Clinical Protocol

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Protocol Title	**A Phase IV Post Approval Clinical Study of ExAblate Treatment of Metastatic Bone Tumors for the Palliation of Pain**

Approvals:

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

A Phase IV Post Approval Clinical Study of ExAblate Treatment of Metastatic Bone Tumors for the Palliation of Pain

The goal of this study is to comply with FDA request to conduct a study to assess the device treatment under actual conditions of use part of PMA approval plan.

The Indications for Use claim for this system is – per approved commercial labeling

> Palliation of Pain Associated with Metastatic Lesions in Bone for radiation failure patient who have received radiation without adequate relief from metastatic bone pain as determined by the patient and treating physician, for whom their treating physician would not prescribe radiation or additional radiation treatments, and those patients who refuse additional radiation therapy.

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1 BACKGROUND and SIGNIFICANCE

1.1 ExAblate delivery of MR guided Focused Ultrasound (MRgFUS) [1]

MRgFUS is an attractive modality for non-invasive thermal ablation of soft tissue tumors [2-6]. Treatment begins by acquiring a series of MR images of the target organ. The physician then reviews the images on the ExAblate system workstation, identifies a target volume on the MR images, 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. During the treatment, an ultrasound transducer generates a point of focused ultrasound energy, called a *sonication* (See **Appendix-A** for Glossary of Terms). The sonication raises the tissue temperature within a well-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 of the sonication and the size of the coagulated region. The sonication process is repeated at multiple adjacent points to cover the entire prescribed treatment volume.

1.2 Metastatic Bone Tumors

Bone is the third most common organ involved by metastatic disease behind lung and liver [7]. Breast and prostate cancer metastasize to bone most frequently, which reflects the high incidence of both these tumors, as well as their prolonged clinical courses.

The increasing longevity of the population coupled with better therapeutic management of cancer patients contributes to the high incidence and prevalence of metastatic bone lesions. Pain from bone metastases is the most common cause of cancer pain and as more patients are living with bone metastases, improving their quality of life becomes a major challenge. In patients who die from breast, prostate, and lung cancer, autopsy studies have shown that up to 85% have evidence of bone metastases at the time of death [7-9].

Current treatments for patients with bone metastases or multiple myeloma bone lesions are primarily palliative and include localized therapies [10], systemic therapies (chemotherapy, hormonal therapy, radiopharmaceutical, and bisphosphanates), and analgesics (opioids and non-steroidal anti-inflammatory drugs). Recently, radiofrequency ablation has been tested as a treatment option for bone metastases [11]. The main goals of these treatments are improvement of quality of life and functional level. These goals can be further described:

Pain relief

Preservation and restoration of function

Local tumor control

Skeletal stabilization

Treatment with external beam radiation therapy (EBRT) is the standard of care for patients with localized bone pain, and results in the palliation of pain in the majority of these patients. More than 66% of patients with a limited number of well-localized bony metastases can be treated effectively by external-beam irradiation. However, approximately 30% of patients treated with radiation therapy do not experience pain relief [8, 12-16]. Furthermore, there is an increased risk of pathologic fracture in the peri-irradiation period due to an induced hyperemic response at the periphery of the tumor. This weakens the adjacent bone and increases the risk of spontaneous fracture. Adding to this, patients who have recurrent pain at a site previously irradiated may not be eligible for further radiation therapy secondary to limitations in normal tissue tolerance. The speed of response to radiation therapy varies; most symptomatic bony metastases begin to respond over the course of 10 to 14 days, 70% of patients experience some pain relief within 2 weeks of starting therapy and, within 3 months 90% of the responding patients achieve pain relief.

Patients, who had EBRT and failed to improve, may need to seek other therapies such as radio frequency ablation, surgical resection, etc., which are less efficient and have higher treatment related morbidity. Because the ExAblate system is designed to non-invasively ablate tissue, ExAblate may meet the need of these EBRT failed patients. The ExAblate system has the potential to achieve the first three of the four above mentioned goals, as well as changing the treatment limits and resulting morbidity in accordance with the above-mentioned goals [17]. The palliative effect of ExAblate is achieved by heating the bone periosteum, thus ablating the sensory origin of the pain and has the potential to achieve some tumor control.

Based on the FDA approved phase-1 initial study (IDE # G050177) results and the results of the study that was performed outside the United States that the sponsor has done, palliation effects are significant in terms of mean improvement, the percent of treated patients who reported symptomatic improvement and in the treatment durability.

1.3 The ExAblate System

The ExAblate system is a non-invasive thermal ablation device that has been used for the ablation of tissue. This system combines a focused ultrasound surgery delivery system and a conventional diagnostic 1.5 T or 3T MRI scanner to implement MR guided focused ultrasound surgery (MRgFUS). The ExAblate 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

ExAblate device is an integrated component of the MR table. The subject is placed on the MRI table and moved into the MRI scanner.

The treatment process begins with the physician acquiring a set of MR images, identifying target volume(s), and drawing the treatment contours. The therapy planning software computes the type and number of sonications required to treat the defined region while minimizing total treatment time. MR images taken during the sonication provide a diagnostic quality image of the target tissue and a quantitative, real-time temperature map overlay to confirm the therapeutic effect of the treatment in real time. The transducer is then automatically moved to the succeeding treatment point and the process is repeated until the entire volume has been treated. Typically, ~30 individual sonications can be delivered over approximately 2 hours period to complete a metastatic bone tumor treatment.

1.4 Clinical Experience with ExAblate

Uterine Fibroids (UF) – FDA Approved Indication

The ExAblate 2000 system received FDA approval for the treatment of UF in November 2004 (PMA #P040003). The ExAblate 2000 had previously received CE Mark (European Authority approval and others) and AMAR authorization (Israel Ministry of Health) for the indication of treating UF. To date, approximately 8,000 treatments for uterine fibroids has been performed worldwide. Since its approval, a number of other studies have been completed or are in process to assess changes in software and hardware or to provide additional information to support labeling changes.

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

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.

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**)**.

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.

