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Approvals:

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A Phase I Clinical Trial of the Management of the Medically-Refractory Motor Symptoms of Advanced Idiopathic Parkinson's Disease With Unilateral Lesioning of the Globus Pallidum Using the ExAblate Transcranial System

The goal of this prospective, one arm, non-randomized, multi-center feasibility study is to develop data to evaluate the safety and initial effectiveness of unilateral focused ultrasound pallidotomy adjunct to PD medications using this ExAblate Transcranial System in the management of dyskinesia symptoms for medication refractory, advanced idiopathic Parkinson's disease.

The Indications for Use claim for this system is: management of medication-refractory dyskinesia symptoms adjunct to PD medication in subjects with advanced idiopathic Parkinson's disease.

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1 Background and Significance

1.1. Idiopathic Parkinson's disease

Idiopathic Parkinson's disease (PD) is a common, progressive, incurable neurodegenerative disease that results in severe disability and eventually, death.[1, 2] 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.[3, 4] In PD, the initial pathology is a progressive loss of dopaminergic neurons within the substantia nigra in the brainstem that manifests initially as a tremor when ~50-70% of nigral dopaminergic cells are lost.[5, 6]. PD tremor is defined as a resting tremor of 4-7 Hertz that abolishes with volitional movement[7] and is usually accompanied by other motor impairments (tremor, bradykinesia, rigidity and gait impairment). 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.[8]

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 is often not as effective in controling bradykinesia and rigidity.[9]. As the disease progresses, many subjects develop medication-refractory PD symptoms, motor fluctuations, and medication-induced dyskinesias.[10] 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. Within 10 years, an estimated 59-100% of subjects suffer from medication-related side effects.[11-13] 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.[14, 15].

1.1.1. 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.[16, 17] Soon thereafter, precise stereotactic techniques were applied to pallidotomy procedures to create more

consistent and reproducible lesioning.[18-20] 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. [21] Similarly, ventrolateral thalamotomy, the primary outflow target of the pallidum, was observed to improve parkinsonian features and especially tremor. [21-23] In the 1960s, dopamine replacement became available for symptomatic therapy of PD, and surgical procedures essentially disappeared for decades. [24] 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. [25]

PD is rarely unilateral, however, and contralateral lesioning is discouraged because of a lesser beneficial effect of the contralateral lesion [26] paired with a higher risk of dysphonia, dysarthria, and cognitive dysfunction. [26-28] This resulted in decreased use of pallidotomy, as disease progression and medication-related side effects eventually involve both sides of the body and warrant bilateral treatment. Deep brain stimulation became the treatment of choice because it can be used bilaterally and is considered reversible.

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. [29] 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. [30, 31] 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 [31], and the efficacy of chronic bilateral pallidal DBS was observed as comparable to pallidal lesioning. [31-33] Like the internal segment of the globus pallidum, the subthalamic nucleus (STN) was recognized in experimental models of Parkinson's disease to be hyperactive.[34-36] 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.[34, 35, 37-40] In the 1990's, bilateral STN DBS in human subjects improved PD symptoms in a manner similar to pallidal DBS or pallidal lesioning [6, 41-43]. 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.[44-46]. 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. [6, 44, 45, 47, 48].

1.1.2. Contemporary surgical treatments for PD tremor

There is no cure or neuroprotective treatment for the neurodegenerative condition of idiopathic PD. Thus, current medical and surgical therapies are aimed toward maximal symptom relief with minimal associated side effects or morbidity. It is now relatively well accepted from rigorous clinical trials that surgical procedures like stereotactic ablation of the GPI [49, 50] and Deep Brain Stimulation "DBS" [6, 51-53] can provide symptom relief for the dopamine-

responsive motor symptoms of PD when medication has failed. Patients with PD and their doctors will seek the easiest and safest treatment assuming that the clinical benefits are comparable. This is the premise for the investigation of focused ultrasound ("FUS") lesioning in the treatment of advanced PD.

It is generally accepted that a well-placed stereotactic lesion is comparable in its magnitude of clinical effect to the high frequency electrical stimulation of the same target. In fact, prospective and retrospective comparative studies with tremor [54-57]and PD [32, 33, 58] have consistently documented similar clinical benefits.

Firstly, Tasker et al. retrospectively reviewed his series of thalamic stimulation and lesioning for ET and PD in Toronto with the conclusion that the two were "equally successful," but that symptom recurrence of progression could often be controlled with DBS readjustment as opposed to repeat thalamotomy [54]. Prospective comparisons have documented a similar magnitude of tremor relief with higher rates of cognitive, dysarthria, and gait morbidity following thalamotomy although hardware-associated complications are unique to DBS and the only mortality of the series occurred in the stimulation group [55]. Recently, Anderson et al. randomized ET patients and noted more improvement in the "regularity" of finger tapping with thalamic lesioning then with DBS [57].

There are fewer direct comparative studies addressing the motor symptoms of PD besides tremor, but unilateral stereotactic radiofrequency pallidotomy seems similar to unilateral pallidal DBS. Both seem to provide approximately 30% reduction (improvement) in the non-medicated motor scores of the UPDRS with the strongest effects on contralateral appendicular motor symptoms and the reduction of medication-induced dyskinesia [59, 60], R.E. Gross, Neurotherapeutics 2008). Merello et al. prospectively randomized thirteen patients to a unilateral pallidal surgery and observed similar UPDRS benefits with perhaps more improvement with hand tapping following GPI DBS whereas dyskinesia improved more substantially with pallidotomy [61]. Blomsted et al. treated five consecutive patients with unilateral pallidotomy followed by contralateral pallidal DBS at a mean of fourteen months later[32]. Even though overall mean off UPDRS reductions were as expected at 32%, the degree of appendicular improvement in dyskinesia reduction was better contralateral to the lesiont. Direct comparisons of subthalamic lesions and stimulation have not been performed like the GPI, and bilateral lesioning is discouraged when compared to bilateral DBS due to a higher risk of procedural morbidity.

While surgical lesions in various areas of the motor system have been useful for decades in providing some degree of clinical benefit for Parkinson's patients, the optimal method for creating a lesion deep within the brain has not been available, but the ExAblate has the potential to create the lesion non-invasively, with real-time visual monitoring, and immediate effect. 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.[62-64] 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 [62-66] By coupling

high intensity focused ultrasound with MRI, detailed treatment plans can be generated and intra-procedural real-time monitoring is available. [67] Standard MR sequences have been shown to reliably predict tissue damage during thermal lesioning with ultrasound.[67, 68] The precision of the technology has already been demonstrated in animal models [69] and is currently being investigated in humans with brain tumors [70, 71], neuropathic pain syndromes [72], and essential tremor (IDE#100169). Unlike stereotactic radiosurgery, the treatment can be monitored continuously in real-time with MRI and MR-thermography.[73-79] Furthermore, clinical testing can be performed during low intensity sonication to potentially test the target prior to permanent lesioning. Similarly to the Essential Tremor studies under IDE # G100169; G120246 and G120017, 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.

Ultimately, patients need options that work for their individual needs. For some patients, the burden of management for the DBS device is too cumbersome, time-intensive, and expensive with the potential for serious side effects, or may even be contraindicated. Other treatment options, such as pallidotomy, offer similar clinical benefit with less bother, expense, and fewer potential side effects. Neither therapy currently is effective in the last stages of the progressive neural degeneration. However, with the advancement of a precise, minimally invasive method of creating a pallidotomy with the ExAblate Transcranial device, pallidotomy may again become an equally attractive treatment alternative.

1.2. 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, [67, 79-83], 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.

Several studies are using the ExAblate Transcranial to create a thalamotomy to treat neurologic conditions. The ExAblate advantage over traditional techniques is that it eliminates the need to drill into the skull and place an electrode deep within the brain, or alternatively, avoids the use of radiation energy while providing immediate clinical response. A feasibility study has been completed in 15 subjects with follow-up through 1 year and a pivotal study is underway. Additionally, a feasibility study is underway to evaluate the use of ExAblate Transcranial for the treatment of arm tremor in tremor dominant Parkinson's disease (TDPD).

The ExAblate Transcranial system has been investigated in the treatment of brain tumors[70, 71], neuropathic pain[72], and more recently for the treatment of medication-refractory essential tremor. Targeting of other structures or nuclei within the brain can be accomplished quite easily with the software of the device. Tumors can be observed on MR and targeted for ablation. Other nuclei of the brain can be stereotactically targeted and ablated in similar fashion.

This proposed study intends to ablate unilaterally the globus pallidus. Unilateral pallidotomy procedure has been determined by the Movement Disorder Society to be an efficacious treatment for motor complications associated with Parkinson's disease in their recent evidence-based medicine review update [84]

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.[85] In adults, blood velocity in the basal arteries may be monitored through the intact temporal bone using the Doppler effect. [86] 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 [87-90]. Fry *et al*. showed that a low frequency (around 0.5 MHz) beam could be focused through the skull [91, 92]. 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 [93]. 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. [94]

For these reasons, previous focused ultrasound treatments of the brain have involved removal of the skull for the sonication pathway [88, 95], 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 [96, 97] (see **Sections 1.7.2.1** 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 [66].

