SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Magnetic Resonance Guided Focused Ultrasound Surgery System (MRgFUS)

Device Trade Name:

System	ExAblate		
Model	2000	2100	
Version		0	1
Cradle Type		1.0, 1.1	1.01, 1.11
Application	Bone		

Device Procode: NRZ

Applicant's Name and Address:

InSightec, Ltd.
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US Representative
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Date of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110039

Date of FDA Notice of Approval: October 18, 2012

Expedited:
Granted expedited review status on November 16, 2011 because the device met the criteria of a device addresses an unmet medical need, and is intended to treat a condition that is life-threatening and is irreversibly debilitating.

II. INDICATIONS FOR USE

The ExAblate is indicated for pain palliation of Metastatic Bone Cancer in patients 18 years of age or older who are suffering from bone pain due to metastatic disease and who are failures of standard radiation therapy, or not candidates for, or refused radiation therapy. The bone tumor to be treated must be visible on non-contrast MR and device accessible.

III. CONTRAINDICATIONS

The ExAblate treatment is contraindicated for use in:

- Patients with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations, weight >110 kg, allergies to MR contrast agent etc.
- Patients who need pre-treatment surgical stabilization of the affected bony structure or targeted tumor is in impending fracture, or have been stabilized with metallic implants.
- Women who are pregnant.
- Patient with extensive scarring in an area in the path of energy planned passage to the treatment area.
- The ExAblate treatment is contraindicated if the clinician is unable to avoid important structures (e.g., scar, skin fold or irregularity, bowel, other bone, surgical clips, or any hard implants) in the path of the ultrasound beam.
- Targeted tumor is in the skull or less than 1 cm from the skin surface
- Patients with advanced kidney disease or on dialysis
- Individuals who are not able or unwilling to tolerate the required prolonged stationary position during treatment (approximately 2 hrs)

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ExAblate labeling.

V. DEVICE DESCRIPTION

ExAblate® is a magnetic resonance image guided focused ultrasound surgery (MRgFUS) device that non-invasively target and ablate tissues. The ExAblate MRgFUS combines two technologies:

- Focused ultrasound: The ultrasound waves are converted to thermal energy at the focal point, with maximum (sonication) focal volume of 20-mm in diameter and 15-mm in height/length, causing a rise in tissue temperature to approximately 65°C to 85°C (150°F to 185°F), and resulting in non-reversible tissue thermal ablation. The tissue at the focus is ablated, while minimizing potential thermal effect outside the focus.

- MRI: The treatment is guided and controlled by magnetic resonance (MR) imaging, allowing anatomical planning of the treatment with real time temperature and anatomical monitoring. The real time monitoring serves as a treatment feedback for enhanced safety and efficacy.

Hardware

The ExAblate system is comprised of the following main components: patient table, operator workstation, equipment cabinet and a cooling system. When using the ExAblate, the patient lies on a patient table that fits into a standard MRI. The position of the patient and the sonication pathway are verified using MR imaging. These MR images are then loaded into the ExAblate workstation and the physician identifies target area and delineates the contour of the bone. Following this, the workstation generated a patient specific (personalized) treatment plan, which avoids damage to non-targeted tissue, while optimizing the required energy level and the number of sonications.

As shown in Figure 1, the patient table, on which the patient lies during treatment, is composed of two parts: the table and the cradle. The cradle houses the focused ultrasound transducer in an acoustically transparent fluid (e.g., water or light oil) bath, as well as the motors that move the transducer. The table houses the power modules that activate elements of the transducer and elements of a cooling system for the bath fluid. The patient table is compatible with high field MR scanners made by GE (Signa, Excite, Discovery and Optima series).

The ExAblate®2000 is equipped with a non-detachable cradle from the patient table. The ExAblate®2100 is equipped with a detachable cradle. Only cradle types 1.0, 1.1, 1.01, and 1.11 may be used with the ExAblate 2100 for the indication of pain palliation in metastatic bone cancer patients.

The workstation is a PC that has the ExAblate® software installed. The operator controls the ExAblate® using graphical interface based software. The workstation communicates user requests and commands to the Control Personal Computer (CPC). The workstation also has a monitor, a mouse and an emergency stop sonication button that cuts the power to the system in case of an immediate need to stop the sonication.

The equipment cabinet houses the electronics and amplifiers required to power the system, along with the CPC. The CPC controls the physical motion of the transducer, and coordinates the power output and focusing of the transducer, as well as the water cooling system.

Software

The ExAblate® software performs the following principal functions:

- Graphical user interface for system operation
- MRI communication and remote operation of the MR
- ExAblate® hardware system operation and control
- MRI image acquisition and viewing
- Graphical treatment planning tools

- Calculations of temperatures and thermal dose, and graphical monitoring of treatment thermal and acoustical parameters

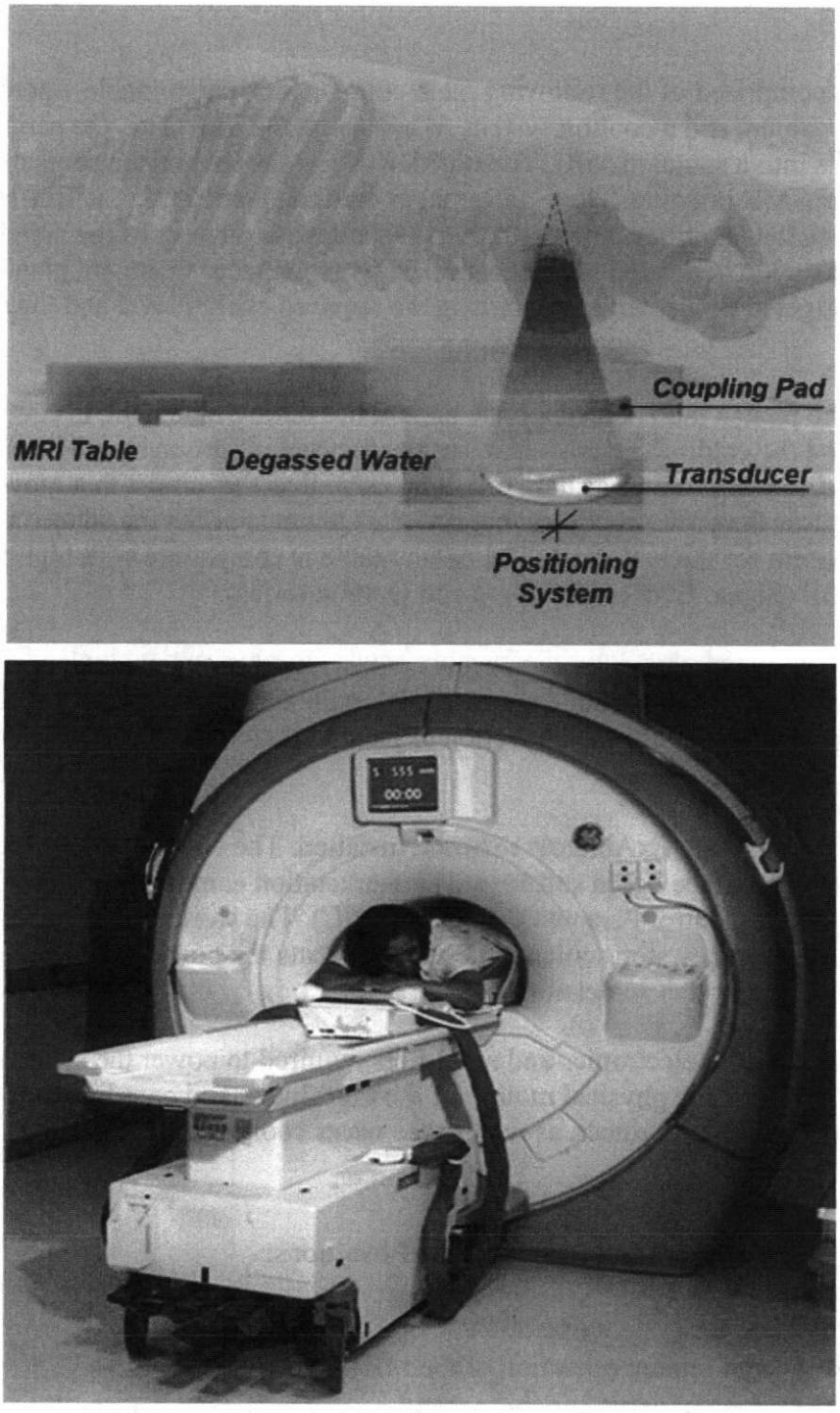


Figure 1 - Diagram of ExAblate® for Bone Treatment. Top: diagram showing the location of the focused ultrasound transducer relative to the patient lying on the Patient table and bone metastasis. Bottom: photograph showing patient lying on the Patient table.

The ExAblate® software is designed to allow operators access only to the functions required for safe operation of the device. A number of maintenance functions are also available for system evaluation and troubleshooting by InSightec service and technical personnel.