Malignant and Benign Breast Studies – Investigational

MRGFUS EXABLATE ABLATION OF BREAST CARCINOMA: CLINICAL STUDY WITH EXCISION

InSightec conducted 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 [1-3]**.** These are studies are closed. Of all the patients treated, only three patients experienced non-significant adverse effects: one patient with mild event of redness at the ablation site, a second patient with mild event of firmness, and a third patient with a 3rd degree skin burn that was due to operator's targeting error and not due to the device.

MRGFUS 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 [4]. Following this feasibility study, InSightec initiated an FDA approved pivotal protocol to study ExAblate ablation of Breast Fibroadenoma (IDE # G010225). A total of 110 patients were approved for this trial, and only 27 patients 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.

ExAblate Transcranial Brain Studies – Investigational

EXABLATE MRGFUS TRANSCRANIAL TREATMENT OF BRAIN TUMORS: IDE # G020182 – EXABLATE TCMRGFUS LOW FREQUENCY SYSTEM

In 2002, the FDA approved an IDE for a feasibility safety clinical study for the ExAblate Transcranial MRgFUS system in the treatment of brain tumors. This study is currently enrolling. A total of 10 patients will be treated under this IDE.

EXABLATE TRANSCRANIAL MRGFUS THALAMOTOMY FOR MEDICATION REFRACTORY ESSENTIAL TREMOR PATIENTS

InSightec received FDA approval for a feasibility of ExAblate Transcranial MRgFUS for unilateral thalamotomy in the treatment of Essential Tremor under IDE # - G100169. Total of 15 patients were treated. This study is currently on-going and 10 out of the 15 patients have been treated to date. Based on the investigator and the patient's feedback, patients have shown a great level of acceptance of the procedure. Furthermore, patients have shown a significant improvement in their Essential Tremor disease following their treatment with the ExAblate Transcranial MRgFUS device. Patients who completed the study requirements have shown stability of the tremor suppression all the way to the end of the study.

Bone Feasibility Study IDE# G050177

The objective of this trial was to evaluate the safety and effectiveness of using ExAblate as a treatment for pain palliation in patients with metastatic bone tumors. This study was designed as a prospective, one arm, non-randomized study. Ten subjects were enrolled at two sites. Nine subjects completed the study; one subject could not complete treatment due to limited device accessibility to the lesion. This study served as the basis for the Pivotal IDE study (IDE # G070022).

EXABLATE CONFORMAL BONE SYSTEM (CBS) STUDY SUMMARY – FDA STUDY: IDE G 080206

InSightec is currently conducting this study 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. The study is still on-going. 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 ExAblate procedure. To date, the safety profile continues to be favorable to the ExAblate procedure, and there were no new events that may be attributed to the device.

BONE PIVOTAL STUDY IDE # G070022 – REVIEWED UNDER PMA P110039

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 is under review under PMA # P110039.

2 OBJECTIVES

2.1 Background

As part of the PMA # P110039 review process and approval, InSightec was requested to conduct a post-approval study. Patients will be treated following the approved commercial treatment guidelines.

For this study, participating sites will use the ExAblate device for the administration of the ExAblate treatment. This study will be performed on either 1.5T or 3T MR scanners.

For this study, a total of 70 patients meeting the approved commercial guidelines will be enrolled and treated with the ExAblate system at from 7 to 10 sites. The proportion of responders is expected to be at least 30% greater than the proportion of subjects experiencing pain progression (i.e., 60% vs. 30%). Additionally, at the 3 month visit, an analysis of both the safety and efficacy profiles will be compared to the original PMA pivotal study group. This comparison will be descriptive with no statistical endpoints.

2.2 Safety

Safety of ExAblate will be determined by an evaluation of the incidence and severity of device related complications from the first treatment day visit through the 3-Months post–treatment time point.

2.3 Effectiveness

This study will follow the gold standard end points as stated by the "International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases" [11, 24, 25]. For this purpose, this study will:

- Capture patient based pain assessment using a 0-10 pain Numerical Rating Scale (NRS) with anchored points in conjunction with a body diagram.
    - Define "pain relief" complete response as a pain score of zero (0) at the treated site without increase in analgesic consumption.

- Define "pain relief" partial response as a reduction of 2 points on a 0–10 scale at the treated site without increase in the analgesic consumption[1].

- Capture the dosage and frequency of analgesics/opiate consumption from baseline through the 3-Months post-treatment follow-up visit for each patient.

- Capture the Quality of Life of each treated patient using the standard Brief Pain Inventory Questions 9A-G (BPI-QoL).

- Following ExAblate treatment have 1-week, and 1, 2, and 3 months follow-up time points.

- Response will be analyzed at 3 months.

Efficacy Assessments

Efficacy assessments used in this study are based on The International Bone Metastases Consensus Working Party on endpoint measurements [11, 24, 25] which recommends a 0-10 point scale such as the NRS or BPI and to include a body diagram.

NUMERICAL RATING SCALE (NRS)

The Numerical Rating Scale is a validated standard instrument widely used for the assessment of cancer pain and have been used to investigate the effectiveness of radiation therapy to relieve pain resulting from bone metastases [26, 27].

We propose to use the NRS to capture pain change at the treatment site during the course of the study and to use a human figure for patients to mark the location of pain [24, 25]. The worst pain NRS will be used to assess pain in the present study and will include a body diagram for marking areas of pain. Additionally, the average pain NRS scores will be collected. Quality of life (BPI-QoL) and medications use will also be captured. Narcotic medications will be converted to morphine equivalents (**Appendix D**)

BPI_QUALITY OF LIFE (BPI_QOL)

To assess the impact of bone pain following targeted/localized treatment on health-related quality of life, the pain interference scale from the BPI-QoL will be included [**Appendix E**]. Pain interference refers to the extent to which pain interferes with day-to-day functioning and is more likely to be sensitive to anticipated changes in the health-related quality of life among the study population. The most common measure of cancer pain interference is the BPI -QoL[30]. This is a validated scale consisting of 7 items that ask respondents to indicate the extent to which pain interferes with general activity,

[1] Meds increase is defined as a change of 25% [1]or more in MEU; per Chow, E., et al., International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. Radiother Oncol, 2002. 64(3): p. 275-80

mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life".

2.4 Study End Points

Safety

A full safety profile will be developed for the ExAblate treatment of bone metastases. All adverse events will be captured and summarized as defined in **Section-6.2.** Adverse events (type, frequency, severity) are expected to be similar to those captured for the original PMA study (PMA # P110039).