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 [98]. 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.

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

1.4.1. 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 [99].

1.4.2. Placement error

Target identification in stereotaxy is derived from preoperative CT or MR scans taken with the subject in a supine position [100]. 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 [101] 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.

1.4.3. 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 [102]. 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.

1.4.4. Risk from DBS

DBS therapy has a lower risk of acute perioperative complications than does RF ablation [102]. 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 GPi 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 globus pallidus without requiring the use of implanted hardware would be more cost-effective and would avoid the inherent risks associated with chronic implants.

1.5. 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 [103]. 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 [62-64, 66]. By coupling CT-based phase tuning with the ExAblate Transcranial system, precise and small (2x2x3mm) lesions have been produced in deep brain areas while real-time thermal monitoring is available to observe the heating caused with each sonication [67]. Standard MR sequences have been shown to reliably predict the precise locus of tissue damage during thermal lesioning with focused ultrasound [67, 68]. The precision of the ExAblate Transcranial device has already been demonstrated in animal models [69] and is currently being investigated in humans with

brain tumors[71], neuropathic pain syndromes[72], essential tremor and Parkinson's disease. In subjects treated under these protocols to date, no new adverse events have been identified that can be solely attributed to the ExAblate Transcranial system.

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 and bone metastasis palliation, and is currently being evaluated under various FDA Investigational Device Exemptions "IDE" (see **Section-1.5** for more details).

There are many potential advantages for applying ExAblate Transcranial pallidotomy for the treatment of medication-refractory, advanced idiopathic 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.

1.5.1. Rational for ExAblate Transcranial System Pallidotomy for the Treatment of Medication-Refractory Advanced Idiopathic PD

Stereotactic radiofrequency lesioning of the thalamus (see Section-1.4.3 above) 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.[33, 49, 104-113] Randomized, prospective clinical trials of unilateral pallidotomy as compared to best medical therapy have confirmed these results [25, 49, 50] with sustained benefits observed over five and ten years. [106, 114] Unilateral pallidotomy is safe, effective, and recognized as an excellent treatment option for a subject suffering from PD. [60]

1.6. Summary

Based on published animal and human studies, we believe ExAblate Transcranial pallidotomy 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. A unilateral lesion of the globus pallidus has been shown to provide reduction of contralateral motor symptoms in PD. Using ExAblate Transcranial MRgFUS to create the pallidotomy 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 pallidotomy can be realized, it could supplant radiofrequency and radiosurgery techniques, and provide a viable alternative procedure for subjects considering DBS, which is invasive, uncomfortable, labor-intensive, and expensive.

1.7. Clinical Experience with ExAblate

1.7.1. Clinical ExAblate Body System

1.7.1.1. 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.

1.7.1.1.1. 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.

1.7.1.1.2. 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.

1.7.1.1.3. 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).

1.7.1.1.4. 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.

1.7.1.2. 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 [115-117]. Both of these studies are now closed. Currently, InSightec has an FDA conditional approval for a new breast cancer phase-2 study (IDE # G060023).

1.7.1.2.1. 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 [115-117]**.** 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.

1.7.1.2.2. 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 [81]. 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.

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

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 have been performed 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 27 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 Canada. In the United States under FDA oversight, InSightec has initiated a feasibility study IDE (G100108) and sites are being recruited.

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

First, InSightec performed FDA approved feasibility study[118] of ExAblate ablation of metastatic bone tumors under IDE # G050177 in a total of 10 subjects at two (2) study sites followed by a pivotal study(PMA # P110039). We received PMA approval in October 2012.

1.7.1.4.1. Bone Feasibility Study IDE# G050177

This study was designed as a prospective, one arm, non-randomized study to evaluate the safety and effectiveness of using ExAblate as a treatment for pain palliation in subjects with metastatic bone tumors. . 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. 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.

Assessments were performed at baseline, on treatment day, and at follow-up time points of 3 days, 2 weeks, 1 and 3 months.

Only 3 mild AEs were reported in the study with no device-related deaths, life-threatening injuries or permanent injuries, nor serious adverse events. All of these events were anticipated side effects that were identified in the study protocol as possible treatment-related complications.

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 A very rapid and sustained relief response was observed in subjects' pain relief [Baseline: mean pain score was 5.6 ± 1.2 (N=10, score range: 4-7); Month 3: the mean pain score 0.4 ± 0.6 (a 93%

decrease from baseline)]. With respect to medication usage, all subjects maintained or decreased their medication usage. 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 demonstrated the safety and effectiveness of using ExAblate as a treatment for pain palliation in subjects with metastatic bone tumors and provided a basis for designing the pivotal study..

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

This study was designed as a prospective, randomized (3 ExAblate :1 Sham), single-blind multicenter sham-controlled clinical trial comparing ExAblate treatment against a Sham treatment with follow-up post-treatment to three months. A total of 148 patients were enrolled and treated under this IDE. This IDE study was reviewed and approved under FDA PMA # P110039 (http://www.accessdata.fda.gov/cdrh_docs/pdf11/p110039a.pdf).

The full FDA approved summary may be accessed at:
http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110039b.pdf

1.7.1.4.1. Conformal Bone System (CBS) Study Summary – FDA Study: IDE G 080206

InSightec is currently conducting a study using a modified the transducer configuration in this protocol at three sites. The study is enrolling and to date seven subjects have been enrolled and treated with this conformal system. The study was cleared for 50 subjects. Although no data is available at this time, all the informal information from the participating investigators is that there is a very high level of patient acceptance of the device configuration and of the procedure. To date, the safety profile continues to be favorable to the ExAblate Bone Metastasis procedure, and there were no new event types attributed to the device.

1.7.2. ExAblate Transcranial 4000 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)
Supports both standard* and burst** sonication regimens	Supports standard* sonications only
**Standard sonication regimen delivers the required energy in a continuous fashion to the target* ***Burst Sonication regimen delivers the energy in a series of bursts (multiple high amplitude, short duration with millisecond pauses between energy bursts). 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 # G1) 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.

1.7.2.1. ExAblate Transcranial Treatment of Brain

1.7.2.1.1. 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.[70, 71] 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.

This study was limited to 10 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.

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. Adverse events included nausea and lip swelling.
- 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.
- During these 3 treatments, all safety subsystems and monitoring of the device provided the intended safety monitoring capabilities.
- Tthe potential of tissue ablation 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 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 suing the same safety protocol.. Utilizing the burst sonication regime, the designated tumor was completely ablated. 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 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 a new exclusion criteria (tumors with a known tendency to bleed, subjects with abnormal clotting studies or on drugs known to affect coagulation) and 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. The study has received IRB approval and has been restarted.

1.7.2.1.2. 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*.

1.7.2.1.3. 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. 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. The full results of this study were published in the *New England Journal of Medicine* [119].

1.7.2.1.1. Pivotal Study for Essential Tremor IDE - G120246 - ExAblate Transcranial System

This is a global, multi-center, randomized, sham-controlled pivotal study to evaluate the safety and efficacy of ExAblate Transcranial unilateral thalamotomy for treating medication-refractory Essential Tremor. A total of 72 subjects will be recruited for this study which has recently gotten

underway. After the last subject completes 1 year follow-up, a Pre-Market Approval submission will follow.

1.7.2.1.2. Feasibility Study for Tremor Dominant Parkinson's Disease IDE - G120017 - ExAblate Transcranial System

This is a, multi-center, randomized, sham-controlled pivotal study to evaluate the safety and efficacy of ExAblate Transcranial unilateral thalamotomy for treating medication-refractory Tremor Dominant Parkinson's Disease. A total of 30 subjects will be recruited for this study; nineteen have been treated as of this date. After the last subject completes the study, a final clinical report will be written and submitted to FDA.

1.7.2.1.3. CE Approval of the ExAblate Transcranial MRgFUS System

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

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

2 OBJECTIVES

The proposed study will evaluate the safety, and initial efficacy of using the ExAblate Transcranial to create a unilateral lesion in the globus pallidus as an adjunct to PD medications in subjects who are over 30 years of age and considered medication-refractory with advanced idiopathic Parkinson's disease (PD).

> **Safety**: To evaluate the incidence and severity of adverse events (AEs) associated with ExAblate Transcranial method of pallidotomy in subjects with medication-refractory, advanced idiopathic PD.
>
> **Effectiveness**: To determine the level of effectiveness of the ExAblate Transcranial pallidotomy to manage the dyskinesia of subjects with medication-refractory, advanced idiopathic PD.

This study is designed as a prospective, multi-center, single-arm feasibility study; all ExAblate-treated subjects will be followed up for 24 months. The primary endpoint measured will be safety of unilateral, 3Tesla, ExAblate Transcranial pallidotomy for PD as determined from adverse events recorded during the 3 month study period. Patients are followed till Month 24 for long-term safety and preliminary efficacy. Data generated through Month 3 may be used for preparation of a pivotal study protocol.

Safety

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 3 month post–treatment time point. All AEs will be reported and categorized by investigators as definitely, probably, possibly, unlikely, or unrelated to the device, pallidotomy 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. Relative safety of the ExAblate Transcranial treatment will be evaluated as compared to other methodologies for creating pallidotomy as reported in the literature.

