a century [138]. Until very recently, lesioning brain by sonication has been difficult because the overlying skull absorbs most of the sound energy and distorts the transmitted acoustic waves. The landmark advance in the ExAblate Transcranial system for neurosurgeons occurred with the ability to sonicate through the intact cranium [103-106]. By coupling CT-based phase tuning with the ExAblate Transcranial system, precise and small (2x2x3mm) lesions have been produced in thalamus while real-time thermal monitoring is available to observe the heating caused with each sonication [5]. Standard MR sequences have been shown to reliably predict the precise locus of tissue damage during thermal lesioning with focused ultrasound [5, 107]. The precision of the ExAblate Transcranial device has already been demonstrated in animal models [108] and is currently being investigated in humans with brain tumors[7], neuropathic pain syndromes[9], and essential tremor. This ExAblate Transcranial system was built atop the ExAblate Body system technology, which has received FDA and CE approvals for the treatment of uterine fibroids, CE approval for bone metastasis palliation, and is currently being evaluated under various FDA Investigational Device Exemptions "IDE" and a PMA submission (see **Section-1.6** for more details).

There are many potential advantages for applying ExAblate Transcranial Vim thalamotomy for the treatment of medication-refractory, tremor-dominant PD subjects:

- The procedure is non-invasive, requiring no incision, no burr hole, and no electrode. The risk of hemorrhagic complication should be reduced, and this non-invasive procedure should eliminate the risk of infectious complications..

- Unlike stereotactic radiosurgery, ExAblate Transcranial system does not use ionizing radiation and does not carry a risk of radiation-induced tumorigenesis

- Unlike radiofrequency ablation, ExAblate Transcranial system thermal lesioning can be performed discretely and accurately.
- The ExAblate treatment can be monitored in real-time with MRI and MR-thermal feedback which permits immediate confirmation of the targeting process.

- Unlike DBS treatment, there is no implanted hardware, no concern of interference with external sources of electromagnetic noise, no need for extensive follow-up for programming, and no need for periodic battery replacement. ExAblate Transcranial treatments represent a simpler treatment algorithm for a subject suffering from PD tremor. Hours of clinic time will be saved from DBS device management and replacement and health care costs may be greatly reduced.

1.5. Summary

Based on published animal and human studies, we believe ExAblate Transcranial thalamotomy can be as safe and as effective as any of the surgical treatments within the currently accepted standard of care including RF lesioning and DBS. Similarly to the Essential Tremors study (IDE # 100169), a single ExAblate lesion targeted to the Vim nucleus should provide reduction of contralateral tremor symptoms in PD. This technology has several potential advantages over current therapies including the fact that noninvasive lesioning can be performed in a precise manner with continuous clinical and radiographic monitoring. If the potential of ExAblate Transcranial thalamotomy can be realized, it could supplant radiofrequency and radiosurgery thalamotomy, and provide a viable alternative procedure for subjects considering DBS, which is invasive, uncomfortable, labor-intensive, and expensive.

1.6. Clinical Experience with ExAblate

1.6.1. Clinical ExAblate Body System

1.6.1.1. ExAblate Body System for the treatment of Uterine Fibroids

The ExAblate 2000 system received FDA approval for the treatment of Uterine Fibroids in October 2004 (PMA # P040003). Furthermore, this system gained both AMAR authorization (Israel Ministry of Health) and CE (European and others) approval for the indication of treating Uterine Fibroids. Subsequent studies lead to a software upgrade and an enhanced sonication protocol. A further upgrade to the system to allow the transducer arm 3-dimensional movement is currently under IDE investigation as IDE G100127

1.6.1.1.1. ExAblate New Software Validation (IDE #G050221)

This was an FDA-approved study to validate the new ExAblate application software as well as the use of the ExAblate system with 3T MR scanners for the treatment of UFs. This was only a safety study. A total of 40 subjects were treated under this protocol IDE. The PMA-S was approved on February 27, 2007 under P040003/S002.

1.6.1.1.2. Enhanced Sonication Protocol (IDE #G060017)

This was an FDA-approved study to validate the new Enhanced Sonication feature of the ExAblate system, a detachable cradle, and several other modifications to the ExAblate 2000 system. This was a safety study only. A total of 50 subjects were treated under this protocol IDE. Following completion of this study, a full PMA supplement was submitted to FDA for review and approval [PMA# P040003]. Approval was granted on 12/22/2009 under PMA Supp P040003/S006. The system is marketed under the trade name ExAblate 2000/2100 and is indicated for use in treating symptomatic uterine fibroids.

1.6.1.1.3. Enhanced Sonication Post Marketing Study-P040003/S007

InSightec is currently recruiting subjects for a post-market study using the FDA approved enhanced sonication feature to demonstrate the safety of the enhanced sonication feature within current treatment guidelines of 100% individual fibroid ablation within established serosal and sacral treatment margins; this study will enroll 115 subjects and is nearing completion (P040003/S007**)**.

1.6.1.1.4. Validation of ExAblate UF V2 – IDE G100127.

InSightec is currently recruiting centers and initiating IRB review for study conduct in order to gain approval for the ExAblate Model 2100 Type 1.1 (also refer to as ExAblate UF V2). This ExAblate system will be operated with a NEW Clinical Application SW utilizing the added 5th degree of freedom of the transducer (A/P movement) in its overall planning and treatment of the uterine fibroids. This study will enroll 106 subjects under IDE # G 100127.

1.6.1.2. ExAblate Body System for the treatment of Breast Cancer

InSightec conducted FDA approved clinical trials under IDE # G990184 and G990201 to evaluate the safety and efficacy of the ExAblate system in the treatment of breast carcinomas [139-141]. Both of these studies are now closed. Currently, InSightec has an FDA conditional approval for a new breast cancer phase-2 study (IDE # G060023).

1.6.1.2.1. ExAblate Ablation of Breast Carcinoma: Clinical Study with Excision

InSightec has been conducting FDA approved clinical trials under IDE # G990184 and G990201 to evaluate the safety and efficacy of the ExAblate system in the ablation of breast carcinomas [139-141]**.** The study under IDE # G990201 is a closed study with total of 20 subjects treated. Histopathological evaluation of the specimen showed that about 97% of the tumor volume was within the targeted volume, and about 87% of the tumor tissue within this target volume was thermally coagulated. Of all the subjects treated, only three subjects experienced non-significant adverse effects: minor skin burns. All were managed with over-the-counter medications, and resolved within a few days. All these adverse events occurred prior to the introduction of the Active Breast Cooling system.

The study under IDE # G990184 is a closed study. A total of 36 subjects of the 45 subjects granted by this IDE were treated. Histopathological evaluation of the specimen showed that since the introduction of Elongated Sonication Spots and the Active Breast Cooling System about 94% of the tumor volume was within the targeted volume, and about 92% of the tumor tissue within this target volume was thermally coagulated. Of all the subjects treated, only three subjects experienced non-significant adverse effects: one subject with mild event of redness at the ablation site, a second subject with mild event of firmness, and a third subject with a 3rd degree skin burn that was due to operator's targeting error and not due to the device.

1.6.1.2.2. ExAblate Ablation of Breast Fibroadenoma

InSightec conducted a feasibility FDA approved clinical trials under IDE # G930140 to evaluate the safety and efficacy of the ExAblate system in the ablation of breast fibroadenoma [2]. Under this study, a total of 11 subjects were treated. The results of this study showed that 8 of the 11 subjects who had ablations were either partially (>50%) or completely (>90%) successful. No adverse effects were reported, except for one case of transient edema in the pectoralis muscle two days after therapy.

Following this feasibility study, InSightec initiated an FDA approved pivotal protocol to study ExAblate ablation of Breast Fibroadenoma (IDE # G010225). A total of 110 subjects were approved for this trial, and only 27 subjects were treated before the study was closed for enrollment due to lack of subjects enrollment. No unanticipated adverse effects have been reported or detected by MRI. Clinically, acute pain and discomfort were tolerable, and no long-term complications occurred.

1.6.1.3. ExAblate Body System for the treatment of Prostate Studies – Investigational Feasibility Studies

Prostate cancer is the second leading cause of cancer death in men in the United States. Most prostate cancers grow slowly with a high survival rate past 10 years if it is still confined to the prostate. The current treatment methods (surgical, external beam radiation therapy and male hormone suppression therapy) have significant side effects, such as impotence, incontinence, post-radiation colitis, etc. Because prostate cancer is usually slow growing, active surveillance at 6 month intervals using a prostate cancer marker (PSA – prostate-specific antigen) has been a primary treatment option. A focal treatment that could destroy the cancerous cells without harming the neurovascular bundle could provide a more palatable treatment with fewer side effects and extend life expectancy from prostate cancer causes.