For his study, the Safety comparison with the data of the Pivotal (IDE Study G070022) study will be descriptive with no statistical endpoints.

Efficacy

A full efficacy profile will be developed for the ExAblate treatment of bone metastases. For this study efficacy will be determined by comparing outcomes at the 3 month visit to baseline within subjects. Additionally the safety and efficacy of treatment Responders and Non-Responders will be tabulated, and compared with that of the original PMA (P110039).

The primary endpoint is the proportion of responders at the 3 month study visit.

Definition of terms:

- Patient Responders: these are all ExAblate treated patients who experience at least a 2 point improvement from baseline on NRS at the treated site without increase in medications

- Patient Non-Responders: these are all ExAblate treated patients who experience less than 2 points improvement from baseline to 3 months on the NRS at the treated site without increase of medication or increased medications.

- Patient Pain Progression: these are all ExAblate treated patients who either experience 2 points worsening from baseline to 3 months on the NRS at the treated site or who increase morphine equivalence 25% or more. Pain progression is a subset of non-responders.

Secondary Endpoints

This study has two secondary end points. The goal of these secondary end points is to assess the impact of the ExAblate treatment of painful bone Mets on the overall quality of life and clinical benefits to ExAblate MRgFUS treated patients:

Quality of life outcomes of all treated patients will be captured during the course of the study. A comparison between baseline and 3 months post-ExAblate treatment of the BPI-QoL will be performed.

Pain Medications of all patients will be captured and summarized. Changes in narcotic medications will be expressed in morphine equivalents.

2.5 Case Report Form Data

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

3 DESCRIPTION OF PATIENT POPULATION

3.1 Patient Selection

Patients with bone lesion(s):

- Who have failed radiation therapy. Radiation failure patients are those who have received radiation without adequate relief from metastatic bone pain as determined by the patient and treating physician, those for whom their treating physician would not prescribe radiation or additional radiation treatments, and those patients who refuse additional radiation therapy.
- That appears to be metastatic disease or multiple myeloma by clinical and or imaging techniques with known history of malignancy.
- Who have persistent intractable pain from a well defined tumor site.
- Who have a fracture risk score ≤ 7, will be eligible for this study

3.2 Subject Enrollment

a) Information concerning eligibility for the study will initially be taken from the patient's case history. Patients who appear to be eligible will be asked if they would like to participate in this study.

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

study will utilize a pre-treatment imaging exam to confirm the diagnosis, and to estimate tumor size, location, and access for treatment. Participation is fully voluntary.

Inclusion Criteria

1. Men and women age 18 and older
2. Patients who are able and willing to give consent and able to attend all study visits
3. Patients who are suffering from symptoms of bone metastases or multiple myeloma bone lesions:

   Patients who have received radiation without adequate relief from metastatic bone pain as determined by the patient and treating physician, those for whom their treating physician would not prescribe radiation or additional radiation treatments, and those patients who refuse additional radiation therapy.

4. Patient with NRS (0-10 scale) pain score ≥ 4 irrespective of medication
5. Targeted bone/tumor interface are ExAblate device accessible and are located in ribs, extremities (excluding joints), pelvis, shoulders and in the posterior aspects of the following spinal vertebra: Lumbar vertebra (L3 – L5), Sacral vertebra (S1 – S5)
6. Targeted bone/tumor interface (most painful lesion) size up to 55 cm^2 in surface area
7. Patient whose targeted (treated) lesion is on bone and the interface between the bone and lesion is deeper than 10-mm from the skin.
8. Targeted (treated) tumor clearly visible by non-contrast MRI, and ExAblate MRgFUS device accessible
9. Able to communicate sensations during the ExAblate treatment
10. Patients on ongoing chemotherapy regimen at the time of eligibility:
    1. with same chemotherapy regime (as documented from patient medical dossier),
       And
    2. Worst pain NRS still ≥ 4

       And

    3. do NOT plan to initiate a new chemotherapy for pain palliation

    should be eligible for the study.

***Note**: Planned multiple courses of chemotherapy are not considered New Chemotherapy.*

11. No radiation therapy to targeted (most painful) lesion in the past two weeks
12. Bisphosphonate intake should remain stable throughout the study duration.
13. Patients will have from 1 to 5 painful lesions and only the most painful lesion will be treated.
14. Patients with persistent distinguishable pain associated with 1 site to be treated (if patient has pain from additional sites, the pain from the additional sites must be evaluated as being less intense by at least 2 points on the NRS compared to the site to be treated).

Exclusion Criteria

1. Patients who either

    - Need surgical stabilization of the affected bony structure (>7 fracture risk score, see Section 7.4)

    OR

    - Targeted tumor is at an impending fracture site (>7 on fracture risk score, see Section 7.4).

    OR

    - Patients with surgical stabilization of tumor site with metallic hardware

2. More than 5 painful lesions, or more than 1 requiring immediate localized treatment

3. Targeted (treated) tumor is in the skull

4. Patients on dialysis

5. Patients with life expectancy < 3-Months

6. Patients with an acute medical condition (e.g., pneumonia, sepsis) that is expected to hinder them from completing this study.

7. Patients with unstable cardiac status including:

    - Unstable angina pectoris on medication

    - Patients with documented myocardial infarction within six months of protocol entry

    - Congestive heart failure requiring medication (other than diuretic)

    - Patients on anti-arrhythmic drugs

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

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

10. Patients with an active infection or severe hematological, neurological, or other uncontrolled disease.

11. Known intolerance or allergies to the MRI contrast agent (e.g. Gadolinium or Magnevist) including advanced kidney disease

12. KPS Score < 60 (See "Definitions" below)

13. Severe cerebrovascular disease (multiple CVA or CVA within 6 months)

14. Individuals who are not able or willing to tolerate the required prolonged stationary position during treatment (approximately 2 hrs.)