Effectiveness

Efficacy endpoints will include comparison of Baseline to each follow-up visit assessment for:

- Unified Dyskinesia Rating Scale
- *Off*-medication, motor score from the MDS-UPDRS, part III
- *On*-medication, motor score from MDS-UPDRS, part III
- *MDS*-UPDRS Parts I, II and IV
- Quality of life assessment with PDQ-39
- Clinician and Patient Global Impression of Change
- Patient Treatment Satisfaction

Baseline and follow-up efficacy assessments of the MDS-UPDRS and Unified Dyskinesia Rating Scale will be performed by the treating neurologist.

Efficacy Assessments

The Unified Dyskinesia Rating Scale will be performed at Baseline and at Months 1, 3, 6, 12, and 24 while on medication. The Month 3 measure as compared to Baseline while *on* medication will serve as the primary clinical effectiveness endpoint while the Month 6, 12 and 24 as compared to Baseline will serve to assess continued durability.

The new Unified Parkinson's Disease Rating Scale refined by the Movement Disorders Society (MDS-UPDRS) in July 2008 [120] will be performed at Screening, Week 1, Months 1, 3, 6, 12, and 24 to assess the patient's motor symptoms. Each treated subject will be examined "*off medication"* and "*on medication"*.

Quality of Life will be assessed using the PDQ-39 at Baseline, Months 3, 6, 12 and 24 will be compared to Baseline. These assessments will similarly be made in the *on*-medication state.

Additional questionnaires such as the Clinician Global Impression of Change, the Patient Global Assessment of Change, and a Patient Satisfaction Questionnaire will be captured during the post-treatment phase of the study to assess global health status and the satisfaction of a unilateral procedure for controlling their disease symptoms. Where possible, three days of patient diary source data (such as http://www.parkinsons.va.gov/resources/motordiary.pdf) will be used for calculating ON and OFF times for MDS-UPDRS Part IV and UDysRS.

Study Hypothesis

The purpose of this study is to evaluate the safety and initial clinical effectiveness of ExAblate Transcranial unilateral thermal ablation of the globus pallidus of subjects suffering from medication-refractory, advanced idiopathic PD.

Data will be collected to establish the basic safety and clinical efficacy of this type of treatment as the basis for later studies that will evaluate the full clinical efficacy.

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, advanced idiopathic 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 24 months. Consented subjects will receive the standard clinical and imaging work-up as part of their study baseline requirements. Subject eligibility will be confirmed independently by two movement disorder specialists on the medial team prior to the procedure.

Up to 200 subjects may be consented in order to qualify twenty (20) medication-refractory, advanced idiopathic PD subjects at up to four sites who will be treated in this feasibility study. 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 agreement on all aspects of the Inclusion/Exclusion criteria listed below.

3.2.1 Inclusion Criteria

1. Men and women, age 30 years and older
2. Subjects who are able and willing to give informed consent and able to attend all study visits through 24 Months
3. Subjects with a diagnosis of idiopathic PD by UK Brain Bank Criteria as confirmed by a movement disorder neurologist at the site
4. Levodopa responsive as defined by at least a 30% reduction in MDS-UPDRS motor subscale in the ON vs OFF medication state.
5. MDS-UPDRS score of ≥ 30 in the meds OFF condition
6. Disabling motor complications of PD on optimum medical treatment characterized dyskinesia or motor fluctuations (MDS-UPDRS item 4.2 score of 2 or 3 in the meds ON condition)

7. Predominant disability from one side of the body.
8. Subjects should be on a stable dose of all PD medications for 30 days prior to study entry.
9. Subject is able to communicate sensations during the ExAblate Neuro procedure.

3.2.2 Exclusion Criteria

1. Hoehn and Yahr stage in the ON medication state of 3 or greater
2. Presence of other central neurodegenerative disease suspected on neurological examination. These include: multisystem atrophy, progressive supranuclear palsy, corticobasal syndrome, dementia with Lewy bodies, and Alzheimer's disease.
3. Any suspicion that Parkinsonian symptoms are a side effect from neuroleptic medications.
4. Subjects who have had deep brain stimulation or a prior stereotactic ablation of the basal ganglia
5. Presence of significant cognitive impairment defined as score ≤ 21 on the Montreal Cognitive Assessment (MoCA) or Mattis Dementia Rating Scale of 120 or lower.
6. 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
7. 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 19[1] on the Beck Depression Inventory.
8. Legal incapacity or limited legal capacity as determined by the neuropsychologist
9. 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:
    a. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (such as repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; or neglect of children or household).
    b. Recurrent substance use in situations in which it is physically hazardous (such as driving an automobile or operating a machine when impaired by substance use)
    c. Recurrent substance-related legal problems (such as arrests for substance related disorderly conduct)

[1] Per 1996 BDI-II Guidelines; Significant depression, such as Moderate and Severe depression is scores of 20 and above. http://www.psychcongress.com/saundras-corner/scales-screenersdepression/beck-depression-inventory-ii-bdi-ii

   d. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (for example, arguments with spouse about consequences of intoxication and physical fights).

10. Subjects with unstable cardiac status including:
    a. Unstable angina pectoris on medication
    b. Subjects with documented myocardial infarction within six months of protocol entry
    c. Significant congestive heart failure defined with ejection fraction < 40
    d. Subjects with unstable ventricular arrhythmias
    e. Subjects with atrial arrhythmias that are not rate-controlled
11. Severe hypertension (diastolic BP > 100 on medication)
12. Current medical condition resulting in abnormal bleeding and/or coagulopathy
13. 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
14. 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
15. Patient with severely impaired renal function with estimated glomerular filtration rate <30 mL/min/1.73m^2 (or per local standards should that be more restrictive) and/or who is on dialysis;
16. Subjects with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, etc.
17. Significant claustrophobia that cannot be managed with mild medication.
18. Subject who weigh more than the upper weight limit of the MR scanner table and who cannot fit into the MR scanner
19. Subjects who are not able or willing to tolerate the required prolonged stationary supine position during treatment.
20. History of intracranial hemorrhage
21. History of multiple strokes, or a stroke within past 6 months
22. Subjects with a history of seizures within the past year
23. Subjects with brain tumors
24. Subjects with intracranial aneurysms requiring treatment or arterial venous malformations (AVMs) requiring treatment.
25. Are participating or have participated in another clinical trial in the last 30 days
26. Any illness that in the investigator's opinion preclude participation in this study.
27. Subjects unable to communicate with the investigator and staff.
28. Pregnancy or lactation.

29. All patients with severe premorbid risks [MDS-UPDRS Part II subsection activities of daily living scores of a three or four in question 2.1 (speech), question 2.2 (salivation), or question 2.3 (swallowing)] will be excluded.

30. Subjects who have an Overall Skull Density Ratio of less than 0.40 as calculated from the screening CT.

4 INVESTIGATION PLAN

4.1 Study Design

This is a multi-center, prospective, open-label feasibility study to evaluate the safety and initial clinical effectiveness of unilateral ExAblate Transcranial pallidotomy of medication-refractory, advanced idiopathic, PD:

- PD subjects will be targeted with unilateral ExAblate Transcranial MRgFUS to the contralateral symptom-dominant side of the globus pallidum, internal segment.

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 PD 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) A Columbia Suicide Severity Rating Scale (Baseline/Screening version) will be obtained.
5) Determination of symptom dominant side must be made and concurrence with second opinion must occur to determine side for ExAblate Transcranial lesioning.
6) Medications for the treatment of PD will be reviewed. 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.
7) Once medication stability has been assessed, a full assessment of Parkinson's disease will be made using the MDS-UPDRS, parts I-IV administered in the *off* (unmedicated) and *on* (medicated) state. Dopamine-responsiveness will be determined by the neurologist by comparing meds *off* and *on* MDS-UPDRS part III, motor subsections. Dopamine-responsiveness will be determined by the neurologist by comparing *off* and *on* MDS-UPDRS part III, motor subsections. Dopamine responsiveness is defined as at least a 30% improvement in on MDS-UPDRS part III motor scores following the administration of

dopaminergic medications. Medication-refractoriness or medication-induced side effects will be determined by the movement disorder neurologist using the MDS-UPDRS and Unified Dyskinesia rating scales.

8) Gait will be assessed using TGUG assessment.

9) Psychological and cognitive assessment will be performed by a neuropsychologist to screen for significant cognitive impairment and unstable mood disorders. See list of tests in **Appendix B**.

10) Additionally, quality of life and functional assessments will be obtained from PDQ-39.

11) Visual field testing will per performed by an ophthalmologist for baseline reference.

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

13) 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.

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

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

16) Pre-treatment imaging will be scheduled prior to treatment.

    1. CT Imaging: For the purpose of this study, a non-contrast head CT Exam should be an Axial scan with bone filter, an image resolution of 512x512, and image thickness of 1mm with zero (0) spacing. This should be performed early in the screening process to determine Overall Skull Density Ratio.
    2. MR Imaging: For the purpose of this study, MR Exams without contrast will be performed. The MR Imaging should include T1, T2, and DTI sequences. Other MR exams may be performed should they be needed.