Feasibility studies have been performed outside the United States to demonstrate the ability of the ExAblate to successfully target the prostate gland and ablate it (Total Gland Ablation – TGA). Additionally studies are now underway using focal therapy to ablate only cancerous foci within the prostate and leave the remainder of the gland intact. The difficulty here is in the methods available to identify the cancerous foci. These cancerous foci are generally not visible on MRI or CT, so careful, methodical biopsy mapping with multiple cores (minimum of 12 cores, commonly 16 cores for larger glands) must be performed in order to identify the portion of the gland with the cancer. In pilot studies with 14 subjects treated to date, the outcomes generally have demonstrated a minimal degree of sexual and urinary side effects (except for transient obstructive urinary symptoms) unless the cancerous foci involve the neurovascular bundles and the conscious decision is made to include them in the treatment region-of-interest. Subjects that are eligible for participation are those with slow cancer growth being followed with active surveillance or with Gleason score of 6 (3+3) and no more than 2 cancerous foci in two or fewer adjacent sectors that would be amenable to ExAblate treatment. To date, feasibility studies are underway in Russia, India, Singapore, Italy, and will soon start in Canada. In the United States under FDA oversight, InSightec has submitted a feasibility study IDE (G100108) which is anticipated to begin in late 2011 or early 2012. This IDE is still not approved.

1.6.1.4. ExAblate Body System for the Palliative treatment of Metastatic Bone Tumors

First, InSightec performed FDA approved study for a feasibility study of ExAblate ablation of metastatic bone tumors under IDE # G050177. A total of 10 subjects were enrolled and treated at two (2) study sites. This study is now completed, and a final report was submitted to the FDA [142]. Most recently a PMA submission (PMA # P110039) with the pivotal study data was submitted to FDA on 5, DEC-2011.

1.6.1.4.1. Bone Feasibility Study IDE# G050177

The objective of this trial was to evaluate the safety and effectiveness of using ExAblate as a treatment for pain palliation in subjects with metastatic bone tumors. This study was designed as a prospective, one arm, non-randomized study. Ten subjects were enrolled at two sites. Nine subjects completed the study; one subject could not complete treatment due to limited device accessibility to the lesion.

Assessments were performed at baseline, on treatment day, and at follow-up time points of 3 days, 2 weeks, 1 and 3 months. Enrolled subjects had a range of primary cancer types and also a range of targeted lesion locations, including the iliac crest, scapula, ischium, and clavicle bone.

Only 3 mild AEs were reported in the study with no device-related deaths, life-threatening injuries or permanent injuries, nor serious adverse events. There were 2 events of mild sonication-induced pain; both resolved the day that sonications ended. In addition, there was 1 event of a mild shivering reaction to conscious sedation lasting only a few minutes during the procedure with subsequent resolution. All of these events were anticipated side effects that were identified in the study protocol as possible treatment-related complications.

As noted above, effectiveness was measured by the level of pain relief (as measured by VAS), decrease in analgesics/opiate medication usage, and improved quality of life (as measured by SF-36). Prior to ExAblate treatment, the mean pain score was 5.6 ± 1.2 (N=10, score range: 4-7). A very rapid and sustained relief response was observed in subjects' pain relief. At 3 months, the mean score had dropped to 0.4 ± 0.6 (a 93% decrease from baseline). With respect to medication usage, all subjects maintained or decreased their medication usage. Using the OTE scale, 78% (7/9) of subjects reported improvement at the 1-month follow-up compared to the 2-week follow-up visit. It should also be noted that at 3 days post-ExAblate treatment 67% (6/9) of subjects reported improvement. Thus, not only did subjects achieve and maintain clinical benefit at 1 month to 3 months following the ExAblate treatment, but most subjects reported clinically meaningful benefit within 3 days of treatment.

Overall, these results demonstrate the safety and effectiveness of using ExAblate as a treatment for pain palliation in subjects with metastatic bone tumors.

1.6.1.4.2. Pivotal Bone Metastasis Study (IDE# G070022) – Brief Overview

InSightec received full approval for a phase-3 Pivotal study for the ExAblate treatment of bone metastases palliation (IDE # G070022). A total of 148 subjects were to be enrolled and treated at up to 20 sites. The pivotal clinical trial was a prospective, randomized (3:1), single-blind, sham-controlled, multicenter, two-arm study with sham-crossover option. Consistent with prior correspondence between the company and FDA, InSightec has conducted an interim analysis of study data, providing for a statistical penalty addressing the early look at the data, in order to initiate PMA approval for this indication. This interim analysis has been performed under the interim statistical analysis plan previously submitted to and approved by FDA (G070022/S54). The study objective is to evaluate the safety and effectiveness of an ExAblate thermal ablation treatment as compared to a sham treatment (where no energy is delivered) to reduce/relieve the pain of metastatic or multiple Myeloma bone tumors in subjects who are not suitable candidates for radiation therapy. The submission is under review at the Agency (PMA # P110039).

1.6.2. ExAblate Transcranial System

InSightec has two ExAblate Transcranial systems: mid (650 KHz) and low frequency (200 KHz). These 2 systems (medium and low range frequency) serve two different purposes:

1. Mid frequency: functional discrete lesioning for deep central locations; focal thermal lesions

2. Low frequency: tumor ablation and has wide treatment envelope

These differences are summarized in the following table:

Table 1: Summary of main differences between the low and mid frequency ExAblate systems	
Low frequency ExAblate Transcranial System	**Mid frequency ExAblate Transcranial System**
Enables access to most of brain volume	Deep brain targets
Spot diameter: 4-12mm	Spot diameter: 2-6mm
Low frequency (~220kHz)	Medium frequency (~650kHz)
Support both standard and burst Sonication regimes	Support standard sonications only
Standard delivers the required energy in a continuous fashion to the target *Burst Sonication: delivers the energy in a series of burst (high amplitude short duration of each burst of energy). The total accumulated energy is the same. The only difference is the way it is delivered to the target.*	

For the proposed study, the same mid-frequency ExAblate Transcranial system that is being investigated for the treatment of Essential Tremor subjects (under IDE # G100169) will be used. The system uses the same transducer, 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.

1.6.2.1. ExAblate Transcranial Treatment of Brain

1.6.2.1.1. Feasibility Study for Brain Tumor IDE # G020182 – ExAblate Transcranial Low Frequency System

In 2002, the FDA approved an IDE for a feasibility clinical study for the ExAblate Transcranial system in the treatment of brain tumors.[7, 8] The purpose of this study is to evaluate the safety of MRI-guided focused ultrasound thermal ablation of brain tumors performed through intact human skull using the ExAblate system. Specifically, the objectives of this non-randomized study are:

a) To evaluate the safety of FUS delivered through intact human skull to the brain, during the treatment, and during the follow-up period of 3 months.
b) To evaluate the effect of thermal ablation in the target tumor with contrast MR imaging to identify viable tumor, and non-viable thermally ablated tissue

This study was limited to subjects with a newly diagnosed glioma, recurrent glioma, or metastatic cancer to the brain for whom surgery was felt to be not indicated by a physician not associated with the study.

Per FDA order under IDE # G020182/S02, this study was approved for a total of 10 subjects. Also, per same FDA order, a report was requested after enrollment and treatment of the first 3 subjects in order to gain the FDA approval for continuation.

For this study, the ExAblate transcranial system was the system that had ~500 elements and operated at ~650 KHz. The treatment of the first 3 subjects showed the following:

- All 3 subjects tolerated the overall treatment procedure well.
- The system registration and use of CT data allowed for a full determination and correction of the variability of subject skull thickness and density
- Thermal imaging and its feedback confirmed the initial targeting
- All 3 subjects were managed with conscious sedation which was sufficient to alleviate any potential procedure-related pain. None of the three subjects experienced pain.
- Detailed analyses of skull temperature demonstrated temperatures ranging between 1-to-5 C for at the skull/dura interface for acoustic powers up to 800-Watts.
- The adverse events that were captured were Non-Significant, Anticipated, Treatment Side Effects and incidental to the treatment. Indeed, of the 3 subjects treated, only one subject experienced Adverse Events (AEs) that were mild in nature: one event of nausea and vomiting and one event of lip swelling. Both of these events resolved without any sequelae within very short time after they occurred. The nausea/vomiting event was judged to be due to either to the IV medication and or to subject anxiety. The lip swelling event was due to the thermal plastic mask being inadvertently too tight on the subject. Since then, a stereotactic frame replaced this thermal plastic mask fixation method.
- During these 3 treatments, all safety subsystems and monitoring of the device provided the intended safety monitoring capabilities.
- During these treatments, we showed also the potential of tissue ablation. The temperature increase from baseline at the focal point in the tumor were as high as 14C

corresponding to about 51C. These findings corroborated the various simulations that were performed to show it is indeed possible to increase the acoustic power/energy that will induce ablation/coagulation of tissue without significant skull heating.

The results of these three subjects' treatments formed the basis of the report approved by the FDA to continue with the trial and implement several changes in the system such as:

- upgrade the transducer from 512 to 1000 elements
- change the subject interface to a stereotactic frame to improve immobilization and subject comfort.
- Use of lower frequency, ~220 kHz, with burst sonication regime.

