CLINICAL PROTOCOL

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Protocol Number	**PCa003**
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Protocol Title	**Focal MR-Guided Focused Ultrasound Treatment of Localized Intermediate Risk Prostate Lesions**

Approvals:

Site	Sponsor
Principal Investigator Date Date	Nadir Alikacem, PhD 10/24/18 VP Regulatory - InSightec Date

A Pivotal Study to Evaluate the Safety and Preliminary Effectiveness of Focal MR-Guided Focused Ultrasound Treatment of Locally Confined Intermediate Risk Prostate Lesions

The goal of this study is to develop data to evaluate the safety and effectiveness of focal MRgFUS treatment of intermediate risk prostate lesions.

Protocol Number: PCa003

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1 BACKGROUND and SIGNIFICANCE

1.1 MR Guided Focused Ultrasound Treatment of Prostate Lesions

"ExAblate" by InSightec is a device for **MR G**uided **F**ocused **U**ltra**s**ound Surgery (MRgFUS). It is a non-invasive thermal ablation device that is integrated with an MR Imaging system to allow real time controlled ablation of tissue (1, 5). Physician acquires a set of MR images, identifies one or more target volume(s) of tissue to be treated, and draws the treatment contours. Therapy planning software calculates type and number of sonications (a sonication is an acoustic transmission burst of 5sec to 50sec) required to completely treat defined region while minimizing total treatment time. During treatment, a small 'bean' shaped volume of focused ultrasound energy is directed into the target for 5-50 seconds and heats the tissue to temperatures around 65°-85°C to induce thermal coagulation. MR images taken during sonication provide visualization of the target tissue and a quantitative, real-time temperature map overlay to confirm therapeutic effect of the treatment (2). The transducer is then automatically moved to a succeeding treatment point and the process is repeated until the entire target volume has been treated. Typically, ~15 - 200 individual sonications can be delivered over a 2 to 3 hours period to complete a treatment.

In recent studies, the ExAblate **MR g**uided **F**ocused **U**ltra**s**ound **S**urgery (MRgFUS) has been evaluated as a source of controlled thermal energy for coagulation of benign and malignant tumors. Specifically, InSightec has completed pivotal study for the use of MRgFUS to treat uterine fibroids and gained FDA-PMA approval for this application at October 2004 (3) under PMA number P040003. In addition, feasibility studies at several sites are done to evaluate the use of MRgFUS for treatment of benign and malignant tumors such as breast cancer and brain tumors, and a pivotal study for treatment of bone metastatic tumors (4).

Furthermore, this system gained both AMAR authorization (Israel Ministry of Health) and CE (European and others) approval for the indication of treating Uterine Fibroids for Bone Mets Palliation.

1.2 Prostate Cancer

In 2009, the American Cancer Society (ACS) estimated that 194,032 new cases of prostate cancer were diagnosed in the United States. This 2009 census of the American Cancer Society reported cancers of the prostate were the most frequently diagnosed cancers in men followed by lung and colorectal cancers.[1] Approximately 1 in 6 men will be diagnosed with prostate cancer during his lifetime, but only 1 in 34 will die of this disease. Over 1.8 million men in the United States are survivors of prostate cancer.

Prostate cancer is the second leading cause of cancer death in American men, exceeded only by lung cancer. The American Cancer Society estimates that 26,328 men in the United States will die of prostate cancer during 2009. Prostate cancer accounts for about 9% of cancer-related deaths in men.

Most prostate cancers grow slowly. Autopsy studies show that many older men who died of other diseases also had a prostate cancer that never affected them and that neither they nor their doctor were aware of. Over 60% of men between ages 60 and 70 will have prostate cancer detected at autopsy. That number climbs to 80% for men in their 80's. Some prostate cancers, however, can grow and spread quickly. Among men diagnosed with prostate cancer, about 99% survive at least 5 years, 92% survive at least 10 years, and 61% survive at least 15 years. These figures include all stages and grades of prostate cancer but do not account for men who die from other causes.

Ninety percent of all prostate cancers are found in the local and regional stages (local means it is still confined to the prostate; regional means it has spread from the prostate to local nodes nearby areas, but not to distant sites such as bone). Of the men whose prostate cancers have already spread to distant parts of the body at the time of diagnosis, about 34% will survive at least 5 years.

Today's prostate cancer screening methods often result in the detection of prostate cancer that is not clinically significant in many patients (i.e., if left untreated, prostate cancer would not threaten health). Traditionally, men diagnosed with localized low risk prostate cancer are required choosing between two therapeutic options, either radical surgery with almost certain impairment in quality of life (i.e., genitourinary dysfunction), or active surveillance, with the risk of disease progression involving significant burden to the patient and health care systems, as well as long-term psychological pressure. It has been shown that about 90% of the patients under active surveillance will eventually undergo some kind of radical treatment. The aim of focal treatment is combining adequate tumor control while avoiding unnecessary treatment related complications. This patients' population will be monitored over time with reasonable criteria for intervention, which will identify more aggressive disease in a timely fashion while avoiding excessive treatment when not required. (14, 15).

Current treatment options and their post treatment concerns are listed below in Table 1.

[1] American Cancer Society – 2009. www.cancer.org

Table 1 Current treatment options for prostate cancer

Procedure	Description	Concerns
Active Surveillance (AS)	Monitoring PCa without administering any treatment until disease progression	Quality of life, risk of cancer progression and metastases without detection.
Radical Prostatectomy	Surgical procedure to remove prostate, surrounding tissue and nearby lymph nodes	Major surgical procedure with early and possibly lasting side effects of impotence and incontinence
Radiation Therapy	External beam radiation (EBRT) therapy uses a radiation source outside the body to irradiate the cancer. Internal radiation therapy uses a radiation sources sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer.	Delayed onset impotence and rarely incontinence, questions about long term toxicity. Post radiation colitis
Hormone Therapy	Suppression or blockage of male hormones (androgen) effects, to stop cancer cells from growing.	Hot flashes, night sweats, impaired sexual function, loss of desire for sex, osteoporosis.

One of the most active areas of prostate cancer treatment research is in the field of high intensity focused ultrasound (HIFU), utilizing trans-rectal ultrasound imaging to image the prostate gland and plan the treatment (6, 7). However, since ultrasound imaging is generally unable to visualize cancerous foci, treatment strategy used with ultrasound (US) guided HIFU is to ablate the entire prostate, or roughly base the treatment volume on pre-diagnosed cancer (by mapping biopsy and multi-parametric MRI). Unfortunately, this often results in inadequate tumor control or over-ablation of unnecessary normal tissue with subsequent genitourinary toxicity.

First reported use of US guided HIFU in human prostate cancer was by Mandersbacher et al in 1995 (8), it showed feasibility of the procedure in ten patients. In a study performed by Gelet et al, 50 patients were treated and followed up for 24 months duration. These patients also received subsequent radiation treatment (9). Among these patients, 56% were cancer free at the time of follow-up. Treatment device used in this study underwent two iterations – first had a 50% complication rate, the second had a 17% complication rate. In another paper by Gelet et al, incontinence and impotency rates were recorded as 14% and 61% respectively at 19 months post-treatment. In both studies, total procedure time was long due to the number of sonications required to cover entire prostate and inability to monitor temperatures. MR thermal monitoring and localization of lesions/zones within prostate should allow optimization of treatment rate while monitoring and improving safety.