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

18) 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.

19) The diagnosis of medication-refractory, advanced idiopathic PD 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.

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

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

4.1.2 Treatment Procedures

WARNING:

In this study, subject responsiveness and interaction with the treating physicians and their clinical team MUST be maintained through the full course of the procedure.

To alleviate the anxiety and discomfort[2] that may develop during this procedure, mild sedation may be administered so long as the subject's level of consciousness is not impaired or compromised. Subjects must always remain responsive to the physician.

Subjects will present to the FUS treatment center on the morning of surgery "*off*" medication. This means that 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. Once the ablative treatment is complete, PD medications will immediately be re-instituted as per the subject's usual schedule.

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

Neurosurgeon: leads the planning and guidance of the treatment. This person will also monitor the neurological performance and clinical status of the subject, and is responsible for the overall management of the subject. He will assess tremor and conduct modified neurologic status tests during the procedure. If the subject is not able to respond to evaluation during the treatment, the procedure will stop until contact with the subject can be re-established and the neurological status can be evaluated.

Neuroradiologist: will be accessible to assist in defining the target area and monitoring the treatment images for potential adverse reactions such as swelling or bleeding.

MRI Technician: will assist in system preparation, and MRI acquisition throughout the procedure.

Subject Monitor (RN or MD): will monitor vital signs and provide necessary medications and support to keep the subject comfortable or stabilize them in the event of an emergency.

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

[2] Based upon our experience with the ExAblate treatment of Essential Tremor (ET001 - IDE#G100169), subject may develop some degree of anxiety during the course of the procedure. Hence for this study, mild sedation may be provided should there be a need to alleviate subject anxiety and discomfort. Subject responsiveness MUST be maintained at all times during the procedure.

The overall treatment procedure steps will be performed as follows:

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

2. An IV line 0.9% sodium chloride will be positioned for the delivery of fluids and any medications required during the procedure. Some of the subjects may require a urinary catheter to keep the bladder empty during treatment.

3. The subject's head will be carefully shaved and examined for pre-existing scalp scars or any other scalp lesions.

4. Graduated compression stockings will be worn to prevent deep venous thrombosis in the lower limbs.

5. 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.

6. A rubber diaphragm will be attached to the subject's head.

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

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

9. 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.

10. MRI compatible, noninvasive blood pressure, systemic arterial oxygen saturation, and electrocardiogram equipment will be placed on the subject.

11. 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.

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

13. 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.

14. 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
    1. The fusion of the CT data is required for the computation of phase correction values to correct for skull aberration, and identification of intracranial calcifications
    2. Scars of the scalp and intracranial calcifications will be designated as 'no pass regions' to ensure the ultrasound beam avoids these specific areas.

ExAblate Procedure

1. The treatment volume and plan will be defined by the neurosurgeon. The ExAblate Transcranial system will automatically compute the phase and amplitude corrections necessary for the system to produce a focal spot at the desired location.

2. The Subject Monitor will be present throughout the procedure to ensure subject's overall well-being. The major role is to monitor and control blood pressure to prevent hypertension during the procedure. Under direct supervision of treating medical doctor (per local site standard requirements), the Subject Monitor may also administer medications for the management of any side effects experienced by the subject during the procedure including nausea. In any events, the subject must be able to communicate during the entire course of ExAblate procedure, and to operate the stop sonication button. Equipment for emergency resuscitation and stabilization will be on hand. In case of such an emergency, the procedure will be immediately terminated and the subject will be transferred to the hospital for further care.

3. 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.

4. To enhance the procedure safety and mitigate some of the inherent risks of thermal lesioning of brain tissue:
    a. The ExAblate Transcranial pallidotomy will be performed as a series of sonications with small increments in power within the designated target volume of the internal segment of the globus pallidum (GPi) in the non-anesthetized subject.
    b. The subject will be examined by the treating physician and his team during & after each sonication for neurologic signs and symptoms, evidence of symptom suppression, and vision side effects occurring during the procedure.

The treating physician is in direct communication with the patient at all times from within the MR suite.

c. The series of sonications will start with low energy prior to permanent thermal ablation. This is to ensure the planned sonication to be centered on the GPi. Low energy sonication will non-destructively warm the target. The warming will be captured by the MR thermometry and the MR thermal images will be displayed in real time to the treating physician. The neurosurgeon will then verify that the warming is centered on the anatomic target. This will allow the centering of the eventual permanent thermal lesion in the planned location.
d. 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.

5. The ExAblate Transcranial system is equipped with Stop Sonication Buttons: One for the subject to utilize, one for the Assessor, and one for the treating neurosurgeon. Hence, in the event of discomfort or pain, the subject will have the ability to abort the sonication at any time by activating the Stop Sonication Button. Once this button is activated, the system will instantly stop the energy delivery. The same thing will happen in the event the treating neurosurgeon or the Subject Monitor or Assessor activates their button. After addressing the subject concerns or discomfort, the procedure may continue without further delay.
6. After the ExAblate Transcranial treatment, a series of MR images will be acquired within 24 hours to assess the treatment effects:
    a. T1 and T2 Weighted imaging exam along at least 2 axes: Axial and Coronal
    b. DWI (including ADC maps, which allows differentiation between lesion-cytotoxic edema-low ADC and vasogenic edema around the lesion-high ADC). Other MR imaging series may also be acquired.
    c. GRE/SWI
    d. DTI
    e. Other imaging as indicated

It should be noted that in the event new neurological deficits or seizures are observed, other imaging modalities (including CT) should be performed immediately in addition to neurological and physical examinations.

7. Once the treatment is complete or otherwise terminated:
    a. Remove the subject from the ExAblate table and remove all monitoring equipment, rubber diaphragm, and stereotactic frame.
    b. Document all adverse events including assessment of skin in the vicinity of the metallic pin for any superficial events.
    c. Document neurological and physical examinations.
    d. Obtain additional images (including CT) as soon as possible post-procedure if warranted by clinical events during the procedure

e. The subject will be transferred to the hospital for recovery and neurological observation until the next morning.

The neurosurgeon will evaluate the subject's neurological and symptom status and make a decision as to whether or not to discharge the subject. Subjects who are found to be neurologically unstable will remain in the hospital until the neurosurgeon determines it is medically indicated to discharge without consideration of the hospitalization constituting a serious adverse event. A postoperative MRI will be obtained prior to discharge from the hospital.

4.1.3 Follow-up

4.1.3.1 Follow-up for ExAblate-treated Subjects

Subject follow-up will be completed at 1-Day, 1-Week, and 1, 3, 6, 2 and 24 months for all subjects.

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

The following measurements should be collected at Day 1(before discharge)

- General physical
- Neurological exam
- C-SSRS (Since last visit)
- Concomitant and PD medications
- Adverse events
- Within 24 hours of treatment - MRI with sequences including T1 and T, weighted images; DWI (including ADC maps, which allows differentiation between lesion-cytotoxic edema-low ADC and vasogenic edema around the lesion-high ADC); GRE/SWI and DTI. Additional MRI sequences may be acquired as indicated.

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

- General physical
- Neurological exam
- C-SSRS (Since last visit)
- Concomitant and PD medications
- Adverse events

The following measurement should be collected at Months 1, 3, 6, 12 and 24 (office visits).

- General physical

- Neurological exam
- C-SSRS (Since last visit)
- Visual field assessment will be performed by an opthamologist at Month 3 only.
- Gait (TGUG)
- MDS-UPDRS, Parts I and II
- *Off*-medication, MDS-UPDRS part III
- *On*-medication, MDS-UPDRS part III
- *On* Medication MDS-UPDRS, Part IV
- *On* medication, Unified Dyskinesia Rating scale
- Patient Clinical Global Impression of Change
- Clinician Clinical Global Impression of Change
- Patient Treatment Satisfaction Questionnaire
- *N*europsychological testing at 6, 12 and 24 months only
- Quality of Life PDQ-39 at Months 3, 6, 12 and 24.
- Concomitant and PD medications at every visit
- Adverse events at every visit
- MR Images: DWI (including ADC maps, which allows differentiation between lesion-cytotoxic edema-low ADC and vasogenic edema around the lesion-high ADC); GRE/SWI and DTI at Month 1 and 6 only

Additional MRI sequences may be acquired as indicated.

All pre-treatment and post treatment MR images will be sent to the Sponsor and anonymized and stored without subject identifiers by study number.