This was accomplished under IDE # 020182/S04.

The treatment of the 4th subject was done with upgraded system. The treatment day safety was no different than those previously reported. The skull/dura temperature change was in the range of previous treatments. Utilizing the burst sonication regime, the designated tumor was completely ablated. This was consistent with our overall plan to achieve the efficacy needed.

Despite an apparently uneventful treatment, this tumor subject died of an intracerebral hemorrhage five days after ExAblate. The Study Safety Committee determined the cause of the hemorrhage to be unknown but possibly multi-factorial. It was related to the propensity of glioblastomas to bleed, exacerbated by radiotherapy, medications and an underlying coagulopathy. The latter was suggested by the fact that this particular subject had a hemorrhage at the biopsy site long before ExAblate, skin bruising, and a peri-orbital hematoma that worsened dramatically at the time of his demise..

The neuropathologic findings raised the possibility that pre-existing changes in the vessels, such as mineralization and wall thickening, may have rendered those vessels more susceptible to damage by ultrasound at the doses or frequencies used. The Study Safety Committee recommended protocol changes in the exclusion criteria (tumors with a known tendency to bleed, subjects with abnormal clotting studies or on drugs known to affect coagulation) and in clarification of the imaging criteria (target volume maximum size requirement < 2.5 cm diameter, or an 8 cc volume - the tumor volume may be larger, as long as true midline shift is < 5 mm and the subject is not clinically compromised; definition of midline shift > 5 mm – does not include tumor growth across midline). With these provisos, the Safety Committee recommended continuation of the study. The FDA approved the recommendation of the Safety Committee under IDE # G020182/S15.

1.6.2.1.2. Feasibility Study for Neuropathic Pain Outside the US - ExAblate Transcranial 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 Transcranial (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.

To date, more than nineteen (19) subjects with chronic, medication-resistant neuropathic pain underwent selective central lateral thalamotomy (CLT) using the ExAblate Transcranial treatment. Therapy-resistance was defined as occurring when the subject's pain was not effectively treated by anti-epileptic and anti-depressant analgesic medications.

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. Furthermore, all symptoms improved significantly 1-hour post treatment. The full event was submitted to the FDA as part of the Essential Tremor IDE submission (IDE # G100169).

As it was shown in the brain tumor study under IDE G020281, for this study there was no clinically significant heating at the skull-brain interface. The mean brain surface temperature was approximately 39° C. Furthermore, 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%). Partial results of this study were published in the *Annals of Neurology Journal* [1] and are attached to this protocol as **Appendix-1** of this protocol.

1.6.2.1.3. Feasibility Study for Essential Tremor IDE - G100169 - ExAblate Transcranial System

InSightec received FDA approval for a feasibility of ExAblate Transcranial 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 is currently in the follow up phase. The full data of the first 13 out of the 15 subjects have been treated as of the most recent annual report which accompanies this submission. 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 treatment with the ExAblate Transcranial device. Subjects who completed the study requirements have shown stability of the tremor suppression all the way to the end of the study. Even though other subjects are still at various stages of the post procedure follow up, they are showing a similar pattern of response as the completed subjects.

[1] Martin, E., et al., *High-intensity focused ultrasound for noninvasive functional neurosurgery.* Ann Neurol, 2009. **66**(6): p. 858-61.

2 OBJECTIVES

The proposed study will evaluate the safety and initial effectiveness of the ExAblate Transcranial thalamotomy of subjects with medication-refractory, idiopathic, tremor-dominant Parkinson's disease (TDPD)

> **Safety**: To evaluate the incidence and severity of adverse events (AEs) associated with ExAblate Transcranial thalamotomy of medication-refractory, tremor-dominant PD.
>
> **Effectiveness**: To determine the level of effectiveness of the ExAblate Transcranial thalamotomy to reduce tremor in medication-refractory, tremor-dominant PD as compared to a sham-treated control group.

This study is designed as a prospective, single-site, two-arm, randomized, sham-controlled feasibility study with sham crossover after 3 months to ExAblate treatment; all ExAblate-treated subjects will be followed up for one year. The primary endpoint measured will be safety of unilateral, 3Tesla, ExAblate Transcranial thalamotomy for TDPD as determined from adverse events recorded during the one year study period. A common description of clinical complications will be used for subjects treated in the study.

> **Note: This study is limited to a 1-year follow up period; however, per FDA order, all participating subjects will be consented for a total of 2 years of follow up.**

Safety

Relative Safety of the ExAblate Transcranial treatment will be evaluated using a common description of Clinical Complications for subjects treated in this study. Safety 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 one year post–treatment time point. All AEs will be reported and categorized by investigators as definitely, probably, possibly, unlikely, or unrelated to the device, thalamotomy procedure, and/or Parkinson's disease progression. Alternative treatments for PD subject tremor will also be captured should they occur. Adverse events will be reviewed by a Data Safety Monitoring Board at periodic intervals.

Effectiveness

Primary effectiveness will be a comparison of subjects receiving active versus sham treatment, on medication, using the Upper Limb tremor subscore (32 point maximum) from the 8 items of Parts A and B of the CRST, based upon TDPD subjects where unilateral ExAblate thalamotomy was attempted (i.e., Intent-to-Treat analysis) at 3 months.

Secondary efficacy endpoints will include comparison of Baseline to Month 3 and Month 12 assessments for:

- On-medication, tremor score from items 20 and 21 of the UPDRS
- On-medication, motor score from UPDRS, part III
- On-medication, total tremor (CRST) score
- Level of disability measured from Part C subsection of CRST
- Quality of life assessment with PDQ-39 and Quality of Life in Essential Tremor Questionnaire (QUEST) in this study.

Baseline and follow-up efficacy assessments will be performed by a blinded assessor.

Note:

While the QUEST assessment tool is not a validated instrument for PD subjects, in view that this procedure has been utilized for the treatment of subjects with Essential Tremors (IDE G100169), we propose to use the QUEST instrument (at same time points as above) for all participating PD subjects. A descriptive comparison between the current PD population and the ET population of IDE G100169 QUEST outcomes will also be performed.

2.1.1 Efficacy Assessments

Each treated TDPD subject will be examined *on medication* at Baseline before treatment and at post-treatment intervals. Complete PD assessments may be assessed in an outpatient clinic setting by a movement disorder neurologist using the validated UPDRS, and per local standard of care. Additional blinded evaluation of functional status and tremor assessment using the CRST and UPDRS may also be performed by a physical therapy neurospecialist.

Thus, efficacy measures will be made while the patient is "on-medication" and compared from Baseline to Month 3 and Month 12 post-treatment. Our primary efficacy endpoint will be the Month 3 post-treatment comparison to Baseline of the contralateral treated, upper limb tremor score which is derived from 8 items of Parts A & B of the CRST. Durability of the treatment will be further assessed in the upper limb with the Month 12 assessment.

Secondary efficacy measures will include changes at Month 3 and Month 12 in overall tremor score (CRST), PD tremor assessment (questions #20 and #21 of UPDRS), overall -PD motor function (UPDRS, part III), level of disability (Part C subsection of CRST), and quality of life (PDQ-39). These assessments will similarly be made in the ON-medication state.

All of these tools are part of the study CRFs, which are included in **Appendix-B** of this protocol.

Study Hypothesis

The purpose of this study is to evaluate the safety and initial effectiveness of unilateral ExAblate thermal ablation of the Vim thalamic nucleus of subjects suffering from medication-refractory,

idiopathic, tremor-dominant PD, using the ExAblate Transcranial system as compared to a Sham Vim thalamotomy procedure:

Data will be collected to establish the basic safety of this type of treatment as the basis for later studies that will evaluate its full clinical efficacy and the Sham treatment data will be used to evaluate placebo effect from treatment.

Case Report Form Data

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

3 DESCRIPTION OF SUBJECT POPULATION

3.1 Subject Selection

Subjects with confirmed medication-refractory, idiopathic, tremor-dominant subtype, Parkinson's disease will be eligible for this study.

Subjects will first be consented (see ICF in **Appendix-A**) in the study for a period of 2 years, as per FDA's request. Consented subjects will receive the standard clinical and imaging work-up as part of their study baseline requirements. Subject eligibility will be confirmed by a second independent neurologist/neuroradiologist/neurotherapist prior to the procedure. .

Up to thirty (30) medication-refractory, tremor-dominant PD subjects at one site will be treated in this feasibility study. It should be noted that for this study a total of 200 subjects may be enrolled and consented with the intent to treat a total of 30 subjects. All those subjects that were consented and then were found not meeting study requirements will be considered as screen failures; See **Section-5.4** for the full sample size discussion.