15. Target (treated) tumor is less than 1cm from nerve bundles, bowels or bladder.

16. Patients initiating a new chemotherapy regime for pain purposes only, or radiation (for the targeted most painful lesion) within the last 2 weeks

    ***Note**: Planned multiple courses of chemotherapy are not considered New Chemotherapy.*

17. Patients unable to communicate with the investigator and staff.

18. Patients with persistent undistinguishable pain (pain source unidentifiable of the targeted lesion)

19. Patient whose bone-lesion interface is < 10-mm from the skin

20. Targeted (most painful) tumor NOT visible by non-contrast MRI,

21. Targeted (most painful) tumor Not accessible to ExAblate

22. The targeted tumor is less than 2 points more painful compared to other painful lesions on the site specific NRS.

4 INVESTIGATION PLAN

4.1 Study Design

This is a prospective, multi-site, one-arm study for evaluating the safety and effectiveness of ExAblate treatment of metastatic bone tumors. Prospective study patients will sign the informed consent, complete study questionnaires and be evaluated in terms of inclusion exclusion criteria. Patients not meeting the study criteria will be exited from the study as screen failures and not included in analyses. All qualifying patients will complete a baseline CT scan, and in the event the CT scan is already available, then it should not be more than 3-months old; should an MR exam be available, it should be also considered (baseline MRI is not requested). Any patients not meeting study criteria at imaging will be exited as screen failures.

Study Optimization Protocol:

Because the standard of care requires physicians to address pain when present and this specific patient population is suffering from painful metastases, the vast majority of patients referred to this study may already be receiving various pain medication regimens. The Inclusion/Exclusion criteria of the protocol require patients to have functionality at study entry of KPS ≥ 60. In most instances, patients with a KPS = 60 at enrollment will be considered to be on an optimized pain medications regimen. Patients not previously on opioids pain medications will be required to proceed to optimization option-1 OR optimization option-2 as described below:

OPTION – 1: THIS OPTION COMBINES PAIN STABILIZATION WITH FUNCTIONALITY

Patients will start on a regimen similar to the NCCN guidelines while maintaining the level of function defined in the protocol (KPS ≥ 60). NCCN guidelines require frequent assessment and re-evaluation of moderate to severe pain generally every 24-48 hours and with long-acting agents after 5 half lives. Study specific forms have been developed to document interventions taken to optimize pain control and to document patient response in regard to impact on pain and function due to medication-related adverse events. Once it has been determined that pain control has been optimized such that a further increase in narcotics:

- is not expected to result in a significant reduction in pain, defined as a 2 point or greater decrease on the NRS,

OR

- that interventions for pain control have resulted in a 10 point or greater decline in KPS

OR

- that commonly recognized opioid-related side effects achieve Grade 3 or greater opioids related AE

The NRS scale will be used to assess changes in pain and the KPS will be used to assess function. Opioid-related side effects will be collected using "Common Terminology Criteria for Adverse Events v4.0 (CTCAE)" (http://ctep.cancer.gov) as a guideline for AE terminology and grade (severity) assessment. Patients meeting any one of the above 3 criteria, and still meeting the study Inclusion/Exclusion requirements, specifically NRS ≥ 4 and KPS ≥ 60, will proceed to the ExAblate.

OPTION – 2: THIS OPTION DETERMINES PAIN STABILIZATION

All Patients who choose to follow Option-2 will be followed for pain stability for at least 1-week. Patients will be counseled to maintain their medication intake unchanged during this period. Daily capture of NRS pain score and medication intake will be performed at the same time of each day. At the end of this period, a patient will be declared on a stable NRS if the NRS Score remains stable during this period; i.e., no more than 2 points change from baseline.

All patients failing this stabilization routine will be followed for another week. All patients failing two consecutive weeks of this routine will be exited from the study and declared as screen failures.

The NRS scale will be used to assess changes in pain and the KPS will be used to assess function. Opioid-related side effects will be collected using "Common Terminology Criteria for Adverse Events v4.0 (CTCAE)" (http://ctep.cancer.gov) as a guideline for AE terminology and grade (severity) assessment.

Patients passing the above stabilization criteria, and still meeting the study Inclusion/Exclusion requirements, specifically NRS ≥ 4 and KPS ≥ 60, will proceed to the ExAblate treatment.

4.2 Pre-Treatment Procedures

Patients potentially qualifying for the study will be offered an Informed Consent to sign prior to further evaluation. Those who accept will complete study forms. Any patients not qualifying will be exited from the study as screening failures and will not be included in the efficacy and safety analyses.

A complete medical history will be obtained to determine the patient's general health status, current symptoms, frequency and dosage of their current analgesic intake etc. Kidney and Liver function tests and coagulation profile will be performed. Baseline pain scores will be established. CT examination (with and without contrast) will also be performed.

All patients will complete a run-in period to optimize patient pain meds at baseline in relation to patient pain, functionality and pain meds side effects, during which time study questionnaires (NRS, BPI-QoL, KPS, medications) will be completed.

Pre-Treatment Procedure

1. At the end of the run-in period and in the event the CT imaging is not already available, then baseline CT examination will be performed to identify the tumor size, location and extent and device accessibility as well as to evaluate the patient's ability to cooperate during the ExAblate procedure.

2. If at this point it is determined that the patient ***does not*** meet all Inclusion and Exclusion criteria and cannot be treated, the patient will be exited from the study. These patients will be considered screening failures, and will not be included in any of the safety or efficacy endpoint analyses.

3. If the patient meets all study criteria, the patient may have the ExAblate treatment.

4. ExAblate-treated patients will complete follow-up visits at, 1 week, and 1, 2 and 3 months.

4.3 Treatment Procedures

1. At the ExAblate treatment visit the patient will complete NRS, BPI-QoL, and KPS questionnaires and mark the primary and other sites where the most pain is felt prior to receiving any pre-treatment medications or seeing the clinician. A quiet, private location may be provided for the patient to complete the questionnaires.

2. An IV line will be positioned for the delivery of medications and will be maintained throughout the procedure. The patient may require a urinary catheter to keep the bladder empty during treatment. Monitoring of heart rate and pO2 will be maintained throughout the procedure using standard MR-compatible monitoring devices.

3. The patients' skin will be closely examined for hair in the treatment path. If necessary, the hair will be shaved around the treatment area and the skin will be cleaned, for example with alcohol, from any oil based skin product.

4. Degassed water and possibly an acoustic gel will be placed atop of the transducers' window to generate acoustic coupling.