4.1.4 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:

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

- 12 Months ± 21 days (i.e. ± 3 weeks)
- 24 Month ± 30 days (i.e. ± 1 month)

Table 2. Schedule of Events

Procedures	Screening	Baseline	Day 0	Day 1	Day 7 (±3 days)	Month 1 (± 7 days)	Month 3 (±14 days)ə	Month 6- (± 21 days)	Month 12 (± 21 days)	Month 24 (± 30 days)
Written Consent	X									
Eligibility Consensus	X									
Demographics, Medical History	X									
Labs	X									
CT		X								
MRI		X	X	X		X		X		
General Physical Exam	X		X	X	X	X	X	X	X	X
Neurological Exam	X		X	X	X	X	X	X	X	X
Visual Field Testing		X					X			
C-SSRS	X			X	X	X	X	X	X	X
Gait (TGUG)	X					X	X	X	X	X
MDS-UPDRS, parts I-II	X					X	X	X	X	X
On MDS-UPDRS,parts IIII	X					X	X	X	X	X
Off MDS-UPDRS,parts III	X					X	X	X	X	X
ON MDS-UPDRS, Part IV	X					X	X	X	X	X
Unified Dyskinesia Rating Scale	X					X	X	X	X	X
Neuropsychological Assessment		X						X	X	X
Quality of Life (PDQ-39)		X					X	X	X	X

Procedures	Screening	Baseline	Day 0	Day 1	Day 7 (±3 days)	Month 1 (± 7 days)	Month 3 (±14 days)ə	Month 6- (± 21 days)	Month 12 (± 21 days)	Month 24 (± 30 days)
Patient Clinical Global Impression of Change					X	X	X	X	X	X
Clinician Clinical Global Impression of Change					X	X	X	X	X	X
Patient Satisfaction Questionnaire						X		X	X	X
PD Medications (mg) Levodopa equivalents	X	X	X	X	X	X	X	X	X	X
ExAblate Pallidotomy			X							
Adverse Events			X	X	X	X	X	X	X	X
Exit										X

Table 3. MR Imaging Requirements by Visit.	
Baseline	T1, T2, and DTI sequences without contrast Other MR exams may be performed should they be needed.
Treatment	"Part of the ExAblate procedure" 3. A localizer scan (quick T1) and a non-contrast T2-FSE MR scan 4. T1 Weighted imaging exam along at least 2 axes: Axial and Coronal 5. Other MR imaging series may also be acquired
Immediately Post-procedure or within 24 hours of procedure	1. T1 and T2 Weighted imaging exam along at least 2 axes: Axial and Coronal 2. DWI 3. GRE/SWI 4. DTI: The ROI would cover the posterior limb of the internal capsule and middle cerebral peduncle. 5. Other MR imaging series may also be acquired
Month 1	o T1 and T2 Weighted imaging exam along at least 2 axes: Axial and Coronal o DWI o GRE/SWI o DTI: The ROI would cover the posterior limb of the internal capsule and middle cerebral peduncle. o Other MR imaging series may also be acquired.
Month 6	o T1 and T2 Weighted imaging exam along at least 2 axes: Axial and Coronal o DWI o GRE/SWI o DTI: The ROI would cover the posterior limb of the internal capsule and middle cerebral peduncle. o Other MR imaging series may also be acquired
NOTE: Copies of all imaging (de-identified using subject ID number) will be sent to InSightec.	

5 DATA ANALYSIS PLAN

Descriptive statistics will be performed for all outcomes after the last subject has attained 3 months follow-up. This data may be used to develop a pivotal study. Additional reports will be generated after the last subject has completed 12 months follow-up, and a study completion report after the last subject has obtained 24 months follow-up. 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.

5.1 Safety

A Data Safety Monitoring Board (DSMB) will be used to review all AEs on the study. Their role is to evaluate all AE's that occur throughout the study and provide their assessment of the study safety profile as well as their recommendations for the study continuation. The DSMB recommendations will be communicated to the FDA as part of the annual reporting for this proposed IDE study.

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

5.2 Efficacy

The primary efficacy endpoint will be focused on determining the change from baseline of the *On* medication Unified Dyskinesia Rating Scale at Month 3 as assessed by a neurologist.

5.3 Additional Evaluations

Additional measures of safety will be obtained during the study. These secondary measures of safety will include evaluations post-treatment which are compared to a baseline assessment. These measures include:

- MR imaging (1 day, 1 and 6 months)
- Cognitive assessment by a neuropsychologist (6, 12 and 24 months months) for comparison of clinically significant changes from baseline; CSSRS assessments at all visits
- Visual field testing (3 months)
- Gait assessment (TGUG) at 1, 3, 6, 12 and 24 month

Secondary efficacy endpoints will include comparison of Baseline to post-treatment assessments for:

- Unified Dyskinesia Rating scale at all other time points

- Total MDS-UPDRS (parts I-IV)
    - *Off* (un-medicated) MDS-UPDRS, part III
    - *On* (medicated) MDS-UPDRS, part III and Part IV
- Patient and Clinician Global Impression of Change
- Patient Treatment Satisfaction
- Levodopa equivalent medication usage (milligrams)
- Quality of life assessment with PDQ-39

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 an open-label feasibility study of 20 subjects to be recruited from a maximum of 5 centers. In order to attain 20 qualified subjects, up to 200 subjects may be consented and screened for participation. Subjects found not to qualify will be exited as a screen failure. For this study, a statistical sample size analysis is not proposed. 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.

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 [121], Ethics Committee or other regulatory bodies, funding groups, and the Data Safety Monitoring Board (DSMB) may receive copies of the study records and may review medical records related to the study. The Sponsor will seek a Certificate of Confidentiality from FDA for this study.

6 RISK ANALYSIS

Worldwide, over 8000 treatments have been performed to date with the MR guided FUS ExAblate body system. Risk analysis for InSightec ExAblate systems/clinical investigations has been conducted as part of previously approved FDA IDE submissions (G930140, G990151, G990184, G990201, G000203, G010225, G020001, G020182, G050177, and G060023, G070022, G080009, G080206, G100127, G100169, P040003 and subsequent supplements, and P110039). This data has been re-examined by the study sponsor and it has been concluded that this risk analysis has limited applicability to the proposed clinical investigation. The key consideration here is the fact that this proposed study is conducted with an ExAblate Transcranial 4000 system (referred to internally as the Brain system) that is completely different

from the ExAblate 2100 body system. However, in principle, the body and brain systems have the same purpose namely to coagulate soft tissue within the body by means of MR guided high intensity focused ultrasound. Additional risks, new and unique to this study are presented in **Section-**6.2**.**

The potential risks described below will be explained to the subject in the informed consent process.

6.1 General Procedure Related Risks

6.1.1 Risk of Magnetic Resonance Scanners:

MRI has no known deleterious biological effects in subjects with no contraindications. The incidence of claustrophobia during MRI examinations is approximately 10-15%. All subjects exhibiting claustrophobia will be exited from the study.

6.1.2 Risk of Intravenous (IV) Catheter:

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

6.1.3 Risk of Urinary Catheter:

There is a potential risk if a urinary catheter is used during the treatment. Participant may expect varying levels of Urinary Tract Infection due to the use of the urinary catheter. In a different study for the ExAblate treatment of uterine fibroid (Pivotal study under IDE G020001 that lead to PMA approval under PMA # P040003), the incidence of this risk was found not to exceed 3.7%. This procedure will follow the "standard of care" at the study site.

6.1.4 Risk of Stereotaxic Headframe:

In this study, the Integra Radionics frame will be used for all treatments. The main part of this frame is a metal based ring that serves as a base for the rest of the fixation components. This frame comes with non-metallic posts mounts. Into the non-metallic post mounts, accompanying nylon encapsulated screws with a metallic tip are fitted through the posts. Only the metal tip of the screw is in contact with the patient. The risk of any skin event at or in the vicinity of the metallic tips is mitigated by the fact that the screws outer shell are out of nylon, and therefore eliminates any electrical conductivity to the skin. This is further mitigated by the fact that these screws are mounted on the non-metallic posts that links them to the metallic ring. Hence, the Integra frame is actually manufactured and sold with built in mitigating steps aimed at reducing / eliminating skin event risks. When the full set up is completed, the metallic ring is NOT in contact with the patient.

6.1.5 Risks generally associated with pallidotomy procedures

The internal segment of the globus pallidum is intimately associated with the junction of the lateral edge of the internal capsule and the superior aspect of the optic tract. As such, complications of pallidotomy procedures are based on these anatomic relationships and particularly when the treatment extends beyond the confines of the nucleus or when perilesional edema develops. Additionally, increased morbidity is often recognized with advanced

Parkinson's disease as patients typically present at the time of surgery at a later age and with more associated co-morbidities. The overall rate of permanent adverse event following pallidotomy procedures ranges from 3.6 to 14% as reported from our literature review. These are permanent adverse events and the rate of transient adverse events is obviously higher and subject to AE reporting and publication bias. The morbidity and mortality of unilateral radiofrequency pallidotomy for the treatment of Parkinson's disease is summarized below:

Table-4. **Morbidity associated with stereotactic radiofrequency pallidotomy**

	Retrospective series[1] (N=1959)	**Prospective series[2] (N=334)**	**Single institution[3] (N=884)**
Mortality	0.4	1.2	
Symptomatic ICH	1.7	3.9	2.7
Permanent AE	14	13.8	3.6
Hemiparesis	0.9 (1.6)	2.1	1.4
Facial weakness	1.3 (3.7)		2.4
Dysarthria	3.2		2.6
Hypophonia	1.3		
Dysphagia	1.2		
Visual field deficit	1.5 (2)	2.4	2.1
Perioperative confusion	(~10)	(3.9)	(6.2)
Infection (meningitis/abscess)	< 0.5		0.2

All results are presented as percentages (%). Transient effects are presented in ( ).