3.2 Subject Enrollment

a) Information concerning eligibility for the study may initially be taken from the subject's case history. Subjects who are potentially eligible will be invited to participate in this study.

b) Written informed consent will be obtained from each participating subject prior to performing any testing or further study screening. The subject will be counseled concerning the investigational nature of this study, and the risks and possible benefits to participation. This study will utilize a pre-treatment examination and imaging to screen for adequacy of trial participation. Participation is fully voluntary.

c) For this study, ALL Inclusion and Exclusion criteria will be reviewed by the Principal Investigator and by a separate investigator of the medical team which may be either a neurologist, neuroradiologist, or neurotherapist. The reviewers must be in FULL agreements on all aspects of the Inclusion/Exclusion criteria listed below

3.2.1 Inclusion Criteria

a. Men and women, age 30 years and older

b. Subjects who are able and willing to give informed consent and able to attend all study visits through 3 Months

c. Subjects with a diagnosis of idiopathic PD as confirmed from clinical history and examination by a movement disorder neurologist at the site

d. All subjects included in this study will have a TD/PIGD ratio $\geq$ 1.5 in the *medicated* [ON] state as calculated from the UPDRS formula as described by Jankovic, *et. al*., [74].

Table 2

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

e. Subject demonstrates a resting tremor severity score of greater than or equal to 3 in the hand/arm as measured by the medicated (*ON*) UPDRS question #20 or a postural/action tremor greater than or equal to a 2 for question #21.

f. Subject exhibits a significant disability from their PD tremor despite medical treatment. A significant disability is defined as a PD tremor with at least a

score of 3 on #16 of the medicated (*ON*) UPDRS or as identified by a score of 2 or more on any item in Part C of the CRST.

g. Tremor remains disabling when medical therapy is optimal or not tolerated for the treatment of other cardinal signs of PD (bradykinesia, rigidity, etc), as determined by a movement disorders neurologist at the site

h. Subjects should be on a stable dose of all PD medications for 30 days prior to study entry.

i. The thalamus must be apparent on MRI such that targeting of the Vim nucleus can be performed indirectly by measurement from a line connecting the anterior and posterior commissures of the brain.

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

3.2.2 Exclusion Criteria

a. Subjects with unstable cardiac status including:

1) Unstable angina pectoris on medication
2) Subjects with documented myocardial infarction within six months of protocol entry
3) Significant congestive heart failure defined with ejection fraction < 40
4) Subjects with unstable ventricular arrhythmias
5) Subjects with atrial arrhythmias that are not rate-controlled

b. Subjects exhibiting any behavior(s) consistent with ethanol or substance abuse as defined by the criteria outlined in the DSM-IV as manifested by one (or more) of the following occurring within the preceding 12 month period:

1) Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household).
2) Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use)
3) Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)
4) Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights).

c. Severe hypertension (diastolic BP > 100 on medication)

d. Subjects with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc.

e. Known intolerance or allergies to the MRI contrast agent (e.g. Gadolinium or Magnevist) including advanced kidney disease or severely impaired renal function (estimated glomerular filtration rate < 45ml/min/1.73 m^2) or receiving dialysis.

f. Significant claustrophobia that cannot be managed with mild medication.

g. Current medical condition resulting in abnormal bleeding and/or coagulopathy

h. Receiving anticoagulant (e.g. warfarin) or antiplatelet (e.g. aspirin) therapy within one week of focused ultrasound procedure or drugs known to increase risk or hemorrhage (e.g. Avastin) within one month of focused ultrasound procedure

i. Subjects with risk factors for intraoperative or postoperative bleeding as indicated by: platelet count less than 100,000 per cubic millimeter, a documented clinical coagulopathy, or INR coagulation studies exceeding the institution's laboratory standard

j. History of intracranial hemorrhage

k. History of multiple strokes, or a stroke within past 6 months

l. Subject who weigh more than 285 lbs (130 kg) as this is the upper weight limit of subjects who will fit into the MR scanner

m. Subjects who are not able or willing to tolerate the required prolonged stationary supine position during treatment.

n. Are participating or have participated in another clinical trial in the last 30 days

o. Subjects unable to communicate with the investigator and staff.

p. Presence of central neurodegenerative disease, including but not limited to Parkinson-plus syndromes, suspected on neurological examination. These include: multisystem atrophy, progressive supranuclear palsy, corticobasal syndrome, dementia with Lewy bodies, and Alzheimer's disease.

q. Any suspicion that Parkinsonian symptoms are a side effect from neuroleptic medications.

r. Presence of significant cognitive impairment as determined with a score ≤ 21 on the Montreal Cognitive Assessment (MoCA).

s. Unstable psychiatric disease, defined as active uncontrolled depressive symptoms, psychosis, delusions, hallucinations, or suicidal ideation. Subjects with stable, chronic anxiety or depressive disorders may be included provided their medications have been stable for at least 60 days prior to study entry and if deemed appropriately managed by the site neuropsychologist

t. Subjects with significant depression as determined following a comprehensive assessment by a neuropsychologist. Significant depression is being defined quantitatively as a score of greater than 14 on the Beck Depression Inventory.

u. Legal incapacity or limited legal capacity as determined by the neuropsychologist
v. Subjects with a history of seizures within the past year
w. Subjects with brain tumors
x. Subjects with intracranial aneurysms requiring treatment or arterial venous malformations (AVMs) requiring treatment.
y. Any illness that in the investigator's opinion preclude participation in this study.
z. Pregnancy or lactation.
aa. Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia
bb. Subjects who have an Overall Skull Density Ratio of 0.45 (±0.05) or less as calculated from the screening CT.

4 INVESTIGATION PLAN

4.1 Study Design

This is a single-center, prospective, randomized (2:1), two-arm, sham-controlled study with sham-crossover to ExAblate after 3 months to evaluate the safety and initial effectiveness of unilateral ExAblate Transcranial thalamotomy of idiopathic, tremor-dominant PD (TDPD):

- TDPD subjects will be targeted with unilateral ExAblate Transcranial focused ultrasound to the contralateral tremor dominant Vim nucleus of the thalamus.

4.1.1 Pre-Treatment Procedures

All the activities that are part of the Pre-Treatment Procedure MUST BE performed at least 24h prior to the actual treatment procedures of Section-4.1.2.

1) Subjects with suspected medication-refractory TDPD will be screened for preliminary eligibility for the study. Potential candidates will be offered an Informed Consent to sign prior to further evaluation (see **Appendix-A** of this protocol for an Informed Consent template). Those who accept will be assigned a Subject study number.
2) A complete medical history will be obtained to determine Subject's general health status.
3) A comprehensive neurological examination will be performed by a neurologist
4) Determination of tremor dominant side must be made and concurrence with second opinion must occur to determine side for ExAblate Transcranial lesioning.
5) Evaluation of functional status and tremor assessment using the CRST will be performed by a physical therapy neurological specialist.
6) Psychological and cognitive assessment will be performed by a neuropsychologist to screen for significant cognitive impairment and unstable mood disorders.
7) Additionally, quality of life and functional assessments will be obtained from PDQ-39

8) Instead of, or in addition to, screening assessment, subjects enrolled in the study will undergo Baseline assessment of their symptoms. Baseline assessment is a blinded assessment occurring after consent and before treatment.

    a) *On* medication UPDRS and CRST will be completed on screening day. CRST Parts A and B will be repeated on treatment day before treatment begins and referenced for intra-procedure response.

9) Medications for the treatment of PD will be reviewed at each study visit. PD medication dosage should be stable and unchanged for at least 30 days prior to entering the study. During the study, all medication changes will be noted and converted to a standard levodopa equivalent. Levodopa equivalent usage will be recorded throughout the study.

10) Blood will be drawn by venipuncture for PT, PTT, CBC including platelets, and creatinine

11) Women of childbearing age will undergo a urinary 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 use a barrier contraception method throughout study. This includes the screening period until study completion at 3 Months post treatment.

12) The subject will have a standard pre-operative visit with an Anesthesiologist or nurse anesthetist

13) Subjects with a prior history of DVT will undergo a DVT screening with lower extremity ultrasound.

14) Pre-treatment imaging will be scheduled

15) The head CT and cerebral MRI will be reviewed to assess the scalp, skull, target accessibility and brain.

16) If at any 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 screen failures, and will not be included in any of the safety or efficacy endpoint analyses. The Screening and Study Exit CRF will be completed with reason for screen failure.

17) The diagnosis of idiopathic TDPD will be confirmed by a neurologist specializing in movement disorders. The neurologist's assessment must concur with the Principal Investigator that the subject meets all inclusion/exclusion criteria to continue in the study.

18) The ExAblate Treatment should be performed no earlier than 24h post consent signing.

19) The subject will be instructed to consume only clear fluids after midnight prior to the ExAblate Transcranial thalamotomy, in order to permit the use of immediate general anesthesia in case of a treatment complication that may require emergency intervention.

4.1.2 Randomization Procedures

Once a subject has passed all criteria and been found eligible by the medial team (unanimous) and eligible to proceed to treatment, the subject will be randomized to treatment assignment; The randomization will be computer generated.