5. Patients will be positioned on the ExAblate therapy bed in a selected position according to the planned treatment area. The patient's area of treatment may be placed in a special-purpose imaging coil and positioned in the magnet in the treatment position.

6. An MRI scan will be performed with T2 weighted sequence in all three orientations to localize and measure the target tumor to be treated (other sequences are allowed should they be needed).

7. The skeletal structure in the treatment area will be evaluated to identify any abnormal anatomy that could prevent safe treatment. Adjacent organs will be evaluated to ensure that no bowel, lung or major nerves are in close proximity to the treatment area, or that other obstructions are present in the pathway of the ultrasound treatment beam. Any prior scar will be identified on the image and the ultrasound treatment plan will be planned to avoid sonicating through the scar whenever possible.

8. If the bone metastasis to be treated is identifiable on the MR images, accessible by the device for treatment, and the patient meets all inclusion and exclusion criteria, treatment planning will begin.

9. The physician will trace the contour of the bone cortex in the targeted area

10. The physician will draw the treatment volume using MR images from one or more scan orientations using the following guidelines:

    a) Only one well defined lesion can be treated.

    b) Three most painful lesions are to be evaluated separately at baseline and throughout the pre-treatment period.

c) The targeted lesion must be at least 2 points more painful on the NRS compared to other painful lesions.

11. A central point on the soft tissue-bone interface of the targeted bone (depending on patient anatomy) will be sonicated with a low thermal dose, generating sub-lethal sonication, to verify targeting accuracy in the patient. Target placement and transducer positioning will be adjusted as necessary.

12. If at this point it is determined that the patient cannot be treated, he or she will be withdrawn from the magnet and the IV line, catheter if inserted and pulse oximeter will be removed. The patient will be taken to the recovery area for observation and release. Follow-up will consist of a phone call at 1-week post treatment. These patients will be considered screen failures, and will not be included in either the safety or efficacy analyses.

13. As part of our treatment procedure Geometric Verification in soft tissue is performed to confirm that the thermal location of the planned sonication spot is accurate. Geometric Verification is used to correct any residual geometric errors. According to the treatment guidelines the procedure will be terminated if no MR thermal signal is observed during this verification phase. Termination of treatment at this phase is before the planned therapeutic dose is administered. These patients will be considered screen failures and will not be included in the efficacy analysis.

14. Treatment will begin. Sonications will be performed on successive points [sonication duration between 15 – 60 sec]. The effect of each sonication will be measured by MR using phase map imaging, reflecting the temperature-dependent change in the proton resonance frequency. Energy will be adjusted throughout the treatment, to achieve temperature between 65°C and 85°C from MR thermal images at the bone-soft tissue interface.

    a) Prior to the delivery of any treatment sonications, all patients MUST be adequately sedated for the treatment. Failure to adequately manage the patient may lead to unnecessary intra-procedure sonication related pain events. For this study, ALL patients must receive adequate level of local medication, for example, intercostal nerve block; failure to manage patients may also lead to under treatment. Note: equivalent methods of patient management may also be performed per local site standards.

    b) Monitoring of heart rate and pO2 saturation will be maintained throughout the procedure

    c) During treatment, the nominal setting of the average of energy density for all treatment is set for 9 J/mm^2 ; While the treating

physician still has the ability to tailor the energy during the treatment, it should be noted that 1) lower energy densities may lead to under-treatment, 2) high energy levels requires appropriate anesthesia regimen selection to ensure patient comfort.

15. Sonications will continue until the prescribed targeted area has been treated. The goal is that the total time from 1st to last therapeutic sonication will be limited to 180-minutes, or to patient tolerance.

16. **If no more than 3 planned sonications can be performed using therapeutic energies**, then these patients will be considered as screen failures, and will NOT be included in the intent-to-treat analysis. However, they will be added to the Safety analyses

17. Criteria to terminate treatment include patient intolerance to the treatment, targeting difficulties due to patient motion or a decision of the treating physician

18. Immediately post-treatment, a series of MR scans will be performed. The scanning will include T2 weighted sequences and T1 weighted contrast enhanced sequences to evaluate general anatomy and to assess treatment effect.

19. The patient will be taken off the therapeutic table and escorted to a recovery area for observation period pending release from hospital.

20. All imaging exams taken during the study will be archived for later analyses

21. If during the treatment session, the physician did not complete the planned treatment, and determines that it would be to the benefit of the patient to continue treatment at a second session, a second treatment session may be completed within two (2) weeks of the first treatment. However, only one painful site can be treated under this protocol and the purpose of the second treatment is to complete the original treatment plan. This protocol does not allow for a second treatment due to continued pain at the treated site or the treatment of additional painful lesions. The preparation procedures for the second treatment will be the same as the first, beginning with Step 4.3.2 above. No more than two treatments should be performed within a two (2) week period.

4.4 Follow-up

The follow-up visits of all patients will be completed at 1 week and 1, 2 and 3 months post-ExAblate treatment. Patients will be evaluated for general health, efficacy measurements as well as for device/procedure related AEs that may have occurred during the follow-up period. Additional data regarding dosage and frequency of analgesic intake for the management of the

metastatic bone tumor induced pain will also be collected. Following treatment the study staff will mark the treatment NRS form indicating the place where the treatment was performed. These marked questionnaires will be provided to the patient to complete by the study staff for each time point in the follow up. The patient will be instructed to indicate the change of pain at the place of treatment. Although the 1-Week, 1-Month, 2-Month and 3-Month visits are office visits, and in view of the patient population general health may change at any given time due to the underlying cancer disease, participating sites may use their discretion to make the visit(s) a phone visit to accommodate the patient best interest. However, all attempts should be made to ensure an office visit. The visits will be used to evaluate the patient's NRS, BPI-QoL, and KPS, pain medication intake, symptoms and their general health, including any safety related issues and any changes in symptoms following treatment. For phone visits, study personnel will contact the patient, inquire about AEs and question the patient according to the pain questionnaire, and pain medication intake, and fill it out in parallel. Because the KPS is a physician completed assessment it may not be required for visits completed by telephone. The study personnel will then sign and date the completed forms.

All pre-treatment and post treatment MR and CT images will be de-identified and archived, and then will be forwarded to the Sponsor

4.5 Study Requirements and Visit Schedule

The tables below summarize the data that will be captured during the course of this study.