1. A Alkhani and AM Lozano. JNS 94:43-49, 2001
2. RM deBie, et al. Neurology 58:1008-12, 2002
3. Y Higuchi, et al. Neurosurgery 52:558-71, 2003

The **mortality** rate with surgical radiofrequency pallidotomy ranges from 0.4 to 1.2%, and primarily occurs from intracerebral hemorrhage. **Symptomatic intracerebral hemorrhage** with stereotactic procedures has been estimated to range from 1 to 2%, and may be slightly higher with pallidotomy procedures which have been reported in large series to almost 4%. Intracerebral hemorrhage with pallidotomy might occur in a slightly higher fashion with microelectrode-guided procedures where additional electrode penetrations are required. In order to mitigate the risk for intracerebral bleeding, patients with severe hypertension will be excluded from trial participation, and normotension will be maintained throughout all procedures.

Additionally, **delayed ischemic infarction** has been observed in pallidotomy procedures. The occurrence of this complication seems unique to lesioning of the globus pallidum. Three cases were recognized in fifty pallidotomy procedures, and these cases occurred in patients with a significant history of vasculopathy identified either clinically or radiographically (J Y Lim, JNS 1997). These ischemic events occurred in a delayed fashion at 10, 51, and 117 days following

the procedure. It is postulated that such an occurrence results from damage to the perforating of vessels of the pallidum.

Hemiparesis contralateral to pallidotomy is likely the most significant morbidity associated with the procedure. This typically relates to the involvement of the motor fibers in the internal capsule, and has been reported with an incidence of about 2%. To reduce the risk for postoperative weakness following focused ultrasound pallidotomy, an event invariably related to extension of the lesion medially into the internal capsule, patients will be awake during the procedure such that intraprocedural clinical testing of their strength and motor condition can be performed after each sonication. We intend to begin sonications at a low acoustic energy and gradually titrate the treatment towards a therapeutic and ablative energy level only as tolerated by the patient.

Facial weakness has been observed more frequently and is likely attributed to the somatotopic organization of the corticobulbar fibers near the pallidal target. Dysarthria, hypophonia, and dysphagia are similar side effects of pallidotomy procedures likely relating to the same corticobulbar fiber projections that are immediately medial to the ventral most aspects of the pallidum. In order to reduce the risks for these, we will exclude all patients with severe premorbid risks as determined from the UDRS Part II subsection: activities of daily living. Those scoring a three or four in question 5 (speech), question 6 (salivation), or question 7 (swallowing) will be excluded.

Visual field deficits have been recognized because of the relationship of the optic tract below the internal segment of the globus pallidum. Over time, this complication has diminished with surgical recognition and intraprocedural testing during open stereotactic surgery to mitigate the risk of optic tract injury. We anticipate that the incidence of visual field deficit in this clinical trial of focused ultrasound pallidotomy may be slightly higher than that reported in the literature. We intend to perform comprehensive visual field assessments before and after the procedure. Many of the studies reporting visual field outcomes did so only by clinical assessment by a neurologist or neurosurgeon. Very few studies document the rate of visual field change with quantitative visual field and ophthalmologic assessment. It is known from pallidotomy and hippocampectomy procedures that a small visual field deficit can occur and is frequently asymptomatic.

Perioperative confusion has frequently been observed following pallidotomy procedures, but fortunately this tends to be transient. The risk of this almost certainly increases with older age and more advanced disease. In order to mitigate the risks of perioperative confusion, all patients will undergo preoperative neuropsychological assessment to gage their cognitive reserve and ability to tolerate unilateral palatal lesioning.

Infection has been rarely observed with pallidal lesioning and certainly with less frequency than occurs with pallidal stimulation. We anticipate a similarly low risk for meningitis or brain abscess with transcranial focused ultrasound pallidotomy as there is no incision required for the procedure.

6.1.6 Risks Incidental to the ExAblate Treatment

There is a potential risk to the subject of deep venous thrombosis from lying in a supine position for 3 to 4 hours, but this risk is substantially mitigated by the avoidance of sedative medications.

The risk to the subject from lying still for this treatment should be no greater than that of lying still for any other reason. Subjects will be provided compression stockings, as described above (Section 4.3), for use during treatment and are able to move their lower extremities during the treatment. DVT screening will be performed at the discretion of the primary treatment team for any subject deemed to be at a high risk for thrombosis.

There is a risk that the subject may experience a sore neck or back, or discomfort / fatigue from lying in the same position for a long time during the treatment.

6.1.7 Risks Associated with the ExAblate Treatment

All efforts are undertaken to reduce risk related to the ExAblate treatment. The following mitigations are in place for all procedures:

1. First, the procedure is performed in the MR scanner. During the treatment MR images will be acquired. Using specific scanning sequences and a rapid post-processing program, changes in temperature can be detected, and a thermal map of the brain generated. This thermal map will reveal any potentially dangerous elevations in temperature.
2. Second, study personnel can regularly assess cognitive and motor function throughout the procedure (i.e.: after each sonication) as well as general neurological function. This will help to reveal any indication that tissue damage may be occurring along the beam paths.
3. Subjects are asked to relay all sensations (i.e., disorientation/dizziness, pain, numbness, etc) occurring during the procedure to the circulating staff so that adjustments can be made to accommodate modifications to the treatment plan or extend time between sonications.
4. Third, MR-compatible pulse oximeter, blood pressure cuff, and EKG monitor will be monitored throughout the procedure. This information will permit detection of tissue damage, edema, or bleeding, if brain or blood vessels along the beam paths are injured by heat.
5. Finally, the subject, Subject Monitor and Assessor, and the neurosurgeon will each have a stop sonication button that can instantaneously interrupt the energy delivery at any time. The subject is given a stop sonication button in case aberrant tissue heating causes any compromise to speech, word finding, or other communication difficulties. The subject will be instructed prior to the proceeding that they should use the stop sonication button any time they feel excessive pain, discomfort, disorientation or any other unusual sensation. The neurosurgeon, Subject Monitor and Assessor, have stop sonication buttons so that if there is any sign of neurological change, the energy delivery can be immediately stopped and the subject carefully evaluated. Temporary interruption of energy delivery will in no way compromise the potential for therapeutic benefit to the subject. Following subject evaluation treatment can resume without delay

The following risks may be associated with the ExAblate Transcranial thermal ablation procedure:

1. Pain and/or discomfort – There is a risk of discomfort to the subject caused by heating of tissue. Focused ultrasound therapy involves precisely controlled pulses of thermal energy resulting in tissue coagulation (typically 55-65°C for several seconds) in small tissue

volumes. This induces thermal coagulation of the targeted soft tissue. The energy intensity at the level of the skin away from the pin sites is quite low and sonication through scar tissue should be avoided.. The subject may experience both a cold sensation from the active cooling circulation of water within the rubber diaphragm as well as a rise in temperature in the skull which should be kept to below pain level by the active cooling. Because the focal point of the beam will be > 2.5 cm from the dura and there are no pain receptors in the brain, there should be no pain associated with ablation, itself.

The subject will be in constant verbal contact with the neurosurgeon and appropriate action can be taken in the event that a subject does experience pain discomfort. Remedies could involve lowering energy levels, or increasing the time interval between consecutive treatment pulses. The subject also has the ability to abort the sonication at any time by activating a handheld cut off circuit (i.e., stop sonication button).

See also Risk 7c regarding heating of the dura mater and the meninges.

2. Headache – The subject may experience a headache during or after the procedure which may be related to the pin site, slight swelling around the ablated brain tissue, or a reaction to the contrast media and should be transient.

3. Disorientation, light-headedness, dizziness, unsteadiness, nausea/vomiting: There is a potential risk that the subject will have sensations of light-headedness, dizziness, unsteadiness or even nausea/vomiting. Based on the current data, these events should be transient and resolve within a day or so.

4. Occurrences of transient numbness, tingling, eye twitch, hyperesthesia and/or paresthesia of the scalp, face and upper extremity have been reported in subjects undergoing Vim ablation for essential tremor. These generally are transient are resolved within minutes to one day. One paresthesia lasted for 4 days, one scalp numbness lasted 2.5 months.

5. BBB disruption, edema, swelling, hemorrhage or stroke: There is a potential risk of hemorrhage during ExAblate procedure

    a. At the focal point or targeted area - In ExAblate thermal ablation, the high temperature at the focal point results in immediate protein denaturation and coagulative necrosis. This should be expected to rapidly stop any bleeding that might occur in the capillary bed and within small vessels.

    b. Outside and remote to the targeted area.. Alternatively, there could be a disruption of the Blood Brain Barrier (BBB) which would allow blood to seep out of the cranial blood vessels into the brain tissue. These events may theoretically occur due to heating effects (i.e. secondary hot spots) and or to the pressure wave of the ultrasound beam. To address the risks due to pressure waves of the ultrasound beam path, the system has been designed to be well below the "pressure wave threshold" that may trigger events of this nature.

In all cases, thermal and regular imaging will be continuously assessed during the procedure. Finally, the subject(s) is continuously monitored during the ablation procedure for any

change in condition. Also, a set of MR images are collected immediately post procedure to evaluate the status of the lesion and surrounding tissues.