4.1.3 Treatment Procedures

All PD-related medications will be withheld after their last evening dose or at least 12 hours prior to the scheduled treatment time and continuing throughout the treatment procedure.

The overall treatment procedure steps will be performed as follows:

1. A brief, pre-treatment tremor assessment will be administered upon subject arrival to the ExAblate FUS center.

2. A stereotactic head frame (as used in stereotactic surgery and radiotherapy) will be placed on the subject's head using a local anesthetic. The immobilization unit will ensure a constant relationship between the target and the transducer during the ExAblate treatment. The pins used to immobilize the head must be MRI compatible.

3.

4. Subject will be positioned supine and headfirst on the MR/ExAblate Transcranial therapy table.

5. The half-spherical helmet containing the transducer elements will be positioned around the subject's head in the treatment position.

6. The diaphragm will be connected to its component in the transducer to create the acoustic coupling system between the ultrasound transducer and the scalp. The helmet 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 the cooling system, the water will be maintained chilled throughout the procedure to avoid undesired heating of the scalp and skull.

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

8. A series of MR images will be acquired to identify the target area, and plan the actual treatment
   - T1 and T2Weighted imaging exam along at least 2 axes: Axial and Coronal
   - Other MR imaging series may also be acquired

9. The neurosurgeon will assure adequate upper extremity mobility in the MR unit to visualize tremor during the treatment and will conduct a Baseline assessment in the fixed treatment position before the ExAblate procedure begins.

10. The pre-treatment CT image datasets will be registered to the T1 weighted MR images that were just acquired. This image fusion of pre-operative imaging assists in

the accurate delineation of the target area and determination of a safe sonication pathway

ExAblate Test Arm Procedure

11. The treatment volume and plan will be defined by the neurosurgeon.

12. 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:

    a. The titration of escalating focal sonications will continue up to full ablation of the targeted planned area for ablation. This would be performed by utilizing the full feedback that is provided by the real time MR Thermometry.

13. After the ExAblate Transcranial treatment, a series of MR images will be acquired to assess the treatment effects

Sham Arm Procedure

The treatment volume and plan will be defined by the neurosurgeon. The energy output will be set to zero ('0'). The full Sham procedure will follow the same steps as above

4.1.4 Follow-up

4.1.4.1 Follow-up for ExAblate-treated Subjects

Subject follow-up will be completed at 1-Day, 1-Week, and 1, 3, and 12-Months for all subjects. A six month assessment will be conducted by telephone interview.

Subjects will be evaluated for general health, neurological changes, and efficacy measurements as well as for device/procedure/PD disease progression- related adverse events that may have occurred during the follow-up period.

<u>The following measurements should be collected at Day 1(before discharge)</u>

- General physical
- Neurological exam
- Concomitant and PD medications
- Adverse events

MR Imaging exams

The following measurements should be collected at Week 1 (office visit)

- General physical
- Neurological exam
- Concomitant and PD medications
- Adverse events

The following measurement should be collected at Month 1, 3, and 12 (office visits). Blinded efficacy assessments are needed through Month 3.

- General physical
- Neurological exam
- On-medication, CRST Tremor Rating Scale
- On-medication, UPDRS part III (motor subsection)
- On-medication, neuropsychological testing at 3 and 12 months only
- Quality of Life PDQ-39 and QUEST at Months 3 and 12 only.
- Concomitant and PD medications at every visit
- Adverse events at every visit
- MRI at Month-1 and Month 12.
    - o

<u>The following measurements should be collected at Month 6 by telephone:</u>

- Concomitant and PD medications
- Adverse events

All ExAblate subjects will continue in the study for long-term follow-up through one year. All Sham crossover subjects may be unblinded and crossed over and treated with ExAblate after completion of their Month 3 study assessment if they still qualify for the study. They will be followed according to the same post-treatment follow-up schedule as that of ExAblate Arm through Month 12 using the crossover set of CRFs.

Crossover

Sham subjects who opt for ExAblate treatment will be assessed to ensure they still meet criteria for treatment. Treatment will be scheduled for subjects still meeting criteria and the same follow up schedule as noted above (Week 1, Month 1, 3, 6 and 12) will be followed with the same tests assessed.

4.1.5 Study Requirements and Visit Schedule

The table below summarizes the study visit schedule and procedures. Appropriate case report forms for each visit must be completed and entered into the electronic data capture system.

The post treatment study visits are as follows:

1 Day, 1 Week (i.e. 7days) ± 3 days, 1 Month ± 7 days, 3 Month ± 14 days (or 2 weeks), 6 Months ± 21 days (or 3 weeks), 12 Months ± 1 Month.

Schedule of Events

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

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

subjects may opt to crossover to ExAblate at Month 3.

β: See MR Table Schedule

5 DATA ANALYSIS PLAN

Descriptive statistics will be performed for all outcomes by treatment group assignment after the last subject has attained 3 months follow-up. Core lab analysis of the images through three months will be evaluated and included in this report. 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. Formal hypothesis testing for efficacy is not proposed for this initial safety and preliminary efficacy trial.

All ExAblate subjects will continue to be seen through Month 12. All Sham subjects who cross over and receive ExAblate therapy will be followed according to the same follow-up schedule as the ExAblate Arm schedule through Month 12 and these data will be summarized separately from the randomized portion of the study. Descriptive statistics will be used to evaluate all data for all subjects through Month 12 following ExAblate treatment.

5.1 Safety

For each treatment group through Month 3, adverse events will be recorded and categorized according to severity, expectedness, and relationship to ExAblate Transcranial system, thalamotomy procedure, and/or disease progression. After 12 months follow-up, all adverse events will be tabulated through Month 12 for all ExAblate procedures in a similar manner.

Standard Code of Federal Regulation definitions for Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs) will be used in assessment of AEs. Furthermore, all events, such as progression of their primary disease that was treated under this protocol and subject alternative treatments post ExAblate treatment, will also be captured during this study.

5.2 Efficacy

Primary effectiveness will be evaluated using validated scores: *on* medication, Upper Limb tremor subscore (32 point maximum) from the 8 items of Parts A & B of the CRST ,based upon TDPD subjects where unilateral ExAblate thalamotomy was attempted *(i.e., Intent-to-Treat analysis*).

Secondary efficacy is defined as a reduction from Baseline in contralateral upper extremity tremor assessed by Upper Limb tremor score at 3-Months post-treatment. Additional efficacy measures will include levodopa equivalent medication usage, On-medication total CRST, On-medication UPDRS (part III motor subsection), On-medication total UPDRS (parts I-IV), the CRST *Disability* subsection Part C, and PDQ-39.

5.3 Subject Health Status

The results from the physical and neurological exams will be recorded in the CRFs and reviewed for possible adverse events.

5.4 Statistical Considerations and Sample Size

This is a feasibility study of 30 subjects (20 ExAblate; 10 Sham) randomized in a 2:1 ratio of ExAblate to Sham procedure. For this study, a statistical sample size analysis is not proposed.

It should be noted that for this study a total of 200 subjects may be enrolled and consented with the intent to treat a total of 30 subjects. All those subjects that were consented and then found not meeting study requirements will be considered screen failures

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. The Sham control is useful in determining a placebo effect.

5.5 Subject Confidentiality

Subject confidentiality will be maintained throughout this study, including all publications. Data collected and entered into the CRFs are the property of the study sponsor. Representatives from the study sponsor or authorized sponsor representatives, the Institutional Review Board [143], Ethics Committee or other regulatory bodies may receive copies of the study records and may review medical records related to the study.

6 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 due to the great risk that would be involved in open resection. 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.