Accessories

The following accessories are needed for ExAblate® operation:

- Treatment Supplies Pack: each pack contains all the necessary disposable items involved in a patient treatment (degassed water, scraper, patient drape, ultrasound gel, and acoustic coupling gel pad).
- MR GE scanner compatible Coil (cleared in K071966): This coil is used to acquire the planning, thermal and post-treatment images.
- DQA (daily quality assurance) phantom: a tissue-mimicking phantom for testing the functionality of the ExAblate.

Principles of Operation

The ExAblate MRgFUS Bone device is designed to achieve local pain palliation of metastatic bone lesions. The "Patient Pain" is alleviated by denervating the periosteal tissue overlaying the painful lesion. Denervation is achieved by ablating the periosteal tissue through the delivery of focused ultrasound energy to the region of interest, with Magnetic Resonance Imaging serving for real-time guidance and control.

When using the ExAblate, the patient lies on a patient table that fits into a standard MRI. Because the targeted bone metastases may be in different areas of the body, positioning of the patient on the table should be optimized by centering the target metastasis directly over the water bath containing ExAblate® transducer, creating a normal incidence angle with as much of the bone surface as possible.

The position of the patient and the sonication pathway are verified using MR imaging. These MR images are then loaded into the ExAblate® workstation and the physician identifies the target area and delineates the contour of the bone. Following this, the workstation generates a patient specific (personalized) treatment plan, with the aim to avoid damage to non-targeted tissue, while optimizing the required energy level for ablation and sonication coverage of planned target.

At the beginning of the treatment, a number of low power sonications are performed to ensure the targeting accuracy in three dimensions. Treatment at therapeutic power levels begins after a mild increase in the temperature at the expected target position is detected.

Throughout the treatment, the location of each sonication and its thermal response in the tissue adjacent to the targeted bone are monitored in real time, using the proton resonance frequency (PRF) shift temperature measurement method. In response to the resulting temperature map, the treating physician may decide to modify treatment parameters such as power, frequency,

sonication duration or spot size. Upon treatment completion, a contrast enhanced MRI scan is performed for immediate evaluation of treatment effect.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Alternative practices and procedures currently available for pain palliation of Metastatic Bone Cancer in patients who had failed radiation therapy may include:

- Surgical resection;
- Radiofrequency ablation - although this procedure is limited in scope due to insertion of probes, and the type of tumor that can be treated;
- Narcotic analgesics and non-opioid analgesics;
- External beam radiation therapy - treating physician may consider other rounds of radiation with varying dosage as a salvage treatment approach with all the morbidity that such procedure(s) may lead to.

VII. MARKETING HISTORY

The ExAblate system received CE mark for bone Mets palliation in January 2009. The ExAblate system also received PMA approval in October 2004 (P040003) in the United States for the treatment of symptomatic fibroids. The ExAblate system received the CE mark in Europe in October 2002 for the treatment of uterine fibroids. The ExAblate is currently in commercial use in the United States, Israel, Europe, Japan, Russia, Korea, Brazil, India, and Australia, among other countries.

The ExAblate has not been withdrawn from the market in any country for any reason relating to the safety or the effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following anticipated side effects have been identified as possible treatment related complications of MRgFUS 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.

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

- Transient fever
- Oral temperature > 100.4°F/38°C
- Pain in the area of treatment.
- Transient pain in the skin.
- Swelling or firmness in the treated area
- Minor (1° or 2°) skin burns less than 2 cm in diameter
- Bruising in the treatment area

Significant Anticipated Treatment Side Effects of MRgFUS 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 an area other than the treatment area.
- Hemorrhage in the treated area requiring emergency treatment.
- Skin burns with ulceration of the skin.
- Skin retraction, and scar formation.
- Venous thromboembolic events.
- Complications of conscious sedation (Cardiac, Pulmonary, Drug reactions)

Table 1 below summarizes all the potential risks to a patient from ExAblate treatment and the time course when they would most likely be observed.

Table 1 - Potential Risks to a Patient from ExAblate Treatment	
Short Term - -Day of treatment up to 2 weeks post-treatment	**Long term- Longer than 2 weeks post-treatment**
Sonication-related pain during treatment.	
Post-procedure pain	
Positional pain	
Skin burns	Scar formation from skin burn and possible numbness
Neuropathy	Possible muscle weakness, numbness and/or sensory loss.
DVT	DVT
Fever	
Fatigue	
Blood in urine or kidney or bladder infection due to urinary catheter	Kidney or bladder infection
Bruising at site of i.v.	
	Pathological fractures

IX. SUMMARY OF PRECLINICAL STUDIES

Functional Testing

The ExAblate System components for bone mets application are identical to the ExAblate System components approved for Uterine Fibroids (UF) application (P040003), and its subsequent PMA supplements (P040003/S012), except the modification of the ExAblate system in the software to support the treatment strategy needed for the painful metastatic bone tumors, together with the new Cradle for bone application.

Pre-clinical testing was performed to demonstrate the ability to focus the transducer on and deliver the required energy to achieve ablation at a predicted point, while monitoring acoustic coupling and cavitation, for successful operations of the ExAblate system for bone application in the following testing configurations:

- Acoustic sub-system lab testing
  - Transducer testing in water.
  - Transducer testing in MR scanner using a tissue mimicking gel phantom and utilizing MR thermometry
  - The ability to have the transducer deliver a desired level of energy
- Acoustic safety monitoring
  - The ability to detect cavitation.
  - The ability to detect reflection from poor acoustic coupling in the beam path.
- Ablation monitoring
  - The ability of MRI thermometry to determine whether or not tissue ablation has occurred both in a gel phantom containing bone model and *in-vivo* experiments.

These testings are summarized in **Table 2.**

Table 2 - Summary of Functional Testings

Functional Testings		
Type of Test	**Purpose**	**Results**
Focusing of Ultrasound beam – Water test	To test focusing ability in water - Hydrophone measurement of focus in water compared to simulated values.	Demonstrated that the ExAblate transducer precisely focused an ultrasound beam at a desired location in water.
Focusing of Ultrasound - Gel phantom test	To test focusing ability in gel - MR thermometry measurement of focus location in phantom.	Demonstrated that the full ExAblate system precisely focused an ultrasound beam at a desired location in phantom
In vitro and in vivo bone temperature testing	To compare the temperature measurements using thermocouples and MR thermometry with Matlab simulations using phantoms containing different bone types (animal).	Demonstrated good correlation between thermometry and simulation

Type of Test	Purpose	Results
Transducer Power Measurements	To verify that ExAblate will deliver prescribed acoustical energy - Radiation force measurements.	Demonstrated that the ExAblate transducer is delivering the prescribed acoustical energy
Cavitation Detection Test	To verify that ExAblate detects cavitation activity - Spectral analysis of hydrophone signals using animal tissues.	Demonstrated that the ExAblate correctly detects when cavitation activity occurs and when it does not occur.
Monitoring and detection of acoustic coupling integrity	To verify the ability of ExAblate to detect poor acoustic coupling using reflected signals from Mylar-Gel pad and DQA phantom interfaces.	Demonstrated that ExAblate correctly detected good and poor acoustic coupling at the interfaces tested.
Optimal Cooling Time Determination between Sonications	To determine optimal delay between sonications to permit adequate tissue cooling using live animal models.	Demonstrated that the optimal cooling time between sonications could be determined from MR thermometry to monitor and prevent thermal build-up *in vivo*.
Animal Studies		
Type of Test	**Purpose**	**Results**
MR thermometry and dosimetry verification in live animal model	To test Echo Planar Image and verify ability of MR to determine thermal dose in an *in vivo* animal model.	Verified that the ExAblate could determine thermal dose by MR thermography and Echo Planar Imaging
Bone sonication optimization	To optimize bone sonication delivery technique in live animals.	A preferred method for sonication delivery was determined through histopathological analysis.
Pre-clinical safety and efficacy study in animals	Using a live animal model, to acquire the ExAblate therapy . delivery system safety and efficacy prior to human clinical testing.	Results demonstrated that the ExAblate system is able to safely and effectively to induce localized thermal damage at the bone-tissue interface. No significant morbidity was observed following treatments

Electrical Safety and Electromagnetic Compatibility (EMC) Testing

The ExAblate system passed testing of applicable electrical safety and electromagnetic compatibility testing standards as summarized in **Table 3.**

Table 3 - Electrical and EMC Testing		
Electrical Safety Testing		
Type of Test	**Purpose**	**Results**
Electrical Safety Test of the ExAblate Device according to applicable standards: IEC 60601-1:1988+A1:1991 +A2:1995	Electrical safety (second edition)	Passed
EN/IEC 60601-1: 2005/2007/2009	Electrical safety (third edition)	Passed
EN 60601-1-2:2007	EMC safety	Passed
EN 60601-1-1: 2001	Safety of medical systems	Passed
IEC 60601-1-4: 2000	Safety of Programmable Electrical Medical Systems	Passed

Biocompatibility Testing

The patient contact materials include the following: an acoustic coupling transmission gel, a patient drape, degassed water and regular ultrasound transmission gel. All of these components are identical materials as legally marketed devices and used under the same conditions, as summarized in **Table 4**.