6. Imprecise focal point and ablation of tissue outside of target. There is a risk of imprecise targeting of the focal point, and ablation of an area of tissue outside the planned treatment volume. If this occurred it is possible that serious neurological deficit or even death could result. To limit the risk of this occurring, the treatment process includes a mandatory verification step that requires the operator to first check the alignment of the subject anatomy, the focal point of the transducer and the MR imaging system. This procedure, done while the subject is in position for treatment, uses a very low energy sonication to confirm of the alignment of the focal point and the targeted treatment point in all three axes. For each sonication delivered during treatment, the operator gets continuous feedback on the position of the intended treatment point superimposed on the thermal dosimetry image and can make corrections where required.

   Careful monitoring must be performed to ensure that the location, size, and shape of the sonications in three planes (2 views) as well as the temperature of the ablative sonication(s) do not extend outside of the target region. Shaping of the sonication may be performed by turning off some of the array transducers. Biofeedback from the subject after each sonication performed at the lower temperatures will guide the placement of the sonication so as to help prevent unwanted side effects.

   At any point in the treatment process this low-power verification of the localization may be repeated prior to full power sonication.

7. Subject movement during the procedure that causes focal point to move/change location – There is a risk associated with subject motion during a sonication or between sonications. This could cause a movement of the tissue relative to the planned treatment volume on the system, and in extreme cases could result in the treatment of a point outside the planned treatment volume. Also, because the skull functions as a defocusing lens, the phase correction map computed for the target spot will become ineffective if the subject moves. To prevent or minimize this risk, there are several precautions taken to prevent motion, and to detect it, if it occurs:

   a. During subject positioning every effort will be made to make the subject comfortable and the subject will be educated as to the importance of maintaining their position during the treatment.

   b. The subject will be placed in a head immobilization unit based on a stereotactic frame. This technology has been effective in preventing movement in stereotactic neurosurgery, and has been adapted and modified to the specification of the ExAblate. The transducer and the immobilizer are locked together so that the transducer moves with the frame.

   c. The system is designed to detect motion and will abort a sonication if motion occurs during the sonication and will indicate that motion has been detected prior to the next sonication being performed.

d. One or more members of the medical team will be in the room throughout the sonication to monitor the subjects' medical status and comfort. Hence, subject motion will also be monitored.

8. Risk of cavitation - There is a risk of cavitation in the tissue at the focal point. Cavitation is the collapse of rapidly developed gas bubbles at the focal point due an extreme intensity of ultrasound excitation. This rapid collapse could cause high pressure, shock waves, and high temperatures. However, we believe that through proper system design and careful selection of system operation envelope, there is a very minimal risk that cavitation could occur during a treatment, even in the event of user error. We have developed an automated treatment planner that takes as its input the targeted ablation area depth in tissue, focal volume and tissue absorption, and based on pre-set safe operating limits selects sonication parameters that will keep the intensity of ultrasound excitation well below the intensity levels that could cause cavitation.

9. Risk related to sonication pathway - There is the risk that the tissue along the path to the target (scalp, skull, dura, brain, etc) could become heated to the point where tissue-damage might occur which could result in significant neurological damage or even death. This heating could be caused by direct improper treatment targeting, irregularities on the skin surface (e.g.: scars), treatment of a volume of tissue too close to the skin or bone, energy absorption by the bone, or the conduction of sufficient heat to cause a burn. The heating in the energy pass zone is always monitored and an additional cooling time can be administered when elevated temperatures are detected. Below are some possible risks related to the sonication pathway through different tissues in the head:. .

    a. **Skin burn** is a potential risk due to improper acoustic coupling. There have been no cases of skin burn in all ExAblate transcranial treatments to date. The treatment set-up process includes filling the gap between the ultrasound transducer and the skull with a water-filled membrane to provide acoustic coupling. There is a possibility of small air bubbles remaining attached to the skin. These could cause a small focal hot spot and cause local pain or a burn to the scalp. The active cooling mechanism unique to this system is designed to reduce the risk of skin burns and improve subject comfort. In previous studies, ExAblate treatments have caused burns of the skin using the ExAblate Body system. To minimize this risk, the scalp will be carefully shaved, and scars or other irregularities (e.g. eczema) will be kept outside the treatment pathway. Subjects with remarkable atrophy and poor healing capacity of the scalp (> 30% of the skull area traversed by the sonication pathway) will be excluded from this study.

    The subject will be in constant verbal contact with the neurosurgeon and appropriate action can be taken in the event that a subject does experience pain discomfort. Remedies could involve lowering energy levels, or increasing the time interval between consecutive treatment pulses. The subject also has the ability to abort the sonication at any time by activating a handheld cut off circuit (i.e., stop sonication button).

b. **Skull and air-filled spaces:** In the treatment planning, air-filled spaces (frontal, ethmoid, sphenoid sinus, mastoid) inside the skull are identified in bone window CT images and kept outside the pathway. Should the operator not identify all air filled cavities on the treatment path, sonication through these areas could cause heating and result in burn of the tissue lining the cavity. Operators are trained to avoid these sonication pathways by marking their existence on the CT scans.

   Other irregularities of the skull, which might scatter the acoustic energy, are compensated for in the system. Skull may become heated by absorbing more acoustic energy than normal soft tissue. The skull cannot sense pain but the overlying soft tissues may sense pain if the bone becomes heated. MRI thermometry at 1.5 T is able to detect changes of ±3 Celsius in soft tissues [122]. Possible heat transfer from the skull bone to the brain by successive sonications is monitored by MRI thermometry of the cortex and white matter. The sonication duration and energy levels, and the cooling times between the sonications are adjusted so that the focus in the target tissue is heated while allowing other tissue to cool down between sonications. Local bone damage is unlikely because the active cooling mechanism system is designed to keep the bone temperature below a temperature that can damage it. Based on the data acquired to date and reviewed by FDA under G020182/S04, the average temperature rise at the skull level ranges between 1° to 5° Celsius. Hence, this active cooling strategy should continue to provide the safety needed.

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

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

e. **Cortex:** In previous studies, ExAblate thermal ablation of deep foci in the rabbit brain there was no detectable heating of the cortex on MRI or evidence of opening of the blood-brain-barrier elsewhere than at the focus of the beam. Elevated temperature in the eloquent cortical areas (motor, sensory, visual, auditory, speech) might cause neurological deficits or seizures Temperatures in the eloquent areas will be monitored by MRI throughout the procedure and the

cooling time between sonications will be increased if unacceptable thermal buildup is detected.

f. **Brain, cranial nerves and cerebral arteries:** In this study the treatment path will avoid cranial nerves and major cerebral arteries. Operators are trained to mark them on the MR for the purpose of avoidance during sonication.

g. **Target ablation and the adjacent brain tissue:** Thermal lesioning for the treatment of Parkinson's Disease through pallidotomy may carry some risks in particular to the internal capsule, ventral posterolateral nucleus of the thalamus. To mitigate these risks, the ExAblate treatment will be performed in small incremental sonications within the designated target volume in the un-anesthetized subject.. The subject will be examined by the Subject Assessor after each sonication for evidence of symptom suppression or clinical side effect. The titration of escalating focal sonications will start from well before evidence of thermal heat is detect by MR thermometry and will continue until clinical symptom suppression. This procedure will allow re-adjusting the targeting based on real time feedback from intra-procedure examination. This process is designed to enhance the procedure safety and minimize the potential adverse events that may be encountered in this study.

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

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

10. Neurological risks: Thermal "lesioning" in the brain may lead to heat transfer to immediately surrounding brain tissue or to hemorrhage. For a short period of time following the treatment, the surrounding tissue may be affected by inflammatory reaction. The length of the period cannot be predicted, but would be expected to resolve

in 2-3 weeks based on our prior experience with sequential imaging in focused ultrasound thalamotomy for patients with Essential Tremor and tremor dominant PD. These mechanisms may cause transient local neurological deficits or symptoms. These complications are not typically permanent. If these symptoms are detected, medical management with dexamethasone and/or mannitol might be effective. In severe cases, a craniotomy can be performed to relieve increased intracranial pressure, and permanent neurological deficits or death could possibly result.

No benefit – The subject may receive no benefit from this procedure. While ablation of the globus pallidus has generally been shown to be effective in motor control, there is the chance that it will not be effective for the subject, or that the effect may not be permanent. Tremor is only one symptom of Parkinson's Disease and relief from tremor may permit other symptoms of the underlying disease, such as rigidity, freezing or dyskinea, incoordination or ataxia or other parkinsonian symptoms, to predominate your symptoms profile after treatment. Similarly, the literature shows that treatment effects may not be permanent as the disease is progressive over time, eventually resulting in dementia, inability to care for oneself, and death. The subject may find that they will need to continue to take their medications or even increase their medications with time.

6.2 Anticipated Treatment Side Effects from ExAblate

All adverse events will be reported in the Case Report Forms (CRFs) and analyzed for their relationship to the treatment device, the procedure, and disease progression. Based on previous treatment experience, the following anticipated side effects have been identified as possible treatment related complications of ExAblate treatment. These can be classified into Non-significant and Significant Anticipated Treatment Side Effects based on their medical severity, additional treatments required, and long-term consequences for the subject.