In a study by Uchida et al (10), transrectal probes utilized for ultrasound guided HIFU have been used to treat large areas of the prostate – however, lack of urethral or rectal cooling methods and lack of real time thermometry resulted in overheating of normal tissues. This resulted in urethral strictures, urinary retention and rectal fistula. Part of this was later addressed by addition of rectal cooling however; real time thermometry is currently impossible with ultrasound imaging.

These previous studies have shown effectiveness of focused ultrasound for use in treating lesions despite significant adverse events. InSightec has reason to believe that MRI as an imaging modality can be used to (a) identify localized prostate lesions in some of the patients (b) identify nerve bundles (c) using MR thermometry to prevent overheating of non-targeted tissues and verify treatment of targeted tissue. Therefore, MRgFUS has the potential of treating localized prostate lesions (instead of the entire prostate), while preventing/reducing the risk of incontinence and impotence.

1.3 Rationale for Focal Therapy

Historically, definitive treatment of solid lesions included whole-gland extirpation with radical surgery. For many organ systems, outcome data have supported more selective, organ-sparing, or even ablative therapies, such as breast-conservation surgery and less extensive surgery for melanoma. [2,3]

Similar trends have been witnessed in urologic oncology. Historically, standard treatment for all solid renal masses was radical nephrectomy. Within the past decade, cancer control following partial nephrectomy has been shown to be equivalent for lesions<4 cm, with the benefit of preserving renal function. [4,5]

Once established as an accepted treatment for smaller lesions, investigators have subsequently shown similar outcomes following partial and radical nephrectomy in patients with masses ≤7 cm.[6] Likewise, partial cystectomy has proven effective for the treatment of bladder cancer in appropriately selected patients. Prostate lesion ablation may be amenable to organ-sparing, focal treatment. Prostate is a small, easily accessible organ, and many urologists are familiar with performing image-guided procedures in the gland through the rectum, perineum, or urethra. Intuitively, treatment would be required solely at the area of lesion with lesion free margins, limiting collateral damage to normal tissue. While the potential of such therapies makes them attractive, the ramifications of treatment failure bear considerable forethought in the development of focal treatment trials. The issues of patient selection, appropriate targeting of lesions, and impact of focal treatments on outcome with salvage surgical or radiation treatment all deserve consideration. Criteria for follow-up and patient evaluation, as well as indications for repeat treatment, also remain to be standardized.

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[2] Morris AD, Morris RD, Wilson JF, White J, Steinberg S, Okunieff P, Arriagada R, Le MG, Blichert-Toft M, van Dongen JA. Breast-conserving therapy vs mastectomy in early-stage breast cancer: a meta-analysis of 10-year survival. Cancer J Sci Am 1997;3:6–12.

[3] de Braud F, Khayat D, Kroon BB, Valdagni R, Bruzzi P, Cascinelli N. Malignant melanoma. Crit Rev Oncol Hematol 2003;47:35–63.

[4] Fergany AF, Hafez KS, Novick AC. Long-term results of nephron sparing surgery for localized renal cell carcinoma: 10-year followup. J Urol 2000;163:442–445.

[5] Lee CT, Katz J, Shi W, Thaler HT, Reuter VE, Russo P. Surgical management of renal tumors 4 cm. or less in a contemporary cohort. J Urol 2000;163:730–736.

[6] Leibovich BC, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Nephron sparing surgery for appropriately selected renal cell carcinoma between 4 and 7 cm results in outcome similar to radical nephrectomy. J Urol 2004;171:1066–1070

The role for focal therapy in the treatment of prostate lesions may be most applicable to patients with lesions that pose little risk of progression, as long as the treatment has minimal effect on quality of life and does not adversely impact survival. Focal ablation of the index lesion, or of the sector of the prostate that harbors that lesion, could be very attractive for patients with intermediate-risk lesions who are uncomfortable with the risks associated with active surveillance and the side effects of radical therapy. The unanswered questions are whether appropriate candidates can be identified, whether the index lesion can be reliably identified and characterized while excluding higher-grade lesions, and whether focal ablation can reliably target and destroy the index lesion with few complications and side effects. Even with effective treatment, such patients will have to be followed closely after focal therapy, since they may be at high risk for developing another lesion in the prostate. Ultimately, benefits of focal therapy will need to be proven with a randomized clinical trial comparing focal ablation to active surveillance or radical therapy. With these considerations in mind, a patient best suited for focal therapy would have a well localized, targetable lesion of relatively small volume with a low-to-intermediate risk of spread and compliant with follow-up including repeat prostate biopsy procedures.

One option for focal treatment that appears to meet several of these criteria is MRgFUS therapy, which involves a thermal treatment with relative sparing of tissue outside of the treatment field. The advantages of MRgFUS are the ability to specifically target identified lesions due to the energy delivering mode that spares the structures on the way between the energy source and the target, and due to the good anatomical visualization of the target and its surroundings. The real-time MR thermometry allows closed loop monitoring and controlling the treatment to ensure selective and adequate lesion ablation.

1.4 The ExAblate System

The ExAblate system is a non-invasive thermal ablation device that has been used for ablation of tissue. This system combines a focused ultrasound surgery (FUS) delivery system and a conventional diagnostic 1.5T or 3T MRI scanner. ExAblate system provides real-time therapy planning algorithm, thermal dosimetry, and closed-loop therapy control. Later is achieved by utilizing the unique interactive MRI scan control features of 1.5/3T MRI system manufactured by General Electric. FUS device is fully integrated into the MR system and cradle. Subject is placed on the MRI table/cradle and moved into the MRI scanner.

The treatment process begins with physician acquiring a set of MR images, identifying target volume(s) of tissue to be treated, and drawing treatment contours. The therapy planning software computes the type and number of sonications required to treat defined region while minimizing total treatment time. MR images taken during the actual sonications provide quality diagnostic image of target tissue and a quantitative, real-time temperature map overlay, to confirm therapeutic effect of the treatment. The focus is then automatically moved electronically or mechanically to succeeding treatment point and the process is repeated until entire volume has been treated. Typically, 15 to 200 individual sonications can be delivered over a 2-3 hours period to complete a treatment.

The ExAblate 2000 system received FDA approval for the treatment of Uterine Fibroids in October 2004 (PMA # P040003). Furthermore, this system gained both Israeli (AMAR) authorization and European (CE) approval for the indication of treating uterine fibroids. In December 2009, FDA approved the ExAblate 2100 System for treatment of women with uterine fibroids. ExAblate 2100 is a multi-application MRgFUS (Magnetic Resonance guided Focused Ultrasound) system platform, designed to work with GE's 1.5T and 3.0T MR line of scanners. The designation of "2100" is to differentiate the system that has a fixed cradle (ExAblate 2000) from the system with a detachable cradle (ExAblate 2100). All the features (system HW and SW) that were part of the 2000 system are still part of the 2100 system. This cradle change became necessary to accommodate the new clinical applications such as the one for prostate cancer. A full description of the ExAblate 2100 Prostate System is provided in the Investigator Brochure, along with relevant preclinical and clinical testing to provide reasonable assurance of potential benefit and safe use in patients with localized, and intermediate- risk prostate lesion.