Table 4 - Biocompatibility Testing		
Biocompatibility Testing		
Type of Test	**Purpose**	**Results**
Biocompatibility of Patient interface Gel Pad	To test gel pad for biocompatibility	Passed - 510k # K851895
Biocompatibility of Patient drape	To test patient drape for biocompatibility	Passed - 510k # K050322.
InSightec Patient interface Gel Pad	To test gel pad for biocompatibility	Passed - meeting ISO 10993 standard of biocompatibility.

Software Testing

The following software functions were also tested satisfactorily (**Table 5**):

- Operator-machine interface, including:
  - display of images and annotation overlays on the images
  - display of geometrical structures and data, and textual data
  - status display for the various system components (HW & MRI)
  - support of operator-generated drawing operations
  - support of operator command activation
- ExAblate-MRI interface (activating MR scans and retrieval of MR images)

- Activation and control of system technical operation (robotic motion, energy transition and sampling of transmitted and reflected energy)
- Interpretation and display of thermometry images and treatment results
- Simulation of sonication results, and treatment planning as a whole (treatment area/volume coverage)

Table 5 - Software Testing		
Software Testing		
Type of Test	**Purpose**	**Results**
User interface and system operation verification	Verifying adherence to functional specification on system operation and treatment planning and thermal feedback, as defined in the clinical SFR and subsequent SRS documents	Passed.
Software validation testing	Testing software and system functionality in its intended use environment ("phantom gel treatments" using the entire ExAblate-MRI system in clinical setting)	Passed.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The primary investigation of this PMA is based on the IDE (IDE # G070022) Pivotal clinical trial. In addition, a preliminary feasibility study was conducted under a previous IDE application.

Table 6 - Summary of Primary Clinical Studies					
Study Type	**Study Design**	**Objective**	**No of Sites**	**No of Subjects**	**Accountability**
Feasibility	Prospective, single-arm study	To evaluate the safety and effectiveness of the ExAblate as a treatment for pain palliation in patients with metastatic bone tumors	2	10	Nine subjects completed the study; one subject could not complete treatment due to limited device accessibility to the lesion
Pivotal Study	Prospective, randomized (3:1), single blind, sham control study	To evaluate the effectiveness and safety of ExAblate in the palliation of pain from metastatic or multiple myeloma bone tumors in patients who are not suitable candidates to receive	20*	139	Of the 104 ExAblate enrolled subjects and 35 Control Sham enrolled subjects, 79 ExAblate Test Arm and 12 Control Sham subjects have completed the study, 3 subjects in the ExAblate group are still in follow-up. In the Control Sham Arm, 17 of the 35

		radiation therapy.			subjects crossed over to Rescue treatment with the ExAblate, though 2 of these subjects discontinued at the 3 month visit before crossing over to the Rescue Arm.

* 17 sites participated and 3 sites did not enroll subjects in the trial.

FEASIBILITY STUDY (IDE G050177)

The feasibility protocol was a prospective, single-arm, non-randomized study to evaluate the safety and effectiveness of the ExAblate as a treatment for pain palliation in patients with metastatic bone tumors. The study objectives were to determine:

Safety: The study evaluated the incidence and severity of adverse events associated with ExAblate for treating bone metastases which are device accessible, i.e., visible by MRI and accessible by equipment

Effectiveness: The study determined the efficacy of ExAblate treatments for pain palliation in patients with metastatic bone tumors. Efficacy was determined by the level of pain relief, decrease in patient use of analgesics/opiate, and improved quality of life from baseline up to 12-Weeks post ExAblate treatment.

Ten subjects were enrolled at two sites. Nine subjects completed the study; one subject could not complete treatment due to limited device accessibility to the lesion. Assessments were performed at baseline, on the day of treatment, and at follow-up visits 3 days, 2 weeks, 1 month, and 3 months after treatment. Enrolled subjects had a range of primary cancer types and target lesion locations, including the iliac crest, scapula, ischium, and clavicle bone.

There were three AEs reported in the study, and all were mild in severity. There were no device-related deaths, life threatening injuries or permanent injuries. All of the adverse events reported were anticipated side effects that were identified in the study protocol as possible treatment-related complications.

The study demonstrated a sustained relief response in subjects' pain relief over the three-month trial period. At 3 months, the mean score had dropped to a 93% decrease from baseline. With respect to medication usage, all subjects maintained or decreased their medication usage.

Using the Overall Treatment Effect Scale (OTE scale), the results indicated that all patients completing the OTE experienced clinical improvement by 1 -Month after treatment and this improvement continued through the 3-Month visit.

PIVOTAL STUDY (IDE G070022)

STUDY DESIGN

The pivotal study was a prospective, randomized (3:1), 2-arm, sham-controlled, multicenter, international clinical study with a sham-crossover option to assess the safety and effectiveness of an ExAblate thermal ablation treatment as compared to a sham treatment (where no energy is delivered) to reduce/relieve the pain of metastatic bone tumors in patients who were not suitable candidates for radiation therapy.

Subjects with intractable pain from a well-defined tumor site in bone (metastasis or multiple myeloma) who refuse available treatments for pain alleviation, or who have received radiation without adequate relief from metastatic bone pain, or those for whom the physician would not prescribe radiation or additional radiation treatments were recruited into the study at 17 United States (US) and outside US (OUS) clinical sites.

Immediately following screening and optimization of their pain medications, subjects were randomized at a 3:1 ratio to either ExAblate treatment arm or sham control arm and preceded to MR screening and geometric target verification where further subjects were ruled ineligible for study participation.

Subjects who were randomized to sham treatment arm and passed the Screen Fail criteria underwent a sham ExAblate treatment with sonication energy disabled. No more than 50% of the planned sonications were to be performed and the entire procedure was to last only approximately 30 minutes. Sham treatment did not include sedation. Subjects randomized to ExAblate treatment arm and passed the Screen Fail criteria preceded in normal fashion to ExAblate treatment at the same session.

Four test sonications were delivered. If a subject discontinued prior to the fourth sonication, they were considered a screen failed subject. All other subjects completed the planned active ExAblate treatment up to a maximum of 180 minutes sonication time.

Eligibility Criteria

The inclusion and exclusion criteria for the ExAblate bone mets pivotal study are listed below:

Inclusion Criteria

- Men and women age 18 and older
- Patients who are able and willing to give consent and able to attend all study visits
- Patients who are suffering from symptoms of bone metastases and are radiation failure patients:
  - Radiation failure candidates 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.

- Patients who refuse other accepted available treatments such as surgery or narcotics for pain alleviation.

- Patient with NRS (0-10 scale) pain score ≥ 4 irrespective of medication

- Targeted tumor(s) 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)

- Targeted tumor (treated) size up to 55 cm^2 in surface area

- Patient whose targeted (treated) lesion is on bone and the interface between the bone and lesion is deeper than 1 cm from the skin.

- Targeted (treated) tumor clearly visible by non-contrast MRI, and ExAblate MRgFUS device accessible

- Able to communicate sensations during the ExAblate treatment

- Patients on ongoing chemotherapy regiment for at least 1 month at the time of eligibility with pain NRS of the targeted lesion that is:

  - Stable over a period of at least 2 weeks prior to ExAblate treatment. Stability is defined as variation in worst pain NRS not bigger than 2 points

    AND

  - Worst pain NRS still >= 4

    AND

  - Do NOT plan to initiate a new chemotherapy for pain palliation should be eligible for the study.

- No radiation therapy to targeted (most painful) lesion in the past two weeks

- Bisphosphonate intake should remain stable throughout the study duration.

- Patients will have from 1 to 5 painful lesions and only the most painful lesion will be treated.

- 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

Exclusion Criteria

- Patients who either
  - Need surgical stabilization of the affected bony structure (>7 fracture risk score)

    OR

  - Targeted tumor is at an impending fracture site (>7 on fracture risk score)

    OR

  - Patients with surgical stabilization of tumor site with metallic hardware
- More than 5 painful lesions, or more than 1 requiring immediate localized treatment
- Targeted (treated) tumor is in the skull
- Patients on dialysis
- Patients with life expectancy < 3-Month
- Patients with an acute medical condition (e.g., pneumonia, sepsis) that is expected to hinder them from completing this study.
- 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
- Severe hypertension (diastolic BP > 100 on medication)
- Patients with standard contraindications for MR imaging such as non-MRI compatible implanted metallic devices including cardiac pacemakers, size limitations (weight >250 pounds), etc.
- Patients with an active infection or severe hematological, neurological, or other uncontrolled disease.
- Known intolerance or allergies to the MRI contrast agent (e.g. Gadolinium or Magnevist) including advanced kidney disease
- KPS Score < 60

- Severe cerebrovascular disease (multiple CVA or CVA within 6 months)
- Individuals who are not able or willing to tolerate the required prolonged stationary position during treatment (approximately 2 hours)
- Target (treated) tumor is less then 1cm from nerve bundles, bowels or bladder.
- Are participating or have participated in another clinical trial in the last 30 days
- Patients initiating a new chemotherapy regime, or radiation (for the targeted most painful lesion) within the last 2 weeks
- Patients unable to communicate with the investigator and staff.
- Patients with persistent undistinguishable pain (pain source unidentifiable)
- Targeted (treated) tumor surface area ≥ 55 cm^2
- Patient whose bone-lesion interface is < 1 cm from the skin
- Targeted (treated) tumor NOT visible by non-contrast MRI
- Targeted (most painful) tumor NOT accessible to ExAblate
- The targeted tumor is less than 2 points more painful compared to other painful lesions on the site specific NRS.