Table 1: Study Visits				
	Window Allowance	**Imaging**	**Questionnaires**	**Additional Data**
Enrollment	N/A	CT**	PE, NRS, BPI, KPS	Freq. and dosage of analgesics.
Run-in Visits:			NRS, BPI, KPS	Freq. and dosage of analgesics.
Visit #1 Baseline MR Imaging and ExAblate Treatment (2nd session permitted).	On Run-in Visit 2 or within 1-week ± 3 days of Run-in	MR	NRS, BPI, KPS	Freq. and dosage of analgesics.
Visit #2 (office): 1-Week Post-Tx	± 3 days		PE, NRS, BPI, KPS	Freq. and dosage of analgesics.
Visit #3 (phone): 1-Month Post-Tx	± 1 Week		NRS, BPI, KPS	Freq. and dosage of analgesics.
Visit #4 (phone) 2-Months Post-Tx	± 2 Weeks		NRS, BPI, KPS	Freq. and dosage of analgesics.
Visit #5(office) 3-Months Post-Tx	± 2 Weeks		PE, NRS, BPI, KPS	Freq. and dosage of analgesics.
****May be completed at any visit before treatment.**				

5 STATISTICAL ANALYSIS PLAN

This study is a designed as a single arm within subjects comparison of outcomes at the 3 month visit to baseline. For this study, a total of 70 patients meeting approved

commercial guidelines for bone metastases will be enrolled and treated with the ExAblate system at from 7 to 10 investigational sites.

Safety

A full safety profile will be developed for the ExAblate treatment of bone metastases. All adverse events will be captured and summarized as defined in **Section-6.2.** Adverse events (type, frequency, severity) are expected to be similar to those captured for the original PMA study (PMA # P110039). For his study, the Safety comparison will be descriptive with no statistical endpoints.

Efficacy

A full efficacy profile will be developed for the ExAblate treatment of bone metastases. For this study efficacy will be determined by comparing outcomes at the 3 month visit to baseline within subjects. Also, the outcomes will be compared with the original efficacy data of the PMA (P110039), where the proportion of treatment Responders and Non-Responders will be tabulated and compared.

The statistical hypothesis is that the proportion of responders will be significantly greater than the proportion of subjects experiencing pain progression (worsened pain or increased pain medications usage) by at least 30% or an odds ratio of at least 2.

Secondary Endpoints

Medications use and quality of life will be analyzed as secondary endpoints.

PATIENT GENERAL HEALTH STATUS

Patient overall quality of life status will be assessed by the BPI-QoL Pain Interference scale which will be administered pre-treatment and post-treatment. The trajectory of change may be analyzed descriptively by regression slopes.

BASELINE DATA ANALYSES

Baseline clinical, demographic and patient reported outcome characteristics will be tabulated and compared descriptively to the original PMA.

HEALTH COST AND SERVICES UTILIZATION

Summary tabulations and figures may be developed for reimbursement purposes only.

5.2 Statistical Considerations and Sample Size

The primary goal of the study is to evaluate the safety and efficacy of the ExAblate palliative treatment of painful bone metastases. This study will be conducted with both the 1.5T and 3T MR scanners. Seventy (70) patients will be enrolled and treated; enrollment will continue at from 7-10 research sites.

A sample size analysis was performed using the McNemar Test Power Analysis from the PASS[2] program using parameters from the pivotal PMA study (PMA # P110039). The response rate in the USA was 18/30 = 60%. The proportion of non-responders experiencing pain progression was 30%. Thus, the proportion discordant was 90%. Given $\alpha = 0.025$ for a one-sided hypothesis, $1 - \beta = 0.7$ requires a sample size of 65 subjects to detect an odds ratio of 2.0. The odds ratio is equivalent to a difference between two paired proportions of 0.30 which occurs when the difference in the proportion of responders (60%) is 30% greater than the proportion of subjects experiencing pain progression (30%). In order to account for potential dropouts 70 subjects will be initially enrolled in the study.

The hypothesis can be specified as follows:

H_0: *P10 = P01.* H_1: *P10 > P01,* where P10 is the proportion of subjects that respond (improve by 2 points without increasing medications) and P01 is the proportion of subjects that worsen.

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 (IRB), Ethics Committee or the FDA may receive copies of the study records and may review medical records related to the study.

5.3 Missing Data

Analyses will be performed on both observed and data with missing values imputed per the method of last observation carried forward (LOCF) where data for missing visits is assigned the value of the previous visit. Analyses will include the presentation of results calculated based on the intent-to-treat principle.

5.4 Study Timeline

The US study sites that participated in the recently approved pivotal study will be offered this protocol. New sites can only be added if ExAblate bone systems are installed. Because this entails a detailed review and approval process, new purchases and installations typically take a minimum of 12-20 months to complete. Thus, the timing for completion outlined below is premised on the assumption that the sites participating in

[2] Hintze, J. (2011). PASS 11. NCSS, LLC. Kaysville, Utah, USA. www.ncss.com.

this post-approval study (PAS) will be started with those already participating in the IDE investigation; should these sites accept to take part in this study. New sites will be added as needed and in compliance with the total number of sites approved for this study.

The following projections are our best evidence based estimates. These estimates will be updated in the progress reports to the FDA.

Facility Recruitment Complete — All available U.S. sites in the IDE will be offered participation in the PAS. All sites that accept will be included. This process will be completed within 3-6 months following final approval of the study.

Physician Recruitment Complete — As InSightec adds sites (i.e. sells more systems), we will offer them participation in the PAS. We will update the FDA of this effort in our progress reports, or per the agency instructions.

IRB Process Complete— The IRB process will be initiated within approximately 3 months after site participation has been confirmed.