1.5 Prior Studies

1.5.1 Focal Treatment for Low-Risk Locally Confined Prostate Cancer - Pilot Study

InSightec conducted pilot studies at the NN Petrov Institute of Oncology, St. Petersburg, Russia, and National Cancer Center in Singapore General Hospital, Singapore to evaluate the safety and preliminary effectiveness of the ExAblate Prostate System for focal treatment of locally confined, low-risk prostate cancer. The actual study protocols are similar to the proposed study protocol. To date, 14 treatments were performed in these two centers and recruitment is ongoing. Additional details are summarized in the Investigator Brochure.

In Sapienza University of Rome, Italy an investigator initiated and sponsored study comprising of focal treatment with subsequent prostatectomy and pathology evaluation is conducted – results are not available for Company's analysis.

In Jaslok Hospital, Mumbai, India - a near-total gland MRgFUS ablation clinical trial is performed. To date only 3 patients were treated.

2 OBJECTIVES

2.1 Background

Objective of this trial is to assess safety and effectiveness of ExAblate MRgFUS in the treatment of intermediate risk, localized (organ confined) prostate lesions. Investigators selected for the study will be trained on proper use of the ExAblate system (**Appendix B**).

ExAblate treatment will be implemented as a focal lesion-selective therapy, directed at pre-defined volume(s)/sector(s) in the prostate, identified abnormal by mapping biopsy and multi-parametric MRI), rather than a whole gland or hemi-ablation treatment.

> ***Safety:*** *evaluate incidence and severity of adverse events associated with ExAblate's MRgFUS focal treatment of intermediate risk organ confined prostate lesions. The risk of ExAblate treatment–related incontinence and impotence will also be assessed in this study.*

Effectiveness: *determine the lesion control effect of ExAblate's MRgFUS focal treatment of intermediate risk organ-confined prostate lesion (confirmed by IMAGE-guided mapping biopsy results).*

The proposed study is to evaluate the preliminary effectiveness and safety of the ExAblate 2100 Prostate System for focal treatment of patients with intermediate risk, localized prostate lesions. Study results will be submitted to FDA as previous discussions with the Agency in a 510k for commercial clearance.

Per FDA requirement, the full 510K submission will be performed following the last treated subject completing their 12-Months visit. Assessments of primary efficacy endpoints will compare the 6-months after ExAblate treatment to Baseline measurements. Safety of ExAblate Prostate treatment will be collected for one year after ExAblate.

It should be noted that all patients will be consented and followed up all the way to 24-Months post treatment.

This study will allow any IMAGE-guided biopsy methodologies (transrectal or transperineal) of 14 cores or more to be used for baseline lesion localization and characterization and for follow-up, but the methodology used should be consistent at all time points for each subject. Successful lesion ablation by ExAblate would result in no residual and/or recurrent lesion at the 6 or 24 month follow-ups. Additional biopsies may be performed between 6- month follow-up visits if judged to be clinically indicated by the investigator.

Post-therapy changes from Baseline to 24 months will be assessed for PSA levels along with results of the patient completed FACT-P (Version 4), ICIQ-SF, IPSS, IIEF-15 and SF12 questionnaire. See Section 5 for the full schedule of events.

Biopsy mapping must be performed to localize the region of interest for the focal ExAblate treatment. The standards of performing biopsy will follow site specific mapping procedures, but the procedure must meet the minimum study guidelines for a 14 core mapping biopsy where 2 of these biopsies are directed anteriorly on the right and left hemi-gland as discussed in **Appendix C**.

2.1.1 Prostate glands should be delineated into at least 14 sectors.

Pathology results will be performed by the center's pathology group according to their standard protocol, but cores must be individually labeled by anatomical location for mapping purposes.

An ExAblate treatment's target volume/ROT (Region of Treatment) will be defined as an intra-prostatic volume containing a lesion that was identified by positive 14 core IMAGE-guided mapping biopsy where 2 of these biopsies are directed anteriorly on the right and left hemi-gland.

The goal of the ExAblate MRgFUS treatment is to completely ablate the lesion, while sparing crucial structures; i.e., rectal wall, external sphincter, bladder wall, and optionally the urethra and one or both neurovascular bundles.

Biopsy-confirmed lesions that are visible on T2w MRI will be treated based on MR visualized lesion margins with surrounding 5 mm lesion-free margins, wherever clinically applicable (i.e., treatment will not include 5 mm lesion free margins if these extend into structures to be spared (e.g., rectal wall, external urethral sphincter, bladder wall, etc.)

When a single lesion extends into an adjacent sector, both sectors will be treated.

Overall treatment volume should be up to 50% of the prostate gland for prostate volume <60cc, and up to 30cc should the entire prostate volume be larger than 60cc and avoid as much as possible vulnerable structures.

Consented and enrolled patients will be assessed for eligibility by undergoing 14 core or more mapping biopsy will use a standard template (such as described in Appendix C, as an example) by either transperineal or transrectal access where 2 of these biopsies are directed anteriorly on the right and left hemigland. Biopsy tissue specimens at screening and post-treatment will be processed and analyzed locally at each clinical site, for determining study eligibility and individual patient care throughout the study. Patients with positive pre-treatment biopsies and correlating multi-parametric MR findings meeting all other inclusion and exclusion criteria may be enrolled into the study.

This proposed study will be a prospective, single arm study of a minimum of 100 and a maximum of 103 patients treated at up to 15 sites.

Study will be performed utilizing either 1.5T or 3T MR scanners with a torso P/A or cardiac P/A coil. MR imaging at screening may include an endorectal coil.

Follow-up will focus on device- or procedure-related adverse events for primary safety analysis. Efficacy will be based on outcomes of mapping biopsy outcome at the 6 month follow-up period or sooner per future discussion(s) with the FDA for the 510K submission.

2.1.2 Regulatory history of the IDE (IDE # G100108) study

The current IDE has had 4 amendments to date. The 4th Amendment aim was to define the patient population that will be part of the 510K submission (IDE G100108/S011). To ensure a cohesive patient population for the 510K FDA review, only those patients treated after site IRB approval of Amendment 4 will be counted toward the primary analysis population. Other safety and efficacy analyses that include data from subjects enrolled prior to the approval of G100108/S011 may be reported as supplementary information.

To date (Sept-20-2018), 81 patients have been treated under protocol Amendment-4.

2.2 Safety

Safety of ExAblate MRgFUS for focal treatment of intermediate risk organ-confined prostate lesion will be determined by evaluation of incidence and severity of device/treatment related complications from treatment day visit through the 24-month follow-up.

2.3 Effectiveness

Results of prostate mapping biopsies will be used to assess lesion control achieved by the treatment.

Post-treatment PSA, non-perfused volume (NPV), FACT-P (Version 4), ICIQ-SF, IPSS, IIEF-15 and SF12 questionnaire results through Month 24 visit will be summarized as secondary measures of effectiveness.

2.3.1 Central Pathology Assessment

To assist in evaluating effects of ExAblate focal therapy for prostate lesion, this study is utilizing a central pathology lab to standardize interpretation of post-treatment effects. If Gleason graded tumor is identified in the 6 month biopsy in the treatment zone of the specimen, then it will be sent to a central pathology lab for confirmation and grading. If a discrepancy is reported between the site and the lab, then the judgment of the central pathology lab will take precedence. Decisions about patient eligibility and post-treatment care will be determined by the local site principal investigator, based upon results of the site pathological findings and clinical examination.