Patient Treatment

Patients who were randomized to sham treatment underwent a sham ExAblate treatment with the sonication energy output disabled. No more than 50% of the planned sonications were to be performed and the entire procedure was to last only approximately 30 minutes. Sham treatment did not include sedation, although anesthesia was permitted to alleviate, for example, pain due to positioning.

Patients randomized to active treatment underwent pre-treatment planning. Any patient deemed not to have a device accessible lesion or who received fewer than 3 therapeutic sonications was considered a screen failure and was exited from the study. If the subject remained eligible, i.e., the lesion was device accessible and they could tolerate 4 therapeutic sonications, the patient had analgesia and sedation or other measures administered to reduce pain and limit patient motion, and the planned treatment for a maximum of 180 minutes sonication time.

Follow-up

Both active and sham treatment patients were seen for follow-up at 1 and 3 days, 1 and 2 weeks and 1, 2, and 3 months. Subjects were evaluated for general health, efficacy measurements as well as for device/procedure related AEs that occurred during the follow-up period.

The Day 1, Day 3, Week 2 visits were completed by telephone. For these calls, the study personnel called the subject to inquire about adverse events, questions the subject according the NRS, quality of life questionnaires, and pain medication intake.

The Week 1, Month 1, 2, and 3 visits were office visits. Subjects completed the NRS, BPI-QOL, EQ-5D, OTE at each office visit. The physician completed a KPS form. Medication intake symptoms and general health were assessed and adverse events collected and followed.

Following the Week 2 visit, study subjects in both arms who were Non-responders at two consecutive visits or experienced an intolerable increase in pain or medication usage were eligible to exit from the study to pursue other treatments. Sham Arm subjects who are non-responders were permitted to opt for a cross-over treatment with the ExAblate. All patients who opted for cross-over were followed in a rescue arm for 3 months, like the active treatment group. **Table 7** provides the full schedule of evaluations in the study.

Table 7 - Patient Follow-up Schedule

	Window Allowance	**Imaging**	**Questionnaires**	**Additional data**
Enrollment (Randomization)	N/A	CT	PE,NRS,BPI, EQ-5D,KPS	Freq and dose analgesics. Economic data
Run-in Visit			NRS,BPI,KPS EQ-5D	Freq and dose analgesics
Visit #1 Baseline MR Imaging and Test or Sham Rx	On Run-in or within 1-week ±3 days of Run-in	MR	NRS,BPI,KPS, EQ-5D, Patient blinding	Freq and dose analgesics
Visit #2(phone): 1-day post Rx	N/A		NRS,BPI,KPS,OTE, EQ-5D.	Freq and dose analgesics
Visit #3(phone): 3-day post RX	±1 day		NRS,BPI,KPS,OTE, EQ-5D	Freq and dose analgesic
Visit #4(office) 1-week post Rx	±3 days		PE,NRS,BPI,OTE EQ5-D, KPS	Freq and dose analgesic. Economic data
Visit #5 (phone): 2 weeks post Rx	± 3 days		NRS,BPI,OTE,KPS EQ-5D	Freq and dose analgesic
Visit #6 (office): 1month post-Rx	± 1 week		NRS,BPI,OTE,KPS EQ-5D	Freq and dose analgesics.

Table 7 - Patient Follow-up Schedule				
	Window Allowance	**Imaging**	**Questionnaires**	**Additional data**
				Economic data
Visit #7 (office): 2 month post Rx	±2 weeks		NRS,BPI,OTE,KPS EQ-5D	Freq and dose analgesic. Economic data.
Visit #8 (office): 3 month post Rx	±2 weeks	MR,CT	PE,NRS,BPI,OTE, KPS, EQ-5D	Freq and dose analgesic. Economic data

Endpoints

Safety Endpoint

The safety of the ExAblate was determined by an evaluation of the incidence and severity of device-related adverse events and serious adverse events from treatment day through the Month 3 post-treatment time point.

Primary Effectiveness Endpoint

The primary endpoints were two-fold as follows:

- A clinically relevant threshold of at least 50% of ExAblate-treated patients in the ExAblate Arm will achieve 2 points or more improvement in the worst pain NRS score from Baseline at the 3-Month time point post ExAblate treatment without increase in medication.

- The response rate in the ExAblate-treated group was significantly greater than the response rate in the Sham-treated group.

The primary success criteria used a combination of the above study variables, utilizing the NRS determination of pain at Month 3 as compared to Baseline (success > 2 points or greater reduction in pain score) AND medications usage (success = no significant increase in pain meds intake within <25% difference from baseline) as the definition of Responder for study success to be declared. Those that failed either or both criteria were categorized as a Non-Responder. The success criteria were that at least 50% of the ExAblate group was categorized as a Responder AND the % response in the Treated Arm was significantly higher than the Sham Arm.

Secondary Effectiveness Endpoint

- NRS score (measured separately from Responder/Non-responder definition for the primary endpoint)

- Medication Use quantified by "morphine equivalent usage" (measured separately from Responder/Non-responder definition for the primary endpoint)

- Quality of life (QoL) as measured by BPI-QoL
- Self assessed Overall Treatment Effect (OTE) measured items
- Self assessed EQ-5D for function and well-being subscales

STATISTICAL ANALYSIS PLAN AND ANALYSIS POPULATION

Sample Size

The proposed sample size of 148 subjects for the study was designed to reflect the two-fold primary endpoint:

- The response to ExAblate treatment is clinically relevant, and
- The response to ExAblate treatment is significantly greater than the Sham group effect.

The sample size did include the allowance for a 20% dropout rate. The sponsor did plan an interim analysis after 116 patients were randomized, 88 treatment and 28 controls, and 107 are considered by the sponsor as part of the effectiveness analysis.

Statistical Analysis

The statistical hypothesis that was to be conducted on the ITT Analysis Set for the primary efficacy analyses was:

$H_0: P_{T\_success} \leq P_{S\_success}$
$H_1: P_{T\_success} > P_{S\_success}$

Where,

$P_{T\_success}$ = Proportion of success on the primary endpoint Responder in the Test group
$P_{S\_success}$ = Proportion of success on the primary endpoint Responder in the Sham group

This hypothesis was to be analyzed using Fisher's Exact Test with two-sided interim Alpha.
The study will have succeeded if the Null is rejected and proportion of success is higher in Test than Sham.

Additionally, a two-sided exact binomial 95% confidence interval about the observed responder rate in the Test group was to be constructed. Overall success in the trial will be declared if:

- Test is significantly superior to Sham on Response Rate
- The lower bound of the confidence interval around Response Rate in the Test group is at or above 0.50.

This hypothesis was to be analyzed using Fisher's Exact Test with two-sided interim Alpha. The study will have succeeded if the Null is rejected and proportion of success is higher in Test than Sham.

Analysis Population

The following analysis populations were used to evaluate study results and are also shown in Figure 2.

Intent-to-Treat (ITT) Population

The ITT population included all randomized subjects receiving treatment (Test or Sham). Subjects receiving three therapeutic sonications or fewer, over all their treatment sessions (one or two), were considered Screen Failures (as allowed by protocol) and excluded from this analysis set.

Per Protocol Imputed Population (PPI)

The PPI population is a subset of the ITT Analysis Set of subjects who had both valid baseline measurements and at least one valid post-baseline measurement at the Day-3 visit or later for the following parameters:

- Numerical Rating Scale (NRS)
- Medication Use quantified by "morphine equivalent units"

Safety Population

The Safety population included all subjects for whom any sonication was performed (ExAblate or Sham) at any stage of the study.

Per Protocol Completers Population (PPC)

The PPC population is a subset of PPI analysis population of subjects who had observed primary efficacy analysis data at three months or discontinued prior to three months due to non-response.

Rescue Population

The Rescue population included all subjects who entered the Rescue stage of the trial.