6.1 Electronic Data Capture (EDC)

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

7 INVESTIGATOR RESPONSIBILITIES

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

REFERENCES

1. Hynynen, K., et al., *Noninvasive mr imaging-guided focal opening of the blood-brain barrier in rabbits.* Radiology, 2001. **220**(3): p. 640-6.
2. Hynynen, K., et al., *MR imaging-guided focused ultrasound surgery of fibroadenomas in the breast: a feasibility study.* Radiology, 2001. **219**(1): p. 176-85.
3. Cline, H.E., et al., *Focused US system for MR imaging-guided tumor ablation.* Radiology, 1995. **194**(3): p. 731-7.
4. Cline, H.E., et al., *MR-guided focused ultrasound surgery.* J Comput Assist Tomogr, 1992. **16**(6): p. 956-65.
5. Cline, H.E., et al., *Magnetic resonance-guided thermal surgery.* Magn Reson Med, 1993. **30**(1): p. 98-106.
6. Hynynen, K., et al., *MRI-guided noninvasive ultrasound surgery.* Med Phys, 1993. **20**(1): p. 107-15.
7. McDannold, N., et al., *Transcranial magnetic resonance imaging- guided focused ultrasound surgery of brain tumors: initial findings in 3 subjects.* Neurosurgery, 2010. **66**(2): p. 323-32; discussion 332.
8. Ram, Z., et al., *Magnetic resonance imaging-guided, high-intensity focused ultrasound for brain tumor therapy.* Neurosurgery, 2006. **59**(5): p. 949-55; discussion 955-6.
9. Martin, E., et al., *High-intensity focused ultrasound for noninvasive functional neurosurgery.* Ann Neurol, 2009. **66**(6): p. 858-61.
10. Hely, M.A., et al., *Sydney Multicenter Study of Parkinson's disease: non-L-dopa-responsive problems dominate at 15 years.* Mov Disord, 2005. **20**(2): p. 190-9.
11. Hely, M.A., et al., *The Sydney multicenter study of Parkinson's disease: the inevitability of dementia at 20 years.* Mov Disord, 2008. **23**(6): p. 837-44.
12. Driver, J.A., et al., *Incidence and remaining lifetime risk of Parkinson disease in advanced age.* Neurology, 2009. **72**(5): p. 432-8.
13. Khandhar, S.M. and W.J. Marks, *Epidemiology of Parkinson's disease.* Dis Mon, 2007. **53**(4): p. 200-5.
14. Riederer, P. and S. Wuketich, *Time course of nigrostriatal degeneration in parkinson's disease. A detailed study of influential factors in human brain amine analysis.* J Neural Transm, 1976. **38**(3-4): p. 277-301.
15. Rodriguez-Oroz, M.C., et al., *Bilateral deep brain stimulation in Parkinson's disease: a multicentre study with 4 years follow-up.* Brain, 2005. **128**(Pt 10): p. 2240-9.
16. Ahlskog, J.E. and M.D. Muenter, *Frequency of levodopa-related dyskinesias and motor fluctuations as estimated from the cumulative literature.* Mov Disord, 2001. **16**(3): p. 448-58.
17. Colosimo, C. and M. De Michele, *Motor fluctuations in Parkinson's disease: pathophysiology and treatment.* Eur J Neurol, 1999. **6**(1): p. 1-21.
18. Grandas, F., M.L. Galiano, and C. Tabernero, *Risk factors for levodopa-induced dyskinesias in Parkinson's disease.* J Neurol, 1999. **246**(12): p. 1127-33.
19. Van Gerpen, J.A., et al., *Levodopa-associated dyskinesia risk among Parkinson disease subjects in Olmsted County, Minnesota, 1976-1990.* Arch Neurol, 2006. **63**(2): p. 205-9.
20. Fahn, S., *How do you treat motor complications in Parkinson's disease: Medicine, surgery, or both?* Ann Neurol, 2008. **64 Suppl 2**: p. S56-64.
21. Metman, L.V. and S.T. O'Leary, *Role of surgery in the treatment of motor complications.* Mov Disord, 2005. **20 Suppl 11**: p. S45-56.
22. Cooper, I.S., *Ligation of the anterior choroidal artery for involuntary movements; parkinsonism.* Psychiatr Q, 1953. **27**(2): p. 317-9.
23. Cooper, I.S., *Surgical occlusion of the anterior choroidal artery in parkinsonism.* Surg Gynecol Obstet, 1954. **92**(2): p. 207-19.

24. Spiegel, E.A. and H.T. Wycis, *Pallidothalamotomy in chorea.* Arch Neurol Psychiatry, 1950. **64**(2): p. 295-6.
25. Spiegel, E.A. and H.T. Wycis, *Effect of thalamic and pallidal lesions upon involuntary movements in choreoathetosis.* Trans Am Neurol Assoc, 1950. **51**: p. 234-7.
26. Spiegel, E.A. and H.T. Wycis, *Ansotomy in paralysis agitans.* AMA Arch Neurol Psychiatry, 1953. **69**(5): p. 652-3.
27. Svennilson, E., et al., *Treatment of parkinsonism by stereotatic thermolesions in the pallidal region. A clinical evaluation of 81 cases.* Acta Psychiatr Scand, 1960. **35**: p. 358-77.
28. Hassler, R., F. Mundinger, and T. Riechert, *Correlations between clinical and autoptic findings in stereotaxic operations of parkinsonism.* Confin Neurol, 1965. **26**(3): p. 282-90.
29. Hassler, R., et al., *Physiological observations in stereotaxic operations in extrapyramidal motor disturbances.* Brain, 1960. **83**: p. 337-50.
30. Birkmayer, W. and O. Hornykiewicz, *[The L-3,4-dioxyphenylalanine (DOPA)-effect in Parkinson-akinesia].* Wien Klin Wochenschr, 1961. **73**: p. 787-8.
31. Laitinen, L.V., A.T. Bergenheim, and M.I. Hariz, *Leksell's posteroventral pallidotomy in the treatment of Parkinson's disease.* J Neurosurg, 1992. **76**(1): p. 53-61.
32. de Bie, R.M., et al., *Outcome of unilateral pallidotomy in advanced Parkinson's disease: cohort study of 32 subjects.* J Neurol Neurosurg Psychiatry, 2001. **71**(3): p. 375-82.
33. Eskandar, E.N., et al., *Stereotactic pallidotomy performed without using microelectrode guidance in subjects with Parkinson's disease: surgical technique and 2-year results.* J Neurosurg, 2000. **92**(3): p. 375-83.
34. Fine, J., et al., *Long-term follow-up of unilateral pallidotomy in advanced Parkinson's disease.* N Engl J Med, 2000. **342**(23): p. 1708-14.
35. Giller, C.A., et al., *Stereotactic pallidotomy and thalamotomy using individual variations of anatomic landmarks for localization.* Neurosurgery, 1998. **42**(1): p. 56-62; discussion 62-5.
36. Kondziolka, D., et al., *Outcomes after stereotactically guided pallidotomy for advanced Parkinson's disease.* J Neurosurg, 1999. **90**(2): p. 197-202.
37. Kopyov, O., et al., *Microelectrode-guided posteroventral medial radiofrequency pallidotomy for Parkinson's disease.* J Neurosurg, 1997. **87**(1): p. 52-9.
38. Kumar, R., et al., *Pallidotomy and deep brain stimulation of the pallidum and subthalamic nucleus in advanced Parkinson's disease.* Mov Disord, 1998. **13 Suppl 1**: p. 73-82.
39. Lai, E.C., et al., *Long-term efficacy of posteroventral pallidotomy in the treatment of Parkinson's disease.* Neurology, 2000. **55**(8): p. 1218-22.
40. Masterman, D., et al., *Motor, cognitive, and behavioral performance following unilateral ventroposterior pallidotomy for Parkinson disease.* Arch Neurol, 1998. **55**(9): p. 1201-8.
41. Melnick, M.E., et al., *Effect of pallidotomy on postural control and motor function in Parkinson disease.* Arch Neurol, 1999. **56**(11): p. 1361-5.
42. Uitti, R.J., R.E. Wharen, Jr., and M.F. Turk, *Efficacy of levodopa therapy on motor function after posteroventral pallidotomy for Parkinson's disease.* Neurology, 1998. **51**(6): p. 1755-7.
43. Vitek, J.L., et al., *Randomized trial of pallidotomy versus medical therapy for Parkinson's disease.* Ann Neurol, 2003. **53**(5): p. 558-69.
44. de Bie, R.M., et al., *Unilateral pallidotomy in Parkinson's disease: a randomised, single-blind, multicentre trial.* Lancet, 1999. **354**(9191): p. 1665-9.
45. Hariz, M.I. and A.T. Bergenheim, *A 10-year follow-up review of subjects who underwent Leksell's posteroventral pallidotomy for Parkinson disease.* J Neurosurg, 2001. **94**(4): p. 552-8.
46. Okun, M.S. and J.L. Vitek, *Lesion therapy for Parkinson's disease and other movement disorders: update and controversies.* Mov Disord, 2004. **19**(4): p. 375-89.
47. De Bie, R.M., et al., *Bilateral pallidotomy in Parkinson's disease: a retrospective study.* Mov Disord, 2002. **17**(3): p. 533-8.