2.4 Study Hypothesis

The hypothesis of this study is that focal treatment with ExAblate MRgFUS has the potential to be an effective non-invasive treatment for intermediate risk, organ-confined prostate lesions, with a low incidence of morbidity. The study hypothesis will be tested by measuring treatment-related safety and effectiveness parameters in the ExAblate MRgFUS treated patients, as described above.

3 DESCRIPTION OF PATIENT POPULATION

This study involves patients with organ-confined, intermediate risk prostate lesions for treatment with the ExAblate 2100 Prostate System.

3.1 Subject Enrollment

Patients will be counseled concerning the research nature of this study, including potential risks and benefits associated with participation in the study. Patients providing written informed consent will be screened for study eligibility.

3.2 Inclusion Criteria

1. Male subjects age 50 and older.
2. Biopsy proven adenocarcinoma of the prostate (using a IMAGE-guided 14+ core mapping biopsy), and targeted cores as needed obtained up to 6 months prior to scheduled treatment.
3. Patient with intermediate risk, early-stage organ-confined prostate cancer (T1a up to T2b, N0, M0) and voluntarily chooses ExAblate thermal ablation as the non-invasive treatment, who may currently be on watchful waiting or active surveillance and not in need of imminent radical therapy.

4. Patient with PSA less than or equal to 20 ng/mL
5. Gleason score r 7 (4 + 3 or 3 + 4), based on mapping prostate biopsy, with no more than 15mm cancer in maximal linear dimension in any single core.
6. Single hemilateral index Gleason 7 lesion, identified in the prostate based on biopsy mapping with supporting MRI; may have secondary Gleason 6 lesion on ipsilateral or contralateral side confirmed with biopsy and/or MRI.
7. Gleason 7 tumors must be MRI visible:
    a. In the event that a tumor is in contact with the capsule, the length of the contact should be ≤ 5 mm, on axial images.
    b. Largest imaging dimension of cancerous finding < 20-mm
8. No definite evidence of extracapsular extension or seminal invasion by MRI
9. Patient should be eligible for both spinal/epidural anesthesia (planned procedure), and general anesthesia (in case of complication, requiring intervention).
10. Patient is willing and able to give consent attend all study visits and complete all questionnaires as defined in the protocol
11. Tumor distance, including tumor free margins, should not be more than 40mm from the rectal wall.

3.3 Exclusion Criteria

1 ASA status > 2

2 Contraindications to MRI

2.1 Claustrophobia

2.2 Implanted ferromagnetic materials or foreign objects

2.3 Known intolerance to the MRI contrast agent

3 Severely abnormal coagulation (INR>1.5)

4 Patients with unstable cardiac status including:

4.1 Unstable angina pectoris on medication

4.2 Patients with documented myocardial infarction within 40 days prior to enrolment

4.3 Congestive heart failure NYHA class IV

4.4 Patients with unstable arrhythmia status, already on anti-arrhythmic drugs

5 Severe hypertension (diastolic BP > 100 on medication)

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

7 History of bilateral orchiectomy, PCa-specific chemotherapy, brachytherapy, cryotherapy, Photodynamic therapy or radical prostatectomy for treatment of prostate cancer; any prior radiation therapy to the pelvis for prostate cancer or any other malignancy.

8 Patient under medications that can affect PSA for the last 3 months prior to MRgFUS treatment (Androgen Deprivation Treatment; alpha reductase inhibitors)

9 Patients with lesions of Gleason 7 or greater outside the planned treatment area.

10 Individuals who are not able or willing to tolerate the required prolonged stationary supine position during treatment (approximately 3 hrs. sonication time)

11 Any rectal pathology, anomaly or previous treatment, which could change acoustic properties of rectal wall or prevent safe probe insertion (e.g., fistula, stenosis, fibrosis, inflammatory bowel disease, etc).

12 Any spinal pathology which can prevent safe administration of epidural/spinal anesthesia

13 Identified calcification of 2 mm or more in largest diameter neighboring the rectal wall (in a distance of less than 5 mm) and interfering with the acoustic beam path.

14 Lower limb musculoskeletal fixed deformities preventing probe insertion or patient positioning during procedure.

15 Prostate with multiple cystic lesions.

16 Evidence of distant prostate cancer, i.e., including lymph nodes and/or metastasis of cancer on imaging

17 Bladder cancer

18 Urethral stricture/bladder neck contracture

19 Active UTI

20 Prostatitis NIH categories I, II and III.

21 Compromised renal function

22 Implant near (≤1 cm) the prostate

23 Interest in future fertility

24 Current participation in another clinical investigation of a medical device or a drug or has participated in such a study within 30 days prior to study enrollment.

4 INVESTIGATION PLAN

4.1 Study Design

This is a multi-center, prospective, single arm study to evaluate MRgFUS treatment of intermediate risk, organ-confined prostate lesions. All subjects will be treated and then followed up clinically for up to 24 months to evaluate any procedure or device related

adverse events as well as to assess efficacy endpoints of the study. Additional data related to quality of life of treated subjects will also be collected.

4.2 Pre-Treatment Procedures

1. Patients will be screened for eligibility for the study. Those meeting the criteria will be offered to participate and sign an informed consent form.

2. Complete medical history, physical exam with DRE and concomitant medications will be obtained to determine patients' general health status, and presence of symptoms. The following questionnaires will be completed by participating subjects: FACT-P, ICIQ-SF, IPSS, IIEF-15, and SF-12.

3. Blood tests (PSA, CBC, serum chemistries), urinalysis and CT will be performed to verify compliance with eligibility criteria.

a. Urinalysis will include Specific gravity, pH, Glucose, Protein, RBC, Casts, WBC, Bacteria, culture, if indicated

4. IMAGE-guided mapping prostate biopsy (TPBx or TRBx per Appendix C) followed by pathology examination and analysis will be performed to evaluate oncology staging of disease and subject's eligibility for the study.

5. Pre-treatment multi-parametric (1.5/3T) MRI scans (E-coil may be used) will be performed not less than 6 weeks after a prostate biopsy. CT will also be performed.

6. Subject will have assessment for anesthesia (general and epidural) by an attending Anesthesiologist.

7. For subjects who met all eligibility criteria and had formally agreed to participate in the study, ExAblate MRgFUS treatment will be scheduled.

8. Treatment will be performed after a minimum of 30 days from IMAGE-guided prostate mapping biopsy.

9. Subject will be instructed to adhere to low residue diet without milk ingredients 48 hours pre-treatment, with no oral intake during the last 12 hours before treatment. On the evening prior to the procedure and on the morning of the treatment, the subject will undergo colon preparation (using laxatives) similar to colonoscopy preparation. To avoid existence of any fecal residue in the rectum during the procedure, two (2) hours prior to anesthesia, a cleansing enema will be performed.

4.3 Treatment Procedures

On day of treatment before any procedures, patient should complete the NRS, ICIQ-SF, FACT-P, IPSS, IIEF-15, and SF-12 questionnaires before prepping for treatment.

1. IV line will be inserted.

2. The recommended anesthesia for the treatment is either epidural or general. Anesthesia should allow continuous pelvic muscle relaxation without any movement throughout the procedure. Analgesics may be administered prior to and during the procedure.

3. Bladder drainage: The procedure requires continuous bladder drainage during treatment including planning and post-treatment imaging scans. A Foley catheter would usually be adequate for continuous bladder drainage unless the urethra is included in treatment area; where a suprapubic catheter will be used for urine drainage, per site standards.