SUBJECT ACCOUNTABILITY

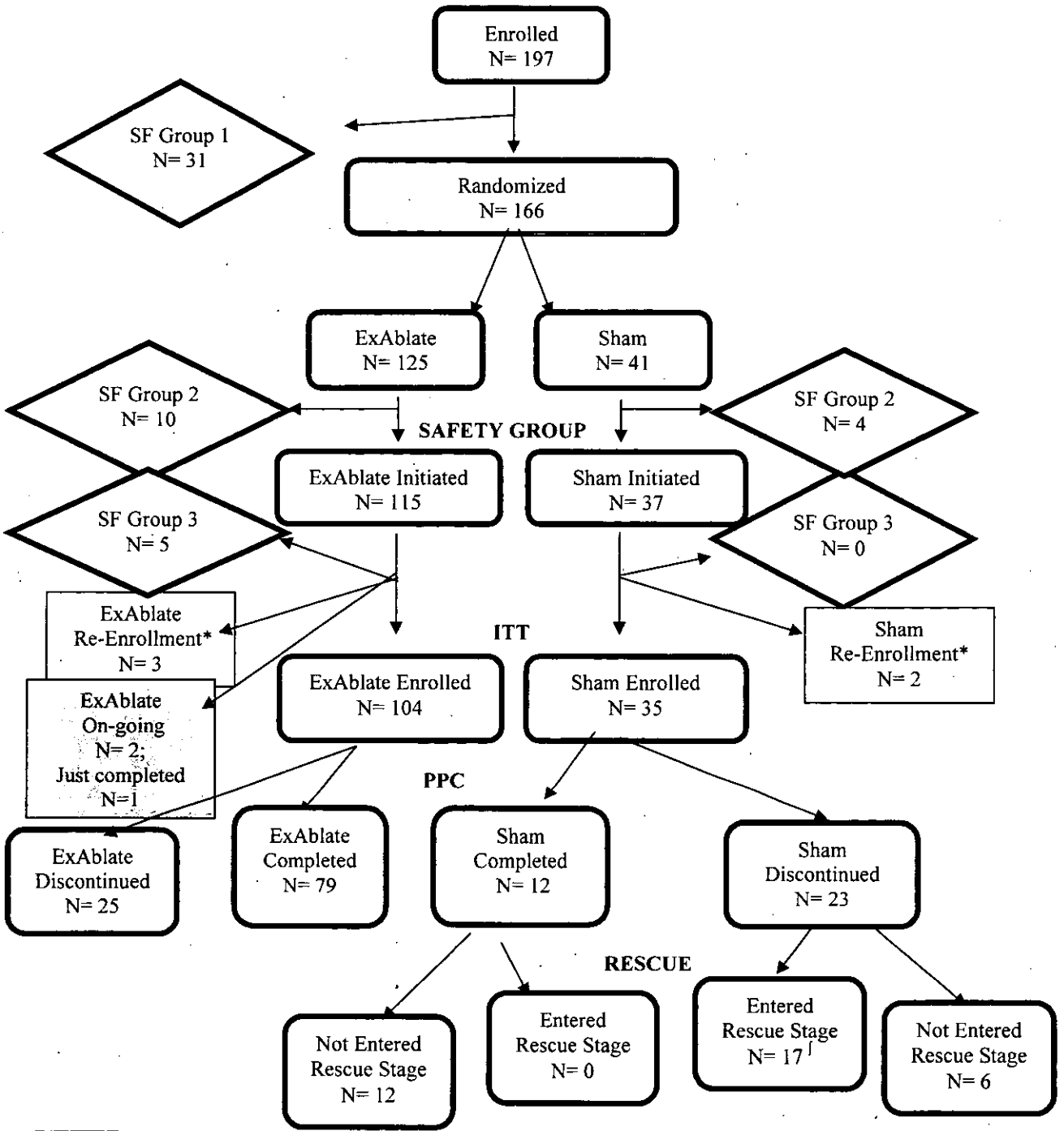
All study data is presented according to the following regional geographic cohorts:

- Non-Russian Cohort (US/OUS Combined) - refers to all study centers located in the United States, Canada, Israel and Europe.

- Russian Cohort- refers to all study centers located within Russia.

As shown in Figure 2, 197 subjects were screened, from all geographic regions, for the pivotal clinical study. Of these, 31 subjects were initial screening failures based on the initial review of inclusion and exclusion criteria. 166 randomized subjects were available for analysis. Of these, 14 subjects were screening failures after MRI review and 152 initiated treatment; these are referred to as the Safety Group Population. Of these, 5 subjects, all at the non-Russian sites (US/OUS Combined), did not receive more than three sonications and, thus, were screening failures per the study protocol. In addition, 5 of the remaining subjects, all at the Russian sites, had been inadvertently enrolled into a second round of treatment in the study. Thus, data from the second round of treatment for those subjects was included in the safety analysis, but excluded from the efficacy analysis, although the data from the first round of treatment was included in both analyses. Thus, 139 subjects are available for the efficacy analysis; these are the Intent-to-Treat (ITT) subject population. Patient Accountability by Treatment Visit and By Treatment Group is also shown in **Table 8**.

Figure 2 - Subject Disposition Flow Chart



*: 2 Subjects shown were inadvertently re-enrolled as new subjects following completion of the original study follow-up. Those subjects are included in all safety analyses, but the data arising from the second enrollment are not included in the Main Efficacy Analysis.
∫: 2 of these subjects actually discontinued at the 3M visit before crossing over to Rescue Arm.

Table 8 - Patient Accountability by Treatment Visit and By Treatment Group

	Baseline		Week 1		Week 2		Month 1		Month 2		Month 3	
	ExAblate	Sham	ExAblate	Sham	ExAblate	Sham	ExAblate	Sham	ExAblate	Sham	ExAblate	Sham
Consented	197											
Screening Failure 1[1]	31											
Screening on-going – not yet randomized												
Randomized[2]	125	41										
Screening Failure 2[3]	10	4										
Screening Failure 3[4]	5	0										
Excluded re-enrolments[5]	3	2										
Theoretical[6]	107	35	107	35	107	35	107	35	107	35	107	35
Not Yet Due[7]	0	0	0	0	0	0	0	0	1	0	3	0
Death **	0	0	0	0	0	0	0	0	2	0	6	0
Failure[8]	0	0	0	0	2	1	2	10	3	13	5	15
Expected[9]	107	35	107	35	105	34	105	25	101	22	94	20
Actual[10]	107	35	106	35	101	34	98	22	89	19	79	14*
Actual %[11]	100%	100%	99%	100%	96%	100%	93%	88%	88%	86%	84%	70%

[1]Screening Failure 1 – Those subjects consented, but did not meet enrollment criteria.
[2]Randomized equals those consented minus Screening Failure 1;
[3]Screening Failure 2 – Post-MRI assessment of eligibility criteria;
[4]Screening Failure 3 – Subjects for whom only 3 or fewer sonications with therapeutic energies could be performed due to patient tolerance;
[5] Subjects who were found to have re-enrolled under new subject numbers.
[6]Theoretical is equal to the number of subjects consented minus Screening Failures 1, 2 and 3. Therefore, theoretical is equal to the number of subjects eligible to receive treatment in either group.
[7]Randomized, but still ongoing in study as they have neither completed nor exited the study.

[8]Failure includes any subject (ExAblate or Sham) determined to be a Non-responder and exited the study early. Failures are cumulative across the row.
[9]Expected equals Theoretical minus Failures minus Death and is cumulative across the row.
[10]Actual is the number of subjects with NRS data present in the database;
[11]Actual % is the number of Actual subjects divided by Expected.
*Figure-2 above shows 12 subjects completed Month 3. Two Sham completed subjects discontinued at Month 3 and opted for crossover; they are shown as attending the Month 3 visit here.

**: The total number of subject death reflect also 1 death event that occurred in the cross over arm.

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline and demographic data for the study are reported by cohort in **Table 9**. The Baseline and Demographic population is composed of all subjects who passed initial screening criteria and received even one sonication. It is observed that the Russian cohort overall was younger that the other cohorts. The Russian cohort had a greater percentage of females. The differences in racial distribution demonstrate the multi-racial mix within the United States as opposed to that of other countries. The Russian cohort had statistically significantly smaller tumors, fewer tumors, less time since being diagnosed with bone metastases, took fewer pain medications, and had higher baseline quality of life and KPS scores.

Table -9 Demographic and Baseline Characteristics by Cohort and by Treatment Group

Variable	Non Russian Cohort (US/OUS Combined Cohort)		Russian Cohort	
Treatment Arm	**ExAblate**	**Sham**	**ExAblate**	**Sham**
Age (yrs± SD)	63.2 ± 12.0	60.6 ± 10.4	53.9 ± 13.9	56.7 ± 10.8
Median	63.7	59.7	53.7	58.5
N	71^	19	43	18
BMI (kg/m2 ± SD)	26.1 ± 5.3	26.2 ± 3.5	26.2 ± 4.8	26.8 ± 4.7
Median	25.1	25.6	25.6	27.3
N	71^	19	43	18
Average height (cm ± SD)				
Median	167.8 ± 9.6	165.2 ± 10.0	164.0 ± 7.7	164.3 ± 6.3
N	167.5	160.0	164.0	164.0
	71^	19	43	18
Average weight (kg ± SD)				
Median	73.6 ± 15.4	71.6 ± 12.5	70.1 ± 11.8	72.5 ± 13.2
N	73.3	69.8	70.0	75.0
	71^	19	43	18
Gender				
Males	42 (58.3%)	5 (26.3%)	9 (20.9%)	2 (11.1%)
Females	30 (41.7%)	14 (73.7%)	34 (79.1%)	16 (88.9%)
N	72	19	43	18
Race				
White	64 (88.8%)	17 (89.5%)	43 (100.0%)	18 (100.0%)
Hispanic	3 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Asian	3 (4.2%)	2 (0.0%)	0 (0.0%)	0 (0.0%)
Other	1 (1.4%)	0 (10.5%)	0 (0.0%)	0 (0.0%)
N	72	19	43	18
Mean Tumor Volume (cm^3)	177.6 ± 234.4	219.0 ± 522.0	97.4 ± 160.8	68.0 ± 69.1
N	68**	19	43	18
Baseline NRS (Mean ± SD)	7.3 ± 1.7	7.9 ± 1.2	6.4 ± 1.4	5.6 ± 1.1
N	72	19	43	18