Non-significant Anticipated Treatment Side Effects of ExAblate treatment are those that normally resolve without sequelae within 1-14 days of the treatment:

- minor pain from subject positioning or system interface (i.e. back pain, soreness in neck).
- transient fever: oral temperature >100.4^{o}F/38^{o}C, lasting less than 24 hours
- minor (1^{o} or 2^{o}) skin burns less than 2 cm in diameter
- bruising of the skin along the treatment path
- increase in edema surrounding the treatment area as shown on MRI.
- headache
- dizziness, nausea or vomiting

Significant Anticipated Treatment Side Effects of ExAblate are those which may require medical treatment, may have sequelae, and for which time of resolution is not defined. The following side effects are thought to be improbable but their relative risk remains to be defined:

Scalp in the sonication pathway:

- skin burns (>2^{o}) with ulceration of the skin
- scar formation
- Loss of sensation

- atrophy

Bone in the sonication pathway:

- bone necrosis

Dura, venous sinuses, and cortical veins

- subdural bleeding
- vein thrombosis
- seizures
- symptoms from disturbances of eloquent cortical areas (motor, sensory, auditory, visual, speech)

Other brain tissue

- necrosis of normal tissue due to incorrect targeting
- thermal damage to adjacent functional brain tissue (e.g.: optical tract)
- bleeding in the treated area
- cerebral infarction
- neurological deficits
- moderate or severe increase in cerebral edema as shown by MRI scans
- symptomatic increase of intracranial pressure
- death

Cerebral arteries

- bleeding
- coagulation thrombosis
- vasospasm
- death

The experience of Significant Anticipated Treatment Side Effects in ExAblate treatment in the breast and uterus have been less than 5% as shown in prior clinical experience. In brain treatments there is limited prior experience with the ExAblate Transcranial system and the probability of an adverse effect is unknown. It is the purpose of this study to gain experience in pallidotomy that will allow us to evaluate the safety of ExAblate Transcranial system of advanced idiopathic PD (See also **Section-**6.1.7**.d**).

6.3 Adverse Reactions and Precautions

The subjects will be educated as to what to expect during the procedure and the importance of immediately communicating any problems, unusual symptoms, or discomfort, to the investigator during the treatment and throughout the follow-up period. Subjects will also be educated as to what sensations or perceptions could indicate that neurological damage may be starting to occur. They will be told to use their handheld stop sonication button if they perceive anything unusual may be happening so that they can be neurologically assessed. All adverse reactions occurring in this study will be recorded in the Case Report Forms. Each AE will be assessed for its cause (i.e., categorized as definitely, probably, possibly, or unrelated to the device, procedure or disease progression). Alternative treatments resulting from post-surgical changes in neurological status will be captured and reported.

6.4 Criteria for Removal from the Study

Subjects can be withdrawn from the study at any time if, in the opinion of the principal investigator, it is not in the best interest of the subject to carry on as planned. In addition, a subject may also chose to exit the study at any time, but will be strongly encouraged to participate in the follow-up visits for safety reasons (continued monitoring of subject safety). Subjects who opt for alternative PD treatments will be withdrawn at the time those procedures are performed.

6.5 Rules for Stopping the Study

This study may be stopped, if, in the opinion of the DSMB, serious risks to the health and welfare of subjects are observed that are directly related to the use of the device. Any two (2) of the following scenarios would invoke this section of the protocol to stop the study until the DSMB and the FDA can review the events and recommend potential study modifications to reduce the risk. InSightec will evaluate the cause of the safety concerns and determine relation of these safety events to the device, along with any possible mitigating steps to protect patients from device harm. Events that could result in a study halt include any two of the following events:

- Any death that is deemed to be caused by the ExAblate treatment
- Any event of intracranial hemorrhage deemed to be caused by the ExAblate device
- Any increase in UDRS at Month 1 as determined by the treating neurologist
- Any increase in MDS-UPDRS Part III of more than 3 points on the treated side at Month 1 as determined by the attending neurologist
- Increase in MDS-UPDRS to a three or four in question 2.1 (speech), question 2.2 (saliva and drooling), or question 2.3 (chewing and swallowing)
- A significant cognitive decline or significant mood/behavioral change as determined by the neuropsychologist.
- A significant and unresolved neurologic impairment (ie hemiparesis or oculomotor deficit) noted at the Month 1 assessment
- A significant MRI finding (ie overt cerebral hemorrhage or infarction). Some degraded blood products at the GPi target are expected as SWI signal.
- A significant and unresolved neurologic impairment (ie hemiparesis or "homonyomous hemianopsia") noted at the Month 1 assessment
- A significant and unresolved MRI finding (ie overt cerebral hemorrhage or infarction). Some degraded blood products at the GPi target are expected as SWI signal.

Investigator(s) shall promptly report the occurrence of any such events to the Sponsor (i.e. InSightec) and the Sponsor shall promptly initiate review by the DSMB as well as reporting such event(s) to the FDA. Once the DSMB has had an initial assessment of an event of this type, it may recommend stopping the study in order to investigate fully the events and circumstances.

This will be communicated to FDA and all IRBs and sites. With full cooperation of the treating investigator and the Sponsor, the DSMB will evaluate the circumstances of the event, determine relation of these events to the ExAblate, and whether any modifications to the protocol or the device must be made to improve safety. The Sponsor will keep FDA informed of the results of the DSMB evaluation and of any potential actions taken by the Sponsor. Once the review is completed and any mitigations are in place, and the DSMB recommends re-opening the study with concurrence by the FDA, then then InSightec will communicate this with all sites and their IRBs to begin to re-open and continue the study.

6.6 Adverse Event Reporting

It is the responsibility of the investigator to document all AE's occurring during the course of the study. At each visit, the investigator will evaluate AE's. AE's not previously documented in the study will be recorded on the Adverse Event Log within the CRF. The nature of each event, date and time (when appropriate) of onset, outcome, frequency, maximum intensity, action taken, expectedness, and causal relationship will be recorded. AEs already documented in the CRF (i.e., at a previous assessment) and designated as 'ongoing', should be reviewed at subsequent visits as necessary. If these have resolved, the documentation in the CRF should be completed including an end date for the event.

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

> ***SAE** [§803.3(aa)(1)] is an injury or illness that:*

- *causes death*
- *is life threatening, even if temporary in nature;*
- *results in permanent impairment of a body function or permanent damage to a body structure; or*
- *necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.*

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

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

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

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

6.7 Data Safety Monitoring Board

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

- Was the adverse event serious?

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

- Was the adverse event device related?

- Was the adverse event unexpected?

- Is there an unreasonable risk in continuing the trial?

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

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

7 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 surgical risk or who oppose deep brain stimulation techniques. 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.

8 MONITORING PLAN

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

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

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

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

Monitoring procedures will follow the Sponsor SOPs.

8.1 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).

9 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.

10 APPENDICES

Appendix – A: Informed Consent

Appendix – B: Neuropsychological Assessments

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Appendix A – Informed Consent Form

Appendix B - NEUROPSYCHOLOGICAL ASSESSMENTS

It is important to screen subjects prior to treatment and to assess subjects post-treatment for potential cognitive and psychological effects of the treatment. Our standard neuropsychological assessments will be used in the screening and cognitive assessment of PD subjects considering DBS surgery at the University of Virginia. This battery of tests is designed to test the major domains of cognitive function with a particular emphasis on the mental functions that are most affected in PD. These measures, administered by a neuropsychologist specializing in neurodegenerative diseases, will be obtained at Baseline and again at Month 3 post-treatment to determine any potential cognitive change resulting from the unilateral MRgFUS GPi pallidotomy. Additionally, the battery will be implemented again at Month 12 post-treatment to assess for any improvement in potential deficits observed at the Month 3 time point.

Estimated Baseline Intellectual Functioning:

Wechsler Test of Adult Reading (WTAR)

Mental Status:

Montreal Cognitive Assessment (MoCA)

Language:

- Action fluency
- Phonemic fluency
- Animal Naming

Visuospatial Functioning:

- Rey Complex Figure Test- Copy portion
- Wechsler Adult Intelligent Scale-4th Edition (WAIS-IV Block Design or Matrix Reasoning)

Learning and Memory:

- Hopkins Verbal learning Test-Revised (HVLT-R)
- Brief Visuospatial Memory Test-Revised (BVMT-R)
- Logical Memory from the Wechsler Memory Scale – Third Edition (WMS-III))

Attention, Working Memory, & Processing Speed:

- Wechsler Adult Intelligent Scale-4th Edition (WAIS-IV Digit Span)
- Trails A & B
- Symbol-Digit Modalities Test
- Stroop Color-Word Test

Executive Functioning:

- Wisconsin Card Sorting Test (WCST)

Motor Functioning:

- Grooved Pegboard

Mood and Behavior:

- Beck Depression Inventory-II (BDI-II)
- Parkinson's Disease Questionnaire-39 (PDQ-39)
- Frontal Systems Behavior Scale (FrSBe)
- Beck Anxiety Inventory (BAI)