4. Prophylactic antibiotics will be administered prior to procedure, in accordance with local standard of care.

5. The system will be prepared for the treatment according to instructions provided in the Operator Manual. Specifically, the endorectal balloon covering the FUS transducer will be prepared by partial filling it with degassed water prior to the patient's arrival; lack of air bubbles in the balloon will be confirmed by the operator. Degassed water temperature inside the rectal balloon during its insertion should be not under ~34°C to avoid anal spasm while inserting the endorectal probe.

6. At this stage subject will be inserted into the MRI-ExAblate suite.

7. Subject will be placed on the treatment table in Head First, supine position with bent knees and slightly elevated legs on the MRgFUS treatment table.

8. Vital signs (i.e., peripheral oxygen saturation, heart rate, and preferably blood pressure) will be monitored throughout entire procedure using MR compatible equipment. Other measurements for applied anesthesia will be based on the decision of the attending Anesthesiologist.

9. Attending physician will perform a rectal examination.

10. After lubricating the probe with non-viscous water-based ultrasound-transparent-gel and carefully filling the patient's rectum with about 10cc of gel (using a large opening syringe to avoid air bubbles formation) the endorectal probe will be inserted through the patient's anus while the patient is in supine position with his knees bent. (Screening imaging may provide some general information regarding expected probe's location, based on specific anatomy).

11. Once inserted and reasonably positioned, the probe will be locked to the positioner system. Additional water will be pumped into the balloon.
The balloon should be inflated to achieve tight contact with the entire circumference of the rectal wall; thus, achieving adequate coupling and avoiding air bubbles to enter between the endorectal balloon and the rectal wall.

12. An MRI localizer will be performed to verify positioning of the probe with relation to the prostate and the treatment area. If positioning corrections will be required, they will be done with repeated localizer imaging.

13. High quality T2w images, and other MR protocols, if clinically beneficial, will be acquired for planning.

14. T1w Axial images will be acquired in order to verify acoustic coupling between the rectum and the cooling balloon.

15. Water temperature in the rectal cooling balloon would be set to 37°C to produce baseline reference for thermometry. Following acquisition of this baseline thermometry, ExAblate system would start circulation of cold degassed water in the balloon, providing sufficient protection of the rectal wall.

16. Meanwhile, treating physician will draw the prostate capsule; the capsule will be further used for motion detection and for treatment planning by the WS.

17. The treating physician will identify the focus/foci or positive sector(s) to be targeted on the current scan and draw the desired ROT (Region of Treatment) using MR images on one scan orientation (preferably, axial view), and verify the ROT(s) on the two other orientations (sagittal and coronal views). In case of clearly visible lesion boundaries on T2w-MRI, the ROT will be drawn to include the entire focus with surrounding 5mm of lesion free tissue margins where applicable (lesion free margins will not be kept if they include the rectal wall or the sphincter, for example). Whenever biopsy confirmed lesion boundaries are not clearly visible on T2-w MRI, the physician will draw the selected sector(s) based on positive core(s) coordinates. In patients with a single biopsy proven focus, when an additional (second) focus which, based on multi-functional MRI, is also in need of treatment based on multi-functional MRI is found, but has not been confirmed by biopsy, the investigator may treat both the biopsy proven focus and the MRI suspicious focus, providing total ablated volume does not exceed 15mm plus 5mm lesion free margins for each lesion. Overall treatment volume should be up to 50% of the prostate gland for prostate volume <u>≤60cc, and up to 30cc should the entire prostate volume be larger than 60cc</u>. (Please note: in case an MRI suspicious focus is found in addition to two biopsy confirmed foci – the patient will be excluded from the study).

18. Treating physician will also mark the following safety regions that should be spared (i.e., rectal wall, urethral sphincters and bladder wall; urethra and NVB's preservation will be per clinical decision)

19. A central location of the ROT will be sonicated using low thermal dose, generating sub-lethal sonication, to reconfirm targeting geometrical accuracy in the patient.

20. Continuing with treatment process, acoustic energy transmission at therapeutic power level, accompanied with thermometry, will be performed to verify that thermal dose correlates well with the system's predicted dose. Energy levels will be adjusted as necessary to achieve sufficient level of heating to allow tissue coagulation.

21. Actual treatment will begin. Per each slice, planning software will compute the treatment plan with the bean path delineated. Treating physician will review/edit the sonications and make modifications as needed. Sonications will be performed according to plan.

22. Effect of each sonication will be measured by MR thermometry. Acoustic power will be adjusted throughout the treatment, to achieve temperatures between 65°C and 85°C at focal point.

23. Sonications will continue until entire target volume has been treated. The goal is a total procedure (i.e. ablation or sonication) time of up to 180 minutes. If the doctor determines the planned treatment is not possible after the first 3 therapeutic sonications, and another treatment session is not planned, the patient will be considered a screen failure and exited from the study. The reason for early exit will be documented on the CRF. The patient will be taken to recovery area for observation and release. The patient will undergo a 1-week follow-up visit for safety purposes, prior to study exit.

24. After completion of the treatment, a final MR scan will be done. This scan will include T2 weighted and T1 contrast enhanced sequences including subtraction to evaluate tissue ablation.

25. Transrectal device will be removed by physician and then patient will be transferred from the magnet/ ExAblate Suite to a recovery room for an observation period, according to clinical considerations.

26. Treatment exports and all MR images taken during the study will be archived by the Sponsor.

27. In the event of an incomplete treatment due to device failure, patient request, physician's decision, or unforeseen circumstance, a second treatment will be offered to the patient, provided no medical contraindications exist. Second treatment will be scheduled within 12 weeks from the original treatment. Patient follow-up visits will be based on the date of the second treatment.

28. Patient should complete a post-treatment NRS.

4.4 Follow-up

1. Immediate post treatment follow-up and monitoring will start in the recovery room. This time period will be used to evaluate the patient's health post-treatment, and any safety related issues.

2. The Foley catheter will be removed at the end of the procedure and the patient will be re-catheterized in case of urinary retention, unless the investigator decides to keep the catheter for a longer period (e.g., due to known pre-existing urinary obstructive symptoms). In case where the urethra was included in the treatment volume, and a suprapubic catheter (SPC) is used, it may remain in the bladder until the patient is able to spontaneously urinate, with a residual post-voiding urine volume of 50 ml or less (per ultrasound imaging). Oral antibiotics will be administered as long as the SPC remains *in situ*.

3. Antibiotics may be administered based on physician's clinical judgment. Administration and cause will be captured in the CRF.

4. For this study, it is recommended that patient will be released after spontaneous urination (in case of using a Foley catheter), or according to physician's clinical decision. When using an SPC, patients should be instructed regarding handling of the catheter prior to their discharge. Catheter may be required for up to 6 weeks post-treatment.

5. Post treatment NSAID's, analgesics or alpha blockers will be administered after procedure per clinical decision and will be captured in the CRF record.