Table -9 Demographic and Baseline Characteristics by Cohort and by Treatment Group				
Variable	**Non Russian Cohort (US/OUS Combined Cohort)**		**Russian Cohort**	
Treatment Arm	**ExAblate**	**Sham**	**ExAblate**	**Sham**
Baseline BPI-QoL (Mean ± SD)	6.19 ± 1.89	6.45 ± 2.23	4.68 ± 1.77	3.96 ± 1.58
Physical Functioning	6.79± 2.07	707± 2.28	5.03± 1.65	4.46± 1.48
Affective Functioning	5.78± 2.41	6.23 ± 2.79	4.29 ± 2.12	3.54 ± 1.81
N	72	19	43	18
KPS Score (Mean ± SD)	77.2 ± 8.6	76.3 ± 10.7	80.2 ± 3.4	81.1 ± 3.2
N	72	19	43	18
Pain Medication Use (MEDD ± SD)	45.1 ± 76.2	74.6 ± 190.2	0.9 ± 2.5	0.6 ± 0.9
Median	12.6	13.5	0.0	0.2
N	69*	19	43	18
^ Age, BMI, height and weight are missing for one subject. *Medication usage was missing for 3 subjects. **One or more dimensions for tumor volume was missing for 4 subjects.				

Table 10 below shows the cancer characteristics between the study groups by cohort and treatment arms. The higher incidence of breast cancer in the Russian Group reflected the greater percentage of women in that group.

Table 10 - Cancer Characteristics by Cohort and By Treatment Arm				
Variable	**Non Russian Cohort (US/OUS Combined Cohort)**		**Russian Cohort**	
	ExAblate N = 72	**Sham N = 19**	**ExAblate N = 43**	**Sham N = 18**
Primary Cancer Type				
Breast	12 (16.7%)	7 (36.8%)	25 (58.1%)	14 (77.8%)
Prostate	14 (19.4%)	1 (5.3%)	1 (2.3%)	1 (5.6%)
Kidney	8 (11.1 %)	2 (10.5 %)	1 (2.3 %)	0 (0.0 %)
Lung	11 (15.3%)	3 (15.8%)	6 (14.0%)	1 (5.6%)
Multiple myeloma	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other	24 (33.3%)	6 (31.6%)	10 (23.3%)	2 (11.1%)
....Missing	2 (2.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Lesion Type				
Osteolytic	39 (54.2%)	11 (57.9%)	21 (48.8%)	10 (55.6%)
Osteoblastic	22 (30.6%)	3 (15.8%)	3 (7.0%)	3(16.7%)
Mixed	10 (13.9%)	5 (26.3%)	19 (44.2%)	5 (27.8%)
Missing	1 (1.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Target Tumor Location				
Coccyx	1 (1.4%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Acetabulum	8 (11.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Femur	2 (2.8%)	1 (5.3%)	2 (4.7%)	2 (11.1%)
Humerus	2 (2.8%)	0 (0.0%)	1 (2.3%)	0 (0.0%)
Ilium	28 (38.9%)	7 (36.8%)	15 (34.9%)	8 (44.4%)
Ischium	5 (7.0%)	1 (5.3%)	7 (16.3%)	2 (11.1%)
Pubic Ramus	3 (4.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 10 - Cancer Characteristics by Cohort and By Treatment Arm				
Variable	**Non Russian Cohort (US/OUS Combined Cohort)**		**Russian Cohort**	
	ExAblate N = 72	**Sham N = 19**	**ExAblate N = 43**	**Sham N = 18**
Rib	9 (12.5%)	3 (15.8%)	9 (20.9%)	2 (11.1%)
Sacroiliac	1 (1.4%)	2 (10.6%)	4 (9.3%)	0 (0.0%)
Sacrum	8 (11.2%)	3 (15.8%)	3 (7.0%)	2 (11.1%)
Scaula	5 (6.9%)	0 (0.0%)	2 (4.7%)	2 (11.1%)
Sternum	0 (0.0%)	1 (5.3%)	0 (0.0%)	0 (0.0%)
Time from Initial Diagnosis of the Bone Metastasis (Yrs)	1.7 ± 2.2	1.7 ± 1.6	0.7 ± 1.8	0.8 ± 2.3
N	69*	19	43	18
Number Bone Metastatic Lesions ± SD	2.5 ± 1.8	1.9 ± 1.0	1.6 ± 1.6	1.6 ± 1.3
Median	2	2	1	1
Range	(1-10)	(1-4)	(1-10)	(1-6)
N**	52	14	34	16
Number of Distinguishable Painful Lesions	1.4 ± 0.8	1.6 ± 0.8	1.0 ± 0.2	1.1 ± 0.2
Median	1	1	1	1
Range	(1-4)	(1-3)	(1-2)	(1-2)
N	72	19	43	18
*Date of Initial Diagnosis was missing for 2 subjects ** missing patients had unknown number of lesions				

Treatment differences are presented in **Table 11** by geographic cohort. "EDBS" is the level of energy density delivered to the bone/tumor interface which is summed across all sonications and determined post-treatment.

Table 11 - Treatment Characteristics by Cohort for ExAblate Arm		
	Non Russian Cohort (US/OUS Combined)	**Russian Cohort**
EDBS (J/mm^2) (Mean +/- SD)	4.5 + 3.0	6.9 + 2.8
Intra-procedure Sonication Pain (percent AE)	37%	0%
Mean Time Inside Scanner (min) (Range)	175.8± 62.2	126.4.4± 47.4
Mean Sonication Treatment Time (min) (Range)	78.1± 48.5	54.5± 38.8
Mean Intra-Procedure Oxygen Saturation (Range)	97.4± 2.4	96.1± 2.4
Sedation Method	Local/Conscious Sedation	Complete

STUDY RESULTS

Safety Results

The safety analysis (**Table-12 and Table-13**) was performed on a dataset that included all the subjects who received at least one sonication; this data includes ExAblate and sham subjects, and subjects who received sham treatment and were crossed-over to ExAblate treatment. **Table-12** presents the adverse event safety profile for the study per geographic region. In the first column of each group (i.e.: ExAblate or Sham group), the actual number of adverse events experienced is presented by body system and coded term. The second column is the number of subjects experiencing these events and the percent incidence based on the number of subjects in each treatment group as the denominator. It should be noted that the majority of all the events at all geographic regions were either mild or moderate and resolved without sequelae.

As anticipated, the Sham subjects experienced far fewer adverse events during "placebo" treatment. This is consistent across both cohorts. When comparing the events of the ExAblate treatment groups between geographic cohorts, the Russian cohort experienced significantly fewer events than the Non-Russian cohort (US/OUS Combined) (See **Table 12** for more details). Of note, under the intra-procedure "Pain/Discomfort" category events, the Russian cohort did not report any intra-procedure events. This is likely a reflection of the type of sedation/anesthesia used during the treatment procedure for patient management at these centers.

Table-12 Frequency and Prevalence of Adverse Events by Coded Terms, by Cohort and by Treatment Group*									
AE Category		Non-Russian Cohort (US/OUS Combined)				Russian Cohort			
		ExAblate N = 83		Sham N = 19		ExAblate N =50		Sham N =18	
		# Events	# Subjects	# Events	# Subjects	# Events	# Subjects	# Events	# Subjects
At least one AE		77	57 (69%)	1	1 (5%)	5	5 (10%)	0	0 (0%)
No AEs		0	26	0	18	0	45	0	18
Cancer Progression	Death	5	5 (6%)	0	0 (0%)	2	2 (4%)	0	0 (0%)
Cardiovascular	Death	0	0 (0%)	0	0 (0%)	1	1 (2%)	0	0 (0%)
	DVT	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Dermatological	Numbness	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Skin Burn	0	0 (0%)	0	0 (0%)	2	2 (4%)	0	0 (0%)
	Skin Rash	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Muscoloskeletal	Myositis	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Neurological	Cognitive Impairment	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Confusion	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Neuropathy – legs	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Pain/Discomfort	Numbness	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Position Pain	9	9 (11%)	1	1 (5%)	0	0 (0%)	0	0 (0%)

Table-12 Frequency and Prevalence of Adverse Events by Coded Terms, by Cohort and by Treatment Group*									
AE Category		Non-Russian Cohort (US/OUS Combined)				Russian Cohort			
		ExAblate N = 83		Sham N = 19		ExAblate N =50		Sham N =18	
		# Events	# Subjects	# Events	# Subjects	# Events	# Subjects	# Events	# Subjects
	Post Procedure Pain	5	5 (6%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Sonication Pain	42	40 (48%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Respiratory	Apnea	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Skeletal	Fracture	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Systemic	Fatigue	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Fever	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Urological	Blood in urine	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
* the data of this table includes also all the rescue subjects treatment safety data									

Relationship to device or procedure was recorded as Unrelated, Non-significant Anticipated (meaning that the events were transient and minor, but related to the device or procedure, such as transient fever, pain, 1° or 2° skin burn, etc.), and Significant Anticipated (meaning that the event may require treatment or may have sequelae, such as skin burns with ulceration, nerve damage, or conscious sedation complications, etc.).