Study Enrollment at 50% Complete— As it was communicated to the agency during the PMA process as well as during the actual IDE study, the enrollment rate in the pivotal IDE study at US sites was approximately 0.07 subjects per month per site. The rate of enrollment was very slow partly because of the terminally ill patient population and their limited life expectancy, and partly because this particular patient population is heavily managed by their oncologists who tend to rely on pain medications and existing familiar technologies. However, in the pivotal IDE study, patients had the opportunity to receive an experimental palliative treatment that was not otherwise available. Now, since the PMA has been approved, patients can elect the ExAblate treatment without participating in the PAS; there may be less of an incentive to participate in the PAS than in the IDE study. Regardless, InSightec will use its best efforts to maintain a similar rate of enrollment in the PAS study as in the IDE study. Based on the pivotal study enrollment rate of 0.07, 1 site enrolled by 2 months, and adding 2 sites each 4 months to a total site enrollment of 10 sites (7 sites by the 6^{th} month and 10 by the 14^{th} month), the 70^{th} subject would be enrolled by the 105^{th} month of the study.

InSightec will continuously consider the possibility of increasing the number of participating sites; however, because of the large capital equipment investment and long installation time, it is expected that the number of sites that could be added to the study each year will be very limited, and would not meaningfully contribute to the increased rate of enrollment. Nonetheless, all newly installed sites will be offered an opportunity to participate in the PAS in an effort to maximize enrollment.

Final Study Report--Study results will be reported within 6 months of completion. Based on the timeline above, this is expected to be approximately 8 years and 10 months after full approval of the study.

6 RISK ANALYSIS

Worldwide, over 8500 treatments have been performed to date with the MR guided FUS ExAblate device. 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, G050221, G060017, G060023, G070022, G080009, G080206, G100127, G100169, and P040003 and P110039). This data has been re-examined by the study sponsor and it has been concluded that this risk analysis is applicable to the proposed clinical investigation. The key consideration here is the fact that this proposed study has the same purpose as the previous ones, namely to coagulate soft tissue within the body by means of ExAblate. Additional risks, new and unique to this study are discussed below.

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

6.1 Potential risks – (ExAblate):

Risk of MR Imaging

- The study subject may find the MR unit claustrophobic and request to leave the study despite pre-procedure sedation.

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

- Gadolinium DTPA (trade name: Magnevist/Omniscan) is an intravenously injectable contrast medium for MRI. The package insert notes that there are no known contraindications. Precautions should be exercised for patients with a history of grand mal seizures, severely impaired renal function or hemolytic anemia. The very unlikely possibility of a reaction, including anaphylactic or cardiovascular reactions, should be considered especially for patients with a known sensitivity to Gd or history of asthma. Adverse reactions include: headache (incidence 8.7%), localized pain, vomiting, paresthesia, and dizziness and localized warmth (incidence less than 2%). Additional adverse effects listed on the package insert occur with an incidence of less than 1%.

Risks incidental to the treatment

There is a potential risk of conscious sedation, which includes reaction to the drugs or over-sedation.

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

There is a potential risk to the patient of deep venous thrombosis from lying stationary for 3 to 4 hours. The risk to the patient from lying still for this treatment should be no greater than that of lying still for any other reason. For treatments under this protocol, it will be the surgeon discretion to provide patients with compression stockings or wraps for the period of the treatment.

There is a risk that the patient may experience a sore neck or discomfort from lying in the same position for a long time during the treatment.

Risks associated with the ExAblate treatment

- There is a potential risk of hemorrhage around the treated area during ExAblate treatment. In ExAblate thermal ablation, the high temperatures result in immediate protein denaturation and coagulative necrosis, with the result that any bleeding that might occur in the capillary bed and within small vessels would be rapidly sealed. At the end of the ExAblate procedure a contrast (Gadolinium or other MRI contrast agent) enhanced MR imaging is performed to assess the blood flow within the treated area and neighboring tissue. In addition to the repeated MR imaging during every sonication of the treatment, this final step is an independent treatment outcome assessment tool that is giving information on blood flow in the treated surroundings and could serve as a final check of tissue status. In the treatments that have been completed to date in other organs, this complication has never been observed.
- Focused ultrasound therapy involves precisely controlled pulses of acoustic energy resulting in tissue heating (typically to 65-85°C for 15 seconds), in small tissue volumes. Discrete small volumes are consecutively treated at operator controlled time intervals without significant overall heat accumulation in the body. Since the beam is localized in the treatment area, there is no significant heating effect on pain sensitive areas such as adjacent normal tissue or skin. The patient will be sedated but in constant verbal contact with the physician and appropriate action can be taken in the event that a patient does experience discomfort. Remedies could involve increasing the time interval between consecutive treatment pulses or increasing the level of anesthesia and/or analgesia. The patient also has the ability to stop the procedure at any time by activating a handheld shutdown circuit switch.
- There is a risk to the patient from improper targeting of the focal point, and ablation of an area of tissue outside the planned treatment volume. At the start of treatment, the system includes a mandatory step that requires the operator to first check the alignment of the patient anatomy, the focal point of the transducer and

the MR imaging system. This procedure is done while the patient is in position for treatment. It achieves alignment within $\pm$ 2 mm in all 3 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. The system also includes an independent safety-monitoring loop that continuously compares the physical position of the transducer to the current intended treatment point to monitor for any un-commanded motion in the system from any source. If such a move is detected, the system immediately stops the delivery of energy to the patient, and notifies the operator of the error.

- The treatment results in the necrosed tissue being left in situ to be naturally removed by the body. There is a potential risk to the patient from a reaction to the volume of treated tissue (fever or infection). This effect has been often observed in other technologies of tissue ablation such as arterial embolization, cryo-therapy or Radiofrequency ablation of other tumors but has not been observed to a significant level thus far in the clinical experience accumulated from over 8500 treatments with ExAblate.
- There is a risk to the patient that the skin can become heated to the point where a burn can occur. This heating can be caused by direct heating of the skin (improper treatment targeting), irregularities on the skin surface, or treatment of a volume of tissue too close to the skin and the conduction of sufficient heat to cause a burn at the surface. In the case of a 1^{o} or 2^{o} burn, the skin should heal without a scar. In the case of a 3^{o} burn, a scar or loss of sensation in the area of the burn could result. Following several reports of skin burns in uterine fibroids treatment that occurred due to tiny air bubbles trapped in the pubic hair, investigators were instructed to shave any hair in the beam path which significantly reduced events of skin burns. No additional burns have been reported in over 30 cases of bone treatments.
- There is a risk from patient motion during a sonication, or between sonications. This could cause a movement of the tumor 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.
- There is a risk of cavitation in the tissue at the focal point. However, we believe that through proper system design, there is a very minimal risk that cavitation could occur during a treatment, even in the event of user error. We have taken extensive steps in the system design to address cavitation as a potential risk and provide two layers of protection. The first is in the design of the sonication treatment planner. This automated process takes as its input tumor depth in tissue, focal volume and tissue absorption, and based on pre-set safe operating limits selects sonication parameters that remain well below the cavitation threshold at the focal point. The system also includes a real time cavitation detection monitor. A graphic output of this system is displayed to the user during

the treatment. If cavitation is observed the user is instructed to immediately terminate the sonication before any harm would come to the patient being treated. It is not believed that a transient event of even a few seconds of cavitation could pose any medical risk to the patient

Risks associated with pathological fractures

Localized structural damage to the bone following ExAblate treatment could occur immediately following the treatment or could be delayed, resulting from death of osteocytes at and near the target zone (from the elevated temperature). No such events have been reported in the bone cases treated to date.