6. Follow up visits will be completed at 1-week, and 1, 3, 6, 9, 12, 18, and 24 months post-ExAblate treatment to assess adverse events and concomitant medications, as well as specific procedures outlined below:

a) At 1 week visit patients will be evaluated for general health (physical exam), ICIQ-SF, and NRS, concomitant medications, and AEs.

b) At the 1 month follow-up, patient will be evaluated by a physical exam with a DRE, concomitant medications, and AEs. Patient will be asked to complete the NRS, ICIQ-SF, and IPSS questionnaires. Proctoscopy and/or uroflowmetry will be performed in the presence of clinical symptoms, based on individual investigator judgment.

c) At 3 months follow-up patients will be evaluated for physical exam with a DRE, concomitant medications, AEs and completion of the ICIQ-SF, FACT-P (v4), IPSS, IIEF-15, and SF-12 questionnaires.

d) At 6-month follow visit patients will be evaluated for physical exam with DRE and urinalysis (culture, if indicated), Multi-parametric MRI, PSA test, concomitant medications, adverse events, and completion of the ICIQ-SF. FACT-P (v4), IPSS, IIEF-15, and SF-12 questionnaires. In addition, all

patients will undergo a mapping biopsy using the same technique as for screening.

e) At 9-month follow-up visit, patients will be evaluated for physical exam, with DRE, concomitant medications, AEs and completion of the ICIQ-SF. FACT-P (v4), IPSS, IIEF-15, and SF-12 questionnaires.

f) At 12-month follow-up visit, patients will be evaluated for physical exam, with a DRE, PSA test, clinical labs for CBC, serum chemistries, urinalysis (with culture if indicated), post-void residual and uroflowmetry if medically indicated based upon the physician's decision, concomitant medications, AEs; and completion of the ICIQ-SF. FACT-P (v4), IPSS, IIEF-15, and SF-12 questionnaires.

g) At 18-month follow-up visit, patients will be evaluated for physical exam, with a DRE, urinalysis (with culture, if indicated) and PSA, concomitant medications, and AEs and completion of the ICIQ-SF. FACT-P (v4), IPSS, IIEF-15, and SF-12 questionnaires.

h) At 24-month follow visit, patients will be evaluated for physical exam, with a DRE, PSA test, clinical labs for CBC, serum chemistries, urinalysis (with culture if indicated); post-void residual and uroflowmetry if medically indicated based upon the physician's decision, concomitant medications, AEs; completion of the ICIQ-SF. FACT-P (v4), IPSS, IIEF1-5, and SF-12 questionnaires In addition, all patients will undergo a mapping biopsy using the same technique as used at Baseline and 6-month follow-up.

i) IMAGE-guided mapping biopsy between the 6-month and the 24-month visits will be done if clinically indicated, based on individual investigator medical opinion.

4.4.1 Early discontinuation of the study may occur for reasons including patient decision, investigator decision, Sponsor decision, decision to pursue alternative treatments for their tumor. Attempts should be made to complete the final visit study procedures prior to exiting the study. The reason for early discontinuation will be captured on the study Case Report Forms.

4.4.2 Wherever possible, in cases of potential surgical resection of the gland MRgFUS-treated patients, pathology results will be evaluated and compared to the treatment and post treatment data.

5 Study Visit Schedule

See visit schedule on next pages.

PCa003 Study Schedule

Visit	Window Allowance	Clinical Office and Lab Tests	Imaging **	Questionnaires
Screening	———	DRE; PSA IMAGE-guided TPBx or TRBx; Clinical labs for CBC, serum chemistries and urinalysis (cultures, if indicated); Physical Exam Concomitant medications	CT, Multi-parametric MRI (E-coil may be used)	FACT-P (v4); ICIQ-SF; IIEF-15 (SHIM); IPSS SF-12
Treatment ***	———	DRE; peripheral oxygen saturation, heart rate, and blood pressure; AEs	MR for planning, treatment and post Tx	Pre-Txt: NRS, FACT-P (v4); ICIQ-SF; IIEF-15 (SHIM); IPSS; SF-12 Post-Txt - NRS
1 week	±3 days	AEs; Physical exam; Concomitant medications		NRS; ICIQ-SF
1 month	± 7 days	AEs; Physical exam with DRE; Proctoscopy and/or post-void residual and Uroflowmetry if indicated; Concomitant medications		ICIQ-SF; IPSS NRS
3 months	± 1 week	AEs; Physical exam; DRE; Concomitant médications		FACT-P (v4); ICIQ-SF; IIEF-15 (SHIM); IPSS; SF-12;
6 months	± 1 month	AEs; Physical exam; DRE; urinalysis (culture, if indicated), PSA; TRBx or TPBx; Concomitant medications	Multi-parametric MRI	FACT-P (v4); ICIQ-SF; IIEF-15 (SHIM); IPSS; SF-12
9 months	±1 month	AEs; Physical exam; DRE; Concomitant medications		FACT-P (v4); ICIQ-SF; IIEF-15 (SHIM); IPSS ; SF-12

12 months	± 2 month	AEs; Physical exam; DRE; PSA Clinical labs for CBC, serum chemistries and urinalysis (cultures, if indicated); post-void residual and Uroflowmetry if indicated; Concomitant medications		FACT-P (v4); ICIQ-SF; IIEF-15 (SHIM); IPSS; SF-12
18 months	± 2 months	AEs; Physical exam; DRE, urinalysis (Culture, if indicated); PSA Concomitant medications		FACT-P (v4); ICIQ-SF; IIEF-15 (SHIM); IPSS; SF-12
24 months	± 2 months	AEs; Physical exam; DRE; PSA Clinical labs for CBC, serum chemistries and urinalysis (cultures, if indicated); post-void residual and Uroflowmetry if indicated; IMAGE-guided TRBx or TPBx; Concomitant medications		FACT-P (v4); ICIQ-SF; IIEF-15 (SHIM); IPSS ; SF-12

6 STATISTICAL CONSIDERATIONS

This study will evaluate the effectiveness and safety of the ExAblate 2100 Prostate System for the treatment of patients with intermediate-risk, localized prostate lesions. All patients will be consented and followed as it would be defined by 510k submission/approval requirements. Data will be analyzed for efficacy based on data collected per FDA agreement for a 510(k) commercial clearance as previously discussed with FDA. Patients will continue to be followed post treatment for long-term outcomes.

6.1 Sample Size

The current IDE has had 4 amendments to date. The 4th Amendment aim was to define the patient population that will be part of the 510K submission (IDE G100108/S011). To ensure a cohesive patient population for the 510K FDA review, only those patients treated after site IRB approval of Amendment 4 will be counted toward the primary analysis population. Other safety and efficacy analyses that include data from subjects enrolled prior to the approval of G100108/S011 may be reported as supplementary information.

To date (Sept-20-2018), 81 patients have been treated under protocol Amendment-4.

Based on our accumulated experience when conducting studies for a new indication, there is a great level of experience and knowledge acquired from a study in which many sites participate in the study. This has proven to be critical in the design and conduct of Pivotal studies. The need for at least 15 sites in the proposed study is further supported by the discussion of the FDA panel meeting discussing prostate focal therapy, and also by the Pivotal study that is running for the Sonablate 500 ultrasound HIFU device for a population that is similar to the proposed study.

6.2 Data Analysis

6.2.1 510(k) Analysis

This is a clinical study involving a minimum of 100 to a maximum of 103 subjects. Descriptive analyses of safety and effectiveness data will be used to summarize results for a 510(k) submission for commercial clearance. Safety and effectiveness data will address both results of biopsy as well as functional analysis.