Events that were deemed to be related to the procedure or the device include 70 events in 55 ExAblate Arm subjects (all regions combined) where relation to the device or procedure was categorized as Non-Significant Anticipated or Significant Anticipated.

Overall, the rate of adverse events in the ExAblate Arm differed between the Non-Russian (US/OUS Combined) and the Russian cohorts primarily due to pain experienced during the procedure. There were a total of 77 events in a total of 57 of Non Russian Cohort subjects (US/OUS Combined) with 48% of these events (in 40 subjects) occurring intra-procedure (Pain/Discomfort related events that were transient and stopped after treatment). By comparison,

5 Russian Cohort subjects experienced 5 adverse events and none of them were Pain related events. Also, the only subjects that experienced skin burns were in the Russian Cohort. This is likely a reflection of the type of sedation/anesthesia used during the treatment procedure for patient management at these two geographic regions (see Table-13 below for more details).

The majority (i.e.: 57%) of all the events in both cohorts were either mild or moderate and resolved without sequelae. By contrast, 27.7% of all the events were sonication induced intra-procedure "severe" pain, and resolved on the day of treatment without sequelae.

Table 13 - Relation of Adverse Events to Device or Procedure by Coded Term, by Cohort and by Treatment Group*

AE category/Name		Non-Russian Cohort (US/OUS Combined)				Russian Cohort			
		ExAblate N = 83		Sham N = 19		ExAblate N = 50		Sham N = 18	
		# Events	# Subjects	# Events	# Subjects	# Events	# Subjects	# Events	# Subjects
RELATED TO DEVICE OR PROCEDURE									
Pain/Discomfort	Sonication Pain	42	40 (48%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Positional Pain	9	9 (11%)	1	1 (5%)	0	0 (0%)	0	0 (0%)
	Post-Procedure Pain	5	5 (6%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Numbness	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Dermatological	Numbness	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Skin pain/skin burn	0	0 (0%)	0	0 (0%)	2	2 (4%)	0	0 (0%)
	Skin rash	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Musculoskeletal	Myositis	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Skeletal	Fracture	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Neurological	Neuropathy	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)

Table 13 - Relation of Adverse Events to Device or Procedure by Coded Term, by Cohort and by Treatment Group*

AE category/Name		Non-Russian Cohort (US/OUS Combined)				Russian Cohort			
		ExAblate N = 83		Sham N = 19		ExAblate N = 50		Sham N = 18	
		# Events	# Subjects	# Events	# Subjects	# Events	# Subjects	# Events	# Subjects
	- leg								
Systemic	Fatigue	2	2 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Fever	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Urological	Blood in Urine	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Subtotal of device or procedure related events		68	53 (64%)	1	1 (5%)	2	2 (4%)	0	0 (0%)
UNRELATED TO DEVICE OR PROCEDURE									
Cancer Progression	Death	5	5 (6%)	0	0 (0%)	2	2 (4%)	0	0 (0%)
Cardiovascular	Death	0	0 (0%)	0	0 (0%)	1	1 (2%)	0	0 (0%)
	DVT	1	1 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Neurological	Cognitive Impairment	1	1 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
	Confusion	1	1 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Respiratory	Apnea	1	1 (1%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Subtotal of Unrelated Events		9	9 (11%)	0	0 (0%)	3	3 (6%)	0	0 (0%)
TOTAL ALL EVENTS		**77**	**57 (69%)**	**1**	**1 (5%)**	**5**	**5 (10%)**	**0**	**0 (0%)**

* the data of this table includes also all the rescue subjects treatment safety data

A total of 71 subjects (53% overall - 26 Non-Russian US /OUS subjects; 45 Russian subjects) experienced no adverse event at all. Of all adverse events experienced that were related to device or procedure, 42 events in 40 subjects (48%, Non-Russian US/OUS cohort) were related to the transient sonication-related procedure pain that resolved by the end of the procedure. Nine (11%) events in 9 Non-Russian US/OUS cohort) subjects were related to positional pain and all other events were less than 6% by category.

There were no unanticipated adverse device effects in this study for subjects in either the ExAblate-treated or Sham-treated groups.

Overall, a total of four Significant Anticipated events occurred including one event of skin burn (third degree burn of 3 cm area), one event of leg neuropathy (leg pain after treatment), and two events of fracture (inherent complication of bone metastases regardless of their treatment or non-treatment).

One serious adverse event reported as "possibly" related to the device or procedure was reported in this study. Three weeks after the ExAblate procedure the subject twisted their foot and experienced a pelvic fracture. Bone fractures are known and frequent complications of the disease process for bone metastases; fractures can also result from radiation therapy which may have been a pre-study failed therapy. Although this event was likely an expected result of disease progression and twisting of the leg, the potential involvement of treatment cannot be entirely ruled out. Thus, this fracture was classified as possibly device related.

Nine additional serious adverse events in nine ExAblate Arm subjects were reported as unrelated to treatment and related to progression of the subject's cancer or other causes in one case. Seven of these events were progression of cancer that resulted in death, and one other death resulted from a heart condition. The ninth event was of a subject experiencing cognitive impairment due to a brain metastasis.

Effectiveness Results

Primary Effectiveness Endpoint

The ITT efficacy analysis was conducted on the group of subjects who met treatment criteria of at least 4 sonications per protocol. Subjects were considered "Responders" if they demonstrated at least a 2-point improvement on the 0-10 pain Numerical Rating Scale (NRS) from Baseline to Month 3 and no more than a 25% increase in opioid pain medical intake (in units of morphine equivalents).

Primary endpoint responders of **Table 14** show greater improvement in the ExAblate arm than Sham arm in both geographic cohorts. The Russian Cohort had the highest responder rate in the ExAblate Arm, 90%, which was significantly greater than for the Russian subjects in the Sham Arm, 13% ($p<0.0001$). The Non-Russian Cohort (US/OUS Combined) ExAblate responder rate was 55%, significantly greater than the 26% responder rate in the Sham ($p=0.04$) and is very close to that assumed *a-priori* in the protocol for calculating power. The ExAblate responder rates were strong in both geographic cohorts, (approximately twice that of Sham responder rates).

The statistical significance of the effectiveness in non-Russian subjects is highly sensitive to assumptions about missing data, but when considering data across geographic cohorts, then the data is quite robust.

Table 14 - Proportion of Responders by Geographic Cohort and Treatment Group

Site	N	% Responders (n/N)		p-value
		ExAblate	Sham	
Non-Russian Cohort (US/OUS combined)*	83	55% (35/64)	26% (5/19)	0.04
Russian Cohort	56	90% (36/40)	13% (2/16)	<0.0001

* This analysis is based on the agreed upon ITT population. However, if the analysis includes subjects in screening failure 3 group (see Table 8), the result for the non-Russian cohort is as follows: N=88, % ExAblate Responders=51% (35/69), % Sham responders=26% (5/19).

It should be noted that the ExAblate was already marketed in Russia for pain palliation of metastatic bone cancer at the time of this clinical trial. Russian investigators were more likely to use a patient management approach that involved deeper sedation/anesthesia which permitted them to respond to the real time thermal feedback to achieve thermally ablative temperatures at the bone/tumor interface without patient complaint. Physician training will emphasize the need for adequate pain control to permit the treating physician to utilize the appropriate energies in response to the real time thermal feedback to achieve ablative temperatures at the bone/tumor interface.

Secondary Effectiveness Endpoints

Quality of life (QoL)

The BPI pain interference results were analyzed in terms of the overall score and also for the affective (mood and relationships) and physical functioning subscales. As shown in **Table 15**, the quality of life (BPI-QoL) secondary analyses, show significantly greater improvement in the ExAblate Arm than Sham Arm at all geographic regions. Furthermore, all geographic regions show a mean change from baseline in the ExAblate Arm was greater than 2 points over Sham Arm, indicating that the improvement was clinically significant.

The overall BPI average score in the ExAblate treated group decreased from 5.7 at baseline to 3.6 at the 2 Week visit and remained at 3.3, 3.1 and 3.3 at the 1 Month through 3 Month visits respectively. The baseline average BPI for the Sham control group was 5.7 at baseline and 4.7, 4.6 and 5.0 at the 1 Month through 3 Month visits respectively.

Table 15 - BPI-QoL by Geographic Cohort and Treatment Arm				
Cohort	**N**	**Change From Baseline**		**p-value**
		ExAblate	**Sham**	
Non-Russian Cohort (US/OUS combined)	83	2.19	0.74	0.048
Russian Cohort	56	2.66	-0.48	<0.0001
Note: A change of 1 points on the BPI-QoL is clinically significant; the "-" sign indicate worsening of QoL				

NRS Score

As shown in **Table 16** below, NRS scores also showed greater improvement in ExAblate Arm than Sham Arm at all geographic regions, with results reaching significance in the Non-Russian Cohort (US/OUS combined) and Russian Cohort. In all cohorts, ExAblate Arm mean improvement was above the 2-point threshold for clinical significance, while in none of the cohorts was Sham Arm close to clinical significance.