48. Intemann, P.M., et al., *Staged bilateral pallidotomy for treatment of Parkinson disease.* J Neurosurg, 2001. **94**(3): p. 437-44.
49. York, M.K., et al., *Short and long-term motor and cognitive outcome of staged bilateral pallidotomy: a retrospective analysis.* Acta Neurochir (Wien), 2007. **149**(9): p. 857-66; discussion 866.
50. Mazars, G., L. Merienne, and C. Cioloca, *Control of dyskinesias due to sensory deafferentation by means of thalamic stimulation.* Acta Neurochir Suppl (Wien), 1980. **30**: p. 239-43.
51. Benabid, A.L., et al., *Long-term suppression of tremor by chronic stimulation of the ventral intermediate thalamic nucleus.* Lancet, 1991. **337**(8738): p. 403-6.
52. Siegfried, J. and B. Lippitz, *Bilateral chronic electrostimulation of ventroposterolateral pallidum: a new therapeutic approach for alleviating all parkinsonian symptoms.* Neurosurgery, 1994. **35**(6): p. 1126-9; discussion 1129-30.
53. Blomstedt, P., G.M. Hariz, and M.I. Hariz, *Pallidotomy versus pallidal stimulation.* Parkinsonism Relat Disord, 2006. **12**(5): p. 296-301.
54. Bergman, H., T. Wichmann, and M.R. DeLong, *Reversal of experimental parkinsonism by lesions of the subthalamic nucleus.* Science, 1990. **249**(4975): p. 1436-8.
55. DeLong, M.R., *Primate models of movement disorders of basal ganglia origin.* Trends Neurosci, 1990. **13**(7): p. 281-5.
56. DeLong, M.R., M.D. Crutcher, and A.P. Georgopoulos, *Primate globus pallidus and subthalamic nucleus: functional organization.* J Neurophysiol, 1985. **53**(2): p. 530-43.
57. Aziz, T.Z., et al., *Subthalamic nucleotomy alleviates parkinsonism in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-exposed primate.* Br J Neurosurg, 1992. **6**(6): p. 575-82.
58. Brotchie, J.M., et al., *Alleviation of parkinsonism by antagonism of excitatory amino acid transmission in the medial segment of the globus pallidus in rat and primate.* Mov Disord, 1991. **6**(2): p. 133-8.
59. Guridi, J., et al., *Subthalamotomy in parkinsonian monkeys. Behavioural and biochemical analysis.* Brain, 1996. **119 (Pt 5)**: p. 1717-27.
60. Wichmann, T. and M.R. DeLong, *Functional and pathophysiological models of the basal ganglia.* Curr Opin Neurobiol, 1996. **6**(6): p. 751-8.
61. *Deep-brain stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease.* N Engl J Med, 2001. **345**(13): p. 956-63.
62. Benabid, A.L., et al., *Acute and long-term effects of subthalamic nucleus stimulation in Parkinson's disease.* Stereotact Funct Neurosurg, 1994. **62**(1-4): p. 76-84.
63. Esselink, R.A., et al., *Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in Parkinson's disease: one year follow-up of a randomised observer-blind multi centre trial.* Acta Neurochir (Wien), 2006. **148**(12): p. 1247-55; discussion 1255.
64. Anderson, V.C., et al., *Pallidal vs subthalamic nucleus deep brain stimulation in Parkinson disease.* Arch Neurol, 2005. **62**(4): p. 554-60.
65. Burchiel, K.J., et al., *Comparison of pallidal and subthalamic nucleus deep brain stimulation for advanced Parkinson's disease: results of a randomized, blinded pilot study.* Neurosurgery, 1999. **45**(6): p. 1375-82; discussion 1382-4.
66. Nakamura, K., et al., *Effects of unilateral subthalamic and pallidal deep brain stimulation on fine motor functions in Parkinson's disease.* Mov Disord, 2007. **22**(5): p. 619-26.
67. Hariz, M.I., et al., *Multicenter study on deep brain stimulation in Parkinson's disease: an independent assessment of reported adverse events at 4 years.* Mov Disord, 2008. **23**(3): p. 416-21.
68. York, M.K., et al., *Cognitive declines following bilateral subthalamic nucleus deep brain stimulation for the treatment of Parkinson's disease.* J Neurol Neurosurg Psychiatry, 2008. **79**(7): p. 789-95.

69. Rajput, A.H., B. Rozdilsky, and L. Ang, *Occurrence of resting tremor in Parkinson's disease.* Neurology, 1991. **41**(8): p. 1298-9.
70. Hughes, A.J., et al., *A clinicopathologic study of 100 cases of Parkinson's disease.* Arch Neurol, 1993. **50**(2): p. 140-8.
71. Deuschl, G., et al., *The pathophysiology of parkinsonian tremor: a review.* J Neurol, 2000. **247 Suppl 5**: p. V33-48.
72. Deuschl, G., P. Bain, and M. Brin, *Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee.* Mov Disord, 1998. **13 Suppl 3**: p. 2-23.
73. Stochl, J., et al., *On the structure of motor symptoms of Parkinson's disease.* Mov Disord, 2008. **23**(9): p. 1307-12.
74. Jankovic, J., et al., *Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson Study Group.* Neurology, 1990. **40**(10): p. 1529-34.
75. Zaidel, A., et al., *Akineto-rigid vs. tremor syndromes in Parkinsonism.* Curr Opin Neurol, 2009. **22**(4): p. 387-93.
76. Rajput, A.H., et al., *Course in Parkinson disease subtypes: A 39-year clinicopathologic study.* Neurology, 2009. **73**(3): p. 206-12.
77. Alves, G., et al., *Changes in motor subtype and risk for incident dementia in Parkinson's disease.* Mov Disord, 2006. **21**(8): p. 1123-30.
78. Bartels, A.L. and K.L. Leenders, *Parkinson's disease: the syndrome, the pathogenesis and pathophysiology.* Cortex, 2009. **45**(8): p. 915-21.
79. Fishman, P.S., *Paradoxical aspects of parkinsonian tremor.* Mov Disord, 2008. **23**(2): p. 168-73.
80. Eidelberg, D., et al., *Early differential diagnosis of Parkinson's disease with 18F-fluorodeoxyglucose and positron emission tomography.* Neurology, 1995. **45**(11): p. 1995-2004.
81. Eidelberg, D., et al., *Assessment of disease severity in parkinsonism with fluorine-18-fluorodeoxyglucose and PET.* J Nucl Med, 1995. **36**(3): p. 378-83.
82. Benamer, H.T., et al., *Prospective study of presynaptic dopaminergic imaging in subjects with mild parkinsonism and tremor disorders: part 1. Baseline and 3-month observations.* Mov Disord, 2003. **18**(9): p. 977-84.
83. Vingerhoets, F.J., et al., *Which clinical sign of Parkinson's disease best reflects the nigrostriatal lesion?* Ann Neurol, 1997. **41**(1): p. 58-64.
84. Sung, Y.H., et al., *Factors predicting response to dopaminergic treatment for resting tremor of Parkinson's disease.* Mov Disord, 2008. **23**(1): p. 137-40.
85. Laitinen, L.V., *Brain targets in surgery for Parkinson's disease. Results of a survey of neurosurgeons.* J Neurosurg, 1985. **62**(3): p. 349-51.
86. Brodkey, J.A., et al., *Tremor cells in the human thalamus: differences among neurological disorders.* J Neurosurg, 2004. **101**(1): p. 43-7.
87. Hirai, T., et al., *The correlation between tremor characteristics and the predicted volume of effective lesions in stereotaxic nucleus ventralis intermedius thalamotomy.* Brain, 1983. **106 (Pt 4)**: p. 1001-18.
88. Pahwa, R., et al., *Comparison of thalamotomy to deep brain stimulation of the thalamus in essential tremor.* Mov Disord, 2001. **16**(1): p. 140-3.
89. Schuurman, P.R., et al., *A comparison of continuous thalamic stimulation and thalamotomy for suppression of severe tremor.* N Engl J Med, 2000. **342**(7): p. 461-8.
90. Tasker, R.R., *Deep brain stimulation is preferable to thalamotomy for tremor suppression.* Surg Neurol, 1998. **49**(2): p. 145-53; discussion 153-4.
91. Obwegeser, A.A., et al., *Quantitative and qualitative outcome measures after thalamic deep brain stimulation to treat disabling tremors.* Neurosurgery, 2001. **48**(2): p. 274-81; discussion 281-4.
92. Obwegeser, A.A., et al., *Thalamic stimulation for the treatment of midline tremors in essential tremor subjects.* Neurology, 2000. **54**(12): p. 2342-4.