Although patients will be screened for possible impending fractures (section 3.2.2 Exclusion Criteria, #1 and Section 7.4), there is still a risk of fracture during the study associated with the bone metastases themselves. Thus, fractures could occur near the treated site or at the site of untreated lesions. All fractures will be captured on the adverse events CRF. Physicians will report the location of any fractures and assess their relationship to the procedure and the ExAblate device.

6.2 Anticipated Treatment Side Effects From ExAblate

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 treatment required and long term consequences for the patient. All Treatment Side Effects will be reported in the Case Report Forms for the study and included in the final study analysis.

Non-significant Anticipated Treatment Side Effects of ExAblate treatment are those, which normally resolve without sequelae within 10-14 days of the treatment:

- Transient fever
- Oral temperature >100.4ºF/38ºC
- Pain in the area of treatment.
- Transient pain in the skin.
- Swelling or firmness in the treated area

- Minor (1º or 2º) skin burns less than 2 cm in diameter
- Bruising in the treatment area

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:

- Necrosis of tissue outside the targeted volume due to heat conduction from heated bone.
- Nerve damage, or loss of sensation in the area other then the treatment area.
- Hemorrhage in the treated area requiring emergency treatment.
- Skin burns with ulceration of the skin.
- Skin retraction, and scar formation..
- Complications of conscious sedation (Cardiac, Pulmonary, Drug reactions)

The table below summarizes all the potential risks to a patient from ExAblate treatment and the time course when they would most likely be observed.

Immediate **(up to 48 hrs post treatment)**	**Mid term** **(up to one month)**	**Long term** **(more than one month)**
Pain in the treatment area.	Pain in the area of treatment	Pain in the area of treatment
Skin burns	Swelling or firmness in the treated area	Nerve damage or loss of sensation in the treated or neighboring areas
Necrosis of normal tissue resulting from incorrect targeting	Nerve damage or loss of sensation in the treated or neighboring areas	Scar formation from skin burn.
Risks of conscious sedation including reaction to drugs and over sedation.	Fever as reaction to treated tissue.	
Adverse reactions to Gadolinium DTPA		

Transient pain in skin or back	Ulceration of skin or scar formation from skin burn.	
Bleeding in the treatment area.		
Pathological fractures	Pathological fractures	Pathological fractures

The anticipated significant treatment side effects of the ExAblate treatment have an estimated combined incidence of less than 5% based on prior clinical experience in other organs.

6.3 Adverse Effects and Precautions

The subjects will be counseled concerning what to expect during the procedure and the importance of communicating any problems to the investigator. All device-related AEs occurring in this study will be recorded in the Case Report Forms. Each AE will be assessed for its probable cause (unrelated to the treatment, device related, procedure related, etc).

6.4 Criteria for Removal from the Study

Subjects can be exited from the study at any time if in the opinion of the principal investigator it is not in the best interest of the patient to carry on as planned. In Addition, patient may also chose to exit the study to pursue other alternative treatment options.

6.5 Adverse Event Reporting

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

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

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

causes death

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

All AE's (related or unrelated) meeting the criteria for an SAE require notification of the sponsor and the reviewing IRB as soon as possible, with subsequent completion of additional paperwork provided by the sponsor fully documenting the course of the event, all treatments, and final outcome. Initial reporting of an SAE should be made to the sponsor no later than two (2) working days after the PI learns of the incident.

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

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

Any UADEs will be reported to 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.

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

7 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 ICH-GCP requirements;
- 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.

7.1 Electronic Data Capture (EDC)

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

7.2 Investigator Responsibilities

All principal investigators will be required to sign an Investigator Agreement (**see Attachment-C** of this submission)

7.3 Definitions

Karnofsky Performance Status (KPS):

SCORE	FUNCTION
100	Normal, no complaint or evidence of disease
90	Able to perform normal activity; minor signs and symptoms of disease
80	Able to perform normal activity with effort; some signs and symptoms of disease.
70	Cares for self, unable to perform normal activity or to do active work
60	Requires occasional assistance, but is able to care for most needs
50	Requires considerable assistance and frequent medical care
40	Requires special care and assistance; Disabled.
30	Hospitalization indicated, although death not imminent; Severely disabled
20	Hospitalization necessary; active supportive treatment required, Very sick.
10	Fatal processes progressing rapidly; Moribund
0	Dead

7.4 Assessment of Fracture Risk

Several radiological features of bone metastases that may contribute to fracture have been identified [31]. Fractures are common through lytic lesions in weight-bearing bones. Features that may be predictive of immanent fracture include larger size, lesions that are primarily lytic, and those that erode the cortex. **(Mirels, 1989 #46)** developed a scoring system based on 1) location (upper limb, lower limb, peritrochanter), 2) pain severity (mild, moderate, severe), 3) lesion type (lytic, blastic, mixed), and the size of the lesion (<1/3, 1/3-2/3, >1/3). Each variable is scored 1, 2 or 3 and summed to provide a score ranging between 3 and 12. Using this system, lesions scoring >7 generally require surgical intervention [31].

8 APPENDICES

Appendix-A: Glossary of Terms

Appendix-B: Informed Consent

Appendix-C: Case Report Forms

Appendix-D: Morphine Equivalence Conversion Table

Appendix-E: BPI_QoL Questionnaire

9 REFERENCES

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