Table 16 - Numerical Rating Scale by Geographic Cohort and Treatment Group				
Sites	**N**	**Change From Baseline**		**p-value**
		ExAblate	**Sham**	
Non-Russian cohort (US/OUS combined)	83	3.17	1.32	0.04
Russia cohort	56	4.80	0.13	<0.0001
Note: A change of 2 points on the NRS is clinically significant.				

Pain Medication Use

Opioid pain medication use, measured in morphine equivalent daily dose, was one of the composite measures for determining Responder status in the primary efficacy endpoint (**Table 17**). All Responder subjects stopped, reduced, or maintained their medication usage. These results were observed while the subjects also demonstrated a clinically significant reduction in pain (2 or more points on the NRS).

Table 17 - Opioid Medications Use at Month 3 Compared to Baseline for all Responder ExAblate Subjects by Cohort				
	Non-Russian Cohort (US/OUS combined) N = 35		Russian Cohort N = 36	
	N	%	N	%
Pain Meds Stopped	10	29%	9	25%
Pain Meds Reduced	10	29%	2	6%
No Change in Pain Meds	15	43%	25	69%
Total	35	100%	36	100%

When comparing the Pain Medications Use in Morphine Equivalent Units by Time Point in the ITT Population for sham and test groups, the result favors treatment as these patients did not increase their pain medication requirements.

Seventeen Sham subjects opted to receive a Rescue treatment using the ExAblate. Of these 17 subjects, 13 were considered Responders to ExAblate treatment (76.5% Responder rate, Rescue Arm) while 4 were Non-Responders. These subjects were unblinded, but the result here shows a similar pattern to the blinded portion of the study. All adverse events experienced by the Rescue subjects were included in the safety analysis.

Overall Treatment Effect (OTE)

Overall treatment effect measured the subject's opinion of the effect (better, same, worse) the treatment has had on their well-being. The question asks the subject to rate this as compared to their last visit, not with baseline or pre-treatment.

In general, the ExAblate Arm showed continuing improvement visit to visit until it begins to stabilize by Month 3. The Sham subjects generally showed No change or Worsening from Week 1 through Month 3 with Worsening becoming more evident.

EQ-5D

This study utilized the descriptive component of the EQ-5D for the five subscales of mobility, self care, usual activities, pain/discomfort and anxiety/depression.

The ExAblate Arm showed clinically significant improvements in all 5 categories. The Sham, in contrast, showed subjects mostly stayed the same and 15-23% actually worsened in a category. All of the questionnaire items except for mobility demonstrate greater improvement in health in the ExAblate Arm than in the Sham Arm as compared to Baseline, particularly the later in time the assessment was performed.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST PANEL ACTION

Due to the specific end-of-life population and the overwhelming benefit demonstrated in the clinical trial, there were no clinical issues warranting comments from an Advisory Panel. This application was not referred to the General and Plastic Surgery Devices Advisory Panel for review and recommendation.

XII. CONCLUSIONS DRAWN FROM THE STUDIES

Effectiveness Conclusions

The results of the present analyses provide reasonable assurance of efficacy and meet the pre-specified criteria for success. The Russian Cohort had the highest responder rate in the ExAblate Arm, 90% (36 subjects), which was significantly greater than for the Russian subjects in the Sham Arm, 13% (2 subjects) ($p<0.0001$). The Non-Russian Cohort (US/OUS Combined) ExAblate responder rate was 55% (35 subjects), significantly greater than the 26% (5 subjects) responder rate in the Sham ($p=0.04$). The ExAblate responder rates were strong in both geographic cohorts, and are much greater than the study hypotheses of the clinically relevant threshold of at least 50%.

When looking at the secondary endpoints, measuring quality of life issues, there was an improvement seen in all variables favoring the treated group.

It is noted that only one patient with multiple myeloma was treated in this trial and it was reported as a non-responder. With this information, it is difficult to determine what the effect of this device may have in this sub-population. Further study is needed to determine if this device is safe and effective for this subpopulation.

Safety Conclusions

The risks of the device are based on data collected in clinical studies conducted to support PMA approval as described above.

The most commonly reported AE was due to pain with treatment. There were a total of 77 events in a total of 57 Non-Russian Cohort subjects with 48% of these events (in 40 subjects) occurring intra-procedure (Pain/Discomfort related events that were transient and stopped after treatment). By comparison, 5 Russian Cohort subjects experienced 5 adverse events and none of them were Pain related events. The majority (i.e.: 57%) of all the events in both cohorts were either mild or moderate and resolved without sequelae. By contrast, 27.7% of all the events were sonication induced intra-procedure "severe" pain, and resolved on the day of treatment without sequelae. Also, the only subjects that experienced skin burns were in the Russian Cohort.

A total of four Significant Anticipated events occurred including one event of skin burn (third degree burn of 3 cm area), one event of leg neuropathy (leg pain after treatment), and two events of fracture (inherent complication of bone metastases regardless of their treatment or non-treatment).

One serious adverse event reported as "possibly" related to the device or procedure was reported in this study. Eight deaths in ExAblate Arm subjects were reported as related to progression of the subject's cancer or other causes in one case, and unrelated serious adverse events to treatment.

There were no unanticipated adverse device effects in this study for subjects in either the ExAblate-treated or Sham-treated groups.

Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above. The main risk of using the device is intra-procedure pain that is often transient in nature and resolved on day of treatment. This may be mitigated with appropriate level of intra-procedure sedation. There is also a slight risk of bone fracture that is often induced by the underlying disease process. Meanwhile, the expected benefit is a reduction in pain over the course of three months, as well as improved quality of life and reduction in pain medication intake over the three months. The device does not increase the life expectancy or treat the disease in any way. Given the available information above, the data supports that, for palliation of pain associated with metastatic lesions in bone for radiation failure patients, the probable benefits outweighs the probable risks.

Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

For this population of patients suffering from bone pain due to metastatic disease, who are failures of standard radiation therapy, or who are not candidates for radiation, or who refuse radiation therapy, the ExAblate treatment is a reasonable alternative to existing treatments. The result from the pivotal study appears efficacious and the safety profile is reasonable and does not cause any increased risks for this population already at significant risk due to the underlying disease process.

In conclusion, the treatment benefits of the device for the target population outweigh the risks of diseases when used in accordance with the directions for use.

XIII. CDRH DECISION

CDRH issued an approval order on October 18, 2012.

The applicant must conduct two Post-Approval Studies to evaluate device performance under actual conditions of use and to further evaluate device safety.

1. *New Enrollment Study*: The applicant must perform a post-approval study (PAS) to evaluate the safety and effectiveness of the ExAblate system when the device is used in the intended patient population under actual conditions of use. This study will be a prospective, multi-site, single-arm cohort study with a total of 70 patients enrolled who meet the indications for use and

are treated with the ExAblate system a7 to 10 sites. Office visits will occur at 1-week, 1-month, 2-months and 3-months post-treatment. Safety will be evaluated by collecting the incidence and severity of device-related complications starting at the first treatment day visit through the 3-months post–treatment time point. The primary effectiveness endpoint will be the proportion of responders in terms of pain relief, which will be captured in a patient based pain assessment using a 0-10 pain Numerical Rating Scale (NRS) with anchored points in conjunction with a body diagram. "Pain relief" complete response will be defined as a pain score of zero (0) at the treated site without increase in analgesic consumption. "Pain relief" partial response will be defined as a reduction of 2 points on a 0–10 scale at the treated site without increase in the analgesic consumption. Response will be analyzed at 3 months. 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%). Pain medication use and quality of life will be analyzed as secondary endpoints. Quality of life will be determined by the Brief Pain Inventory - Quality of Life (BPI-QoL) score. 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 hypothesis. The Agency expects that at least 85% follow-up will be achieved.

2. *Enhanced Surveillance Registry Study*: The applicant must perform a two-year enhanced surveillance registry study ("ESRS") of the Exablate System to more fully characterize adverse events when the device is used in a broader patient population in a real world setting. The purpose of this ESS is to collect information regarding adverse events that are possibly related to the ExAblate System ("ExAblate") that are received by InSightec ("InSightec") following PMA approval. Information regarding the total number of subjects treated with the device at each participating site will be collected. All patients planned to undergo the ExAblate procedure in a commercial setting will be asked to consent for participation in the ESRS. . Information to be collected will include all adverse events possibly related to ExAblate device regardless of whether the event would qualify as an MDR. For patients having adverse events, information collected will include patient characteristics, cancer characteristics, bone metastasis characteristics, treatment parameters (including number of lesions treated and re treatments), concomitant treatments, event onset, severity and resolution. A descriptive analysis of reported adverse event rates will be provided. There are no scheduled follow-up visits for the subjects in this Registry.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Patient information: See patient labeling.

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.