93. Putzke, J.D., et al., *Bilateral thalamic deep brain stimulation: midline tremor control.* J Neurol Neurosurg Psychiatry, 2005. **76**(5): p. 684-90.
94. Carpenter, M.A., et al., *Reduction in voice tremor under thalamic stimulation.* Neurology, 1998. **50**(3): p. 796-8.
95. Diamond, A. and J. Jankovic, *The effect of deep brain stimulation on quality of life in movement disorders.* J Neurol Neurosurg Psychiatry, 2005. **76**(9): p. 1188-93.
96. Fields, J.A., et al., *Neuropsychological and quality of life outcomes 12 months after unilateral thalamic stimulation for essential tremor.* J Neurol Neurosurg Psychiatry, 2003. **74**(3): p. 305-11.
97. Hariz, G.M., M. Lindberg, and A.T. Bergenheim, *Impact of thalamic deep brain stimulation on disability and health-related quality of life in subjects with essential tremor.* J Neurol Neurosurg Psychiatry, 2002. **72**(1): p. 47-52.
98. Mohadjer, M., et al., *Long-term results of stereotaxy in the treatment of essential tremor.* Stereotact Funct Neurosurg, 1990. **54-55**: p. 125-9.
99. Sydow, O., et al., *Multicentre European study of thalamic stimulation in essential tremor: a six year follow up.* J Neurol Neurosurg Psychiatry, 2003. **74**(10): p. 1387-91.
100. Benabid, A.L., et al., *Long-term electrical inhibition of deep brain targets in movement disorders.* Mov Disord, 1998. **13 Suppl 3**: p. 119-25.
101. Hariz, M.I., et al., *Tolerance and tremor rebound following long-term chronic thalamic stimulation for Parkinsonian and essential tremor.* Stereotact Funct Neurosurg, 1999. **72**(2-4): p. 208-18.
102. Yamamoto, T., et al., *Deep brain stimulation for the treatment of parkinsonian, essential, and poststroke tremor: a suitable stimulation method and changes in effective stimulation intensity.* J Neurosurg, 2004. **101**(2): p. 201-9.
103. Clement, G.T. and K. Hynynen, *A non-invasive method for focusing ultrasound through the human skull.* Physics in Medicine & Biology, 2002. **47**(8): p. 1219-36.
104. Clement, G.T., et al., *A magnetic resonance imaging-compatible, large-scale array for trans-skull ultrasound surgery and therapy.* Journal of Ultrasound in Medicine, 2005. **24**(8): p. 1117-25.
105. Hynynen, K., et al., *Pre-clinical testing of a phased array ultrasound system for MRI-guided noninvasive surgery of the brain--a primate study.* European Journal of Radiology, 2006. **59**(2): p. 149-56.
106. Hynynen, K. and F.A. Jolesz, *Demonstration of potential noninvasive ultrasound brain therapy through an intact skull.* Ultrasound in Medicine & Biology, 1998. **24**(2): p. 275-83.
107. McDannold, N., et al., *MRI investigation of the threshold for thermally induced blood-brain barrier disruption and brain tissue damage in the rabbit brain.* Magn Reson Med, 2004. **51**(5): p. 913-23.
108. Cohen, Z.R., et al., *Magnetic resonance imaging-guided focused ultrasound for thermal ablation in the brain: a feasibility study in a swine model.* Neurosurgery, 2007. **60**(4): p. 593-600; discussion 600.
109. Jolesz, F.A., A.R. Bleier, and R.S. Lauter, *Laser surgery benefits from guidance by MR.* Diagn Imaging (San Franc), 1990. **12**(9): p. 103-8.
110. Jolesz, F.A. and S.M. Blumenfeld, *Interventional use of magnetic resonance imaging.* Magn Reson Q, 1994. **10**(2): p. 85-96.
111. Jolesz, F.A. and N. McDannold, *Current status and future potential of MRI-guided focused ultrasound surgery.* Journal of Magnetic Resonance Imaging, 2008. **27**(2): p. 391-9.
112. Jolesz, F.A., et al., *Response to and control of destructive energy by magnetic resonance.* Invest Radiol, 1989. **24**(12): p. 1024-7.
113. Moonen, C.T., et al., *Thermal therapies in interventional MR imaging. Focused ultrasound.* Neuroimaging Clinics of North America. **11**(4): p. 737-47.
114. Salomir, R., et al., *Image-based control of the magnetic resonance imaging-guided focused ultrasound thermotherapy.* Topics in Magnetic Resonance Imaging, 2006. **17**(3): p. 139-51.

115. Kleiner-Fisman, G., et al., *Subthalamic nucleus deep brain stimulation for parkinson's disease after successful pallidotomy: clinical and electrophysiological observations.* Mov Disord, 2004. **19**(10): p. 1209-14.
116. White, D.N., *Neurosonology pioneers.* Ultrasound Med Biol, 1988. **14**(7): p. 541-61.
117. Aaslid, R., T.M. Markwalder, and H. Nornes, *Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries.* J Neurosurg, 1982. **57**(6): p. 769-74.
118. Fry, W.J., et al., *Production of focal destructive lesions in the central nervous system with ultrasound.* J. Neurosurg, 1954. **11**: p. 471-478.
119. Fry, W.J., et al., *Ultrasonically produced localized selective lesions in the central nervous system.* Am. J. Phys. Med, 1955. **34**: p. 413-423.
120. Lele, P.P., *Production of deep focal lesions by focused ultrasound--current status.* Ultrasonics, 1967. **5**: p. 105-12.
121. Fry, F.J., et al., *Threshold ultrasonic dosages for structural changes in the mammalian brain.* J Acoust Soc Am, 1970. **48**(6): p. Suppl 2:1413+.
122. Fry, F.J. and J.E. Barger, *Acoustical properties of the human skull.* J Acoust Soc Am, 1978. **63**(5): p. 1576-90.
123. Fry, F.J., S.A. Goss, and J.T. Patrick, *Transkull focal lesions in cat brain produced by ultrasound.* Journal of Neurosurgery, 1981. **54**(5): p. 659-63.
124. Lynn, J.G., et al., *A new method for the generation and use of focused ultrasound in experimental biology.* J. Gen. Physiol., 1942. **26**: p. 179-193.
125. Smith, S.W., et al., *Some Advances in Acoustic imaging through Skull.* Symposium on Biological Effects, 1997: p. 37-52.
126. Guthkelch, A.N., et al., *Treatment of malignant brain tumors with focused ultrasound hyperthermia and radiation: results of a phase I trial.* J Neurooncol, 1991. **10**(3): p. 271-84.
127. Clement, G.T., et al., *A hemisphere array for non-invasive ultrasound brain therapy and surgery.* Phys Med Biol, 2000. **45**(12): p. 3707-19.
128. Clement, G.T., J. White, and K. Hynynen, *Investigation of a large-area phased array for focused ultrasound surgery through the skull.* Phys Med Biol, 2000. **45**(4): p. 1071-83.
129. Vykhodtseva, N., et al., *MRI detection of the thermal effects of focused ultrasound on the brain.* Ultrasound Med Biol, 2000. **26**(5): p. 871-80.
130. Niranjan, A., et al., *A comparison of surgical approaches for the management of tremor: radiofrequency thalamotomy, gamma knife thalamotomy and thalamic stimulation.* Stereotact Funct Neurosurg, 1999. **72**(2-4): p. 178-84.
131. Sansur, C.A., et al., *Incidence of symptomatic hemorrhage after stereotactic electrode placement.* J Neurosurg, 2007. **107**(5): p. 998-1003.
132. Deogaonkar, M., et al., *Clinical problem solving: finding the target.* Neurosurgery, 2007. **61**(4): p. 815-24; discussion 824-5.
133. Elias, W.J., K.M. Fu, and R.C. Frysinger, *Cortical and subcortical brain shift during stereotactic procedures.* J Neurosurg, 2007. **107**(5): p. 983-8.
134. Xiaowu, H., et al., *Risks of intracranial hemorrhage in subjects with Parkinson's disease receiving deep brain stimulation and ablation.* Parkinsonism Relat Disord. **16**(2): p. 96-100.
135. Duma, C.M., et al., *Gamma knife radiosurgery for thalamotomy in parkinsonian tremor: a five-year experience.* J Neurosurg, 1998. **88**(6): p. 1044-9.
136. Niranjan, A., et al., *Functional outcomes after gamma knife thalamotomy for essential tremor and MS-related tremor.* Neurology, 2000. **55**(3): p. 443-6.
137. Ohye, C. and T. Shibazaki, *Treatment of functional disorders with gamma knife thalamotomy.* Prog Neurol Surg, 2009. **22**: p. 170-81.
138. Jagannathan, J., et al., *High-Intensity Focused Ultrasound Surgery of the Brain: Part 1-a Historical Perspective with Modern Applications.* Neurosurgery, 2009. **64**(2): p. 201-211.

139. Gianfelice, D., et al., *MR imaging-guided focused US ablation of breast cancer: histopathologic assessment of effectiveness-- initial experience.* Radiology, 2003. **227**(3): p. 849-55.
140. Gianfelice, D., et al., *MR imaging-guided focused ultrasound surgery of breast cancer: correlation of dynamic contrast-enhanced MRI with histopathologic findings.* Breast Cancer Res Treat, 2003. **82**(2): p. 93-101.
141. Gianfelice, D., et al., *Feasibility of magnetic resonance imaging-guided focused ultrasound surgery as an adjunct to tamoxifen therapy in high-risk surgical subjects with breast carcinoma.* J Vasc Interv Radiol, 2003. **14**(10): p. 1275-82.
142. Gianfelice, D., et al., *Palliative treatment of painful bone metastases with MR imaging--guided focused ultrasound.* Radiology, 2008. **249**(1): p. 355-63.
143. Kirby, R.S., J.M. Fitzpatrick, and J. Irani, *Prostate cancer diagnosis in the new millennium: strengths and weaknesses of prostate-specific antigen and the discovery and clinical evaluation of prostate cancer gene 3 (PCA3).* BJU Int, 2009. **103**(4): p. 441-5.
144. McDannold, et al., *MRI evaluation of thermal ablation of tumors with focused ultrasound.* J Magn Reson Imaging, 1998. **8**(1): p. 91-100.