Primary effectiveness analyses will be based on the 6-month biopsy results. Proportions of treated patients reporting a negative biopsy and/or MRI verification of index lesion ablation at 6-months.

Descriptive summaries will be presented for: PSA testing, NRS, FACT-P (v4), IPSS, and SF-12 questionnaires and percentage of non-perfused volume (NPV).

Baseline assessment of erectile dysfunction and incontinence will be captured as per the incontinence/ED questionnaires and they will be followed also using the same questionnaires. Any

worsening of the baseline condition to a worsened CTCAE grade will be captured as an adverse event and will be graded on CTCAE Version 4.0 published May 28, 2009 (v.4.03:June 14, 2010) and will be reviewed by the Data Safety Monitoring Board.

6.2.2 Final Analysis

Final safety and effectiveness analyses will be presented to the FDA per 510K submission requirements.

7 RISK ANALYSIS

Worldwide, over 5000 treatments have been performed to date with the MR guided FUS ExAblate 2000 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, and G060023, G070022, G080009, G080206, G100127, G100169, G120017, G120246, G140018, G140082, P040003 and subsequent supplements, P110039, and P150038). 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. The original risks and additional risks, new and unique to this study are discussed below.

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

7.1 Potential risks

7.1.1 Risk of Transperineal Mapping Biopsy

Transperineal biopsy is associated with[7,8]:

- ~10% risk of urinary retention after biopsy in patients with large prostates (>60 mL)
- 20-42% of hematuria
- 13-50% of hematospermia
- 31% of pain (18% requiring analgesia after procedure)
- 6:1000 -1.2% risk for sepsis

[7] Webb JA, Shanmuganthan K, McLean A. Complications of ultrasound guided transperineal biopsy. A prospective study. Br J Urol. 1993; 72: 775-7

[8] Miller J, Perumalla C, Heap G. Complications of transrectal versus transperineal prostate biopsy. ANZ J Surg. 2005; 75:48-50.

7.1.2 Risk related with Transrectal Mapping Biopsy

Transperineal biopsy is associated with

- Urinary retention requiring catheterization for bladder drainage is seen in ~1%
- Discomfort and pain in the rectal area in > 80% of the patients
- Hematuria occurs in about 66% of the patients and may persist for 3-7 days in about 50% of the patients
- Hematospermia is reported in about 1-2% of the patients
- Rectal bleeding occurs roughly in 9%-27% of the patients
- Infection (most frequently – UTI) requiring hospitalization occurs in about 0.7% of the patients undergoing prostate biopsy

7.1.3 Risk of MR Imaging

- Study subject may find 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 (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%.
- Nephrogenic Systemic Fibrosis (NSF) or Nephrogenic Fibrosing Dermopathy (NFD), kidney disorders, may occur in patients with moderate to end-stage kidney disease after they have had a MRI scan with gadolinium-based contrast agent. NSF causes fibrosis of the skin and connective tissues throughout the body. Patients develop skin thickening that may prevent bending and extending joints, resulting in decreased mobility of joints. NSF usually starts in the lower extremities. Fibrosis can also develop in the diaphragm, muscles in the thigh and lower abdomen, and lung vessels.

7.1.4 Risks related to the use of a urinary catheter:

- Local discomfort and/or pain that might last up 1 or 2 days after catheter removal

- Partial or complete urinary retention is expected in all patients for the first post-treatment 48 hours. It may last however longer or occur after successful voiding (in 1-9% of the patients).
- Urinary retention requiring surgical intervention may occur in 2% of the cases. Occurrence, severity, duration and management will be recorded in the CRF and AE form
- Urethral stricture requiring intermittent sound dilatation or bladder neck stricture requiring bladder neck incision is reported in 1-25%. (Usually rates are less with SPC than with Foley catheter.) The use of SPC and the ability to plan around structures, such as the bladder wall by using the editor function of the software (LEDR) expected to reduce the risk of bladder neck injury.
- Dysuria – immediate dysuria due to prostatic urethral sloughing occurs in all patients for a week following treatment, but dysuria may last even 6 weeks. Dysuria may be associated with urinary tract infection. Measurement will be by NRS score during post-treatment visits; duration and treatment will be recorded in the CRF.
- Perineal edema may occur in some patients and this usually resolves spontaneously and completely within 7 days.
- Urinary tract infection (UTI) is frequent (reported in 5-48%) due to the prolonged catheterization and non-sterile handling. Patients and their supporting family members will be instructed to handle the catheter adequately, and patients will be under oral antibiotics until catheter extraction, but it should be expected that even then symptomatic UTI will occur. Occurrence of symptomatic UTI, symptoms, severity, duration and management will be recorded in the CRF and AE form.
- Occasionally, infection persists and leads to such complications as prostatitis, epididymitis, cystitis, pyelonephritis.[9] Prostatitis (reported in less than 2%) and/or epididymo-orchitis (manifested as pain, swelling and tenderness in the scrotum) is reported in 5-7.5% of the patients who were fitted with a SPC (as opposed to 8.5% in patients with urethral catheter. occurrence, duration and treatment will be recorded in the CRF and AE form.

7.1.5 Risks Related to Anesthesia

7.1.5.1 Epidural anesthesia may involve the following risks:

- Low blood pressure, which is the reason the patient is routinely hydrated prior to the placement of either of these forms of anesthesia.

[9] Kunin CM. Detection, prevention, and management of urinary tract infections. 3rd ed. Philadelphia: Lea and Febiger, 1979.

- Postdural puncture headache occurs infrequently with these techniques. The risk is 1% with Epidural. This is believed to be due to a leak of Cerebrospinal fluid from the needle hole in the dura.
- Backache is an infrequent problem. It most likely is due to ligament strain due to profound muscle relaxation or surgical positioning.
- Other complications that can occur include, but are not limited to, infection, nerve damage (including paralysis, loss of bladder and bowel function, loss of sexual function), allergic reactions, seizures, cardiac arrest and death. Although the result of these is severe they occur very rarely.

7.1.5.2 General anesthesia may involve the following risks:

- Serious side effects of general anesthesia (GA) are uncommon in people who are relatively healthy when conducted by a certified Anesthesiologist with required resuscitation skills (as required in this study).

  Estimated death rate 1:2,000,000-250,000 cases; and overall complication rate is <3%
- Aspiration - GA suppresses the normal throat reflexes that prevent aspiration, such as swallowing, coughing, or gagging. To help prevent aspiration, an endotracheal (ET) tube is inserted during general anesthesia. When an ET tube is in place, the lungs are protected so stomach contents cannot enter the lungs. Aspiration during anesthesia and surgery is very uncommon. To reduce this risk, patients are instructed not to eat or drink anything for 12 hours before anesthesia so that the stomach is empty, per local site standards.
- Changes in blood pressure or heart rate or rhythm
- Cardiac event, or stroke
- Damage to teeth and lips
- Swelling in the larynx
- Sore throat and/or hoarseness caused by injury or irritation of the larynx.
- Allergic reactions to medications are rare – potential allergies will be evaluated by the anesthetist before anesthesia.
- Nausea and vomiting after anesthesia – occur in less than 10% of the patients

7.1.6 Risks incidental to the treatment

- 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 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.

7.1.7 Risks associated with the ExAblate MRgFUS treatment and/or biopsy mapping

- While the goal of the ExAblate treatment is to completely ablate the prostate tissue lesion(s), there is a risk that abnormal tissue may still exist for varying reasons including failed biopsy detection at screening and/or incomplete ablation of the entire lesion.
- Pain or discomfort requiring oral analgesia is expected to occur in almost all patients after treatment.
- Severe pain in the treatment areas (pelvis, rectum or scrotum area) for which patients return to the physician/hospital is reported in 1.4-3% of the treatments. Pain symptoms will be specified for location and recorded in the CRFs for occurrence and duration; severity will be measured by NRS score during post-treatment follow-up.
- Incontinence rates following resolution of immediate dysuria are <2%. In patients undergoing primary HIFU treatment. In the treatment performed with the ExAblate MRgFUS device, the urethral sphincters are preserved by marking them as LEDR's, thus avoiding therapeutic dose accumulation at these structures. The ability to customize the energy to the specific case and the real-time monitoring and control of the applied energy, associated with the MRI which provides high resolution visualization of the anatomical structures, significantly reduces the risk of urinary sphincters injury. Thus, we expect even lower rates of incontinence after ExAblate treatments.
- Erectile dysfunction in previously potent men is reported to range between 40 and 50% in ultrasound-guided HIFU treatments. In ExAblate MRgFUS treatments, the NVB's are clearly visualized and can be protected if needed by marking them as LEDR's. We expect therefore, that in potent patients that have no evidence for cancer adjacent to the NVB's – post-treatment impotence rate will not exceed 10%.
- Retrograde ejaculation - since the treatment includes the orifices of the seminal vesicles in the urethra, retrograde ejaculation may be permanent in 3% of the patients; occurrence, duration and treatment will be recorded in the CRF's.
- Perineal hematoma development as a result of treatment is very low. The probe is inserted, manipulated extracted by authorized experienced Urologists. No sharp edges are in contact with the rectum At the end of the ExAblate procedure, a contrast (Gadolinium) enhanced MR imaging is performed to assess the blood flow within the treated area and neighboring tissue.
- Unintended ablation of vulnerable structures outside the planned treatment volume due to improper targeting of the focal point 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 in all three axes. This procedure is done while the patient is in position for treatment. Then the operator has to mark the prostate capsule (to detect potential movements of the organ during the treatment), the desired treatment boundaries and the structures that should be preserved (i.e., rectum, sphincters, bladder wall, urethra, NVB). For each sonication delivered during treatment, the operator gets continuous feedback on the position of the treatment point superimposed on the anatomical image and can make geometrical and dose corrections where required. The system also includes an independent safety-monitoring loop that continuously compares the physical position of the transducer 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 rectal wall is especially protected by cooling the degassed water inside the balloon to 14°C.

- The protocol 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 Cryo-therapy or Radiofrequency ablation of other lesions but rarely seen in ExAblate MRgFUS ablation. Furthermore, since the treatment in this protocol is a focal treatment that will never exceed 35 cc this concern practically almost does not exist. Overall treatment volume should be up to 50% of the prostate gland for prostate volume <60cc, and up to 30cc should the entire prostate volume be larger than 60cc.

- A risk of damage to the rectal wall from either targeting a prostate area that is too close to the rectal wall or from problems in acoustic coupling between the balloon and the rectal wall or from unexpected high acoustic absorption at the rectal wall. Fistulae were reported in about 0.5% of the Ultrasound-guided HIFU patients. The system includes water cooling of the interface, planning aimed to protect the rectal wall; automatic warning to the user if an edited spot is too close to the rectal wall, and use of acoustic gel as a coupler between the balloon and the rectum. Based on animal trials and few initial feasibility studies, the rectal wall is adequately protected from thermal injury.

- There is a risk of 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. Motion tracking is being done by the operator using fiducials placed on the anatomic images and by integrated 3D tracker inside the transducer. The use of epidural anesthesia with muscle relaxants.

- There is a risk of damage to the anal sphincter from the insertion, extraction or repositioning of the rectal probe. To reduce this risk the probe would be inserted by a trained physician and with care, after pelvic muscle relaxation by epidural anesthesia.

- There may be a risk of damage to the bladder from targeting a prostate area that is too close to the bladder. To mitigate this risk, the treating physician may utilize the system treatment tools as part of treatment planning to delineate the bladder area in question so that no "sonication" is allowed when they are close to the bladder. In any event, should a bladder injury event occur, cystoscopy may potentially be used to evaluate injury.
- Nerve damage, or loss of sensation in the area other than the treatment area.
- Risk of mechanical damage to the rectal wall by the insertion, extraction or repositioning of the transducer. To reduce this risk the probe would be inserted by a trained physician and with care.
- Hematuria – occurrence, duration and treatment will be recorded in the CRF and AE form
- Proteinuria – measurement will be by urine values; occurrence and duration will be recorded in the CRFs
- Hematospermia – occurrence, duration and treatment will be recorded in the CRF and AE form

7.1.7.1 Other Treatment Related Risks

- Deep Vein Thrombosis (DVT) - lying stationary for 3 to 4 hours, increases risk for DVT. 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.
- Minor bruises redness and pain at the site of the intravenous catheter insertion – is common and usually subsides spontaneously within a few days.
- Phlebitis (local hardening of the vein) or infection from the intravenous catheter may occur in ~5% of the patients.

7.1.8 Anticipated MRgFUS Treatment Side Effects

Based on previous treatment experience, the above listed side effects have been identified as possible treatment-related complications of ExAblate treatment and procedure. 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 treatments are those, which normally resolve without sequelae within 10-14 days of the treatment.

Significant Anticipated Treatment Side Effects of ExAblate are those which may require medical treatment, may have sequelae, and for which time of resolution is not defined. The

rate of anticipated significant treatment side effects of the ExAblate treatment is unknown, but expected to be infrequent based on prior clinical experience in other organs.

7.2 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 and procedure-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).

7.3 Criteria for Removal from the Study

Early discontinuation from the study may occur for reasons including patient decision, investigator decision, Sponsor decision, protocol compliance and decision to pursue alternative treatments for their tumor. Attempts should be made to complete the final visit study procedures prior to exiting the study. The reason for early discontinuation will be captured on the study Case Report Forms.

7.4 Adverse Event Reporting

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

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

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

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

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

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

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

Any UADEs will be reported to 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.

7.5 Adverse Events Analysis – Data Safety Monitoring Board

Data safety monitoring will review all AE's that occur throughout the study and determine if they are in fact related to the ExAblate, or some other cause.

- *Was the adverse event serious?*

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

- *Was the adverse event device related?*

- *Was the adverse event unexpected?*

- *Is there an unreasonable risk in continuing the trial?*

If in fact it is determined that an ExAblate-treated patient experienced an AE that met all of the above criteria, we would stop the trial pending further investigation. If deemed appropriate, the protocol would be amended and submitted to FDA for approval to assure patient safety. Any such amendment would be reported to the IRB and other regulatory body, as required by local applicable regulations.

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

7.6 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 local IRB 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.

7.7 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 Oracle Software system, and is designed, run and hosted by the Sponsor (Haifa, Israel).

7.8 Investigator Responsibilities

Principal investigator will be required to sign an Investigator Agreement that defines their responsibilities.

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9 APPENDICES

Appendix A: Sample Informed Consent

Appendix B: Training Manual

Appendix C: Examples of 14 core: Mapping TransPerineal and Trans Rectal Biopsy Procedure