INSIGHTEC

Exablate

For Prostate Cancer

INFORMATION FOR PRESCRIBERS

May 2021

Exablate 2100V1 Cradle Type 3.0 (Prostate), Information for Prescribers, PUB71002245, Revision 4

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Caution	**The anticipated population of end-users of this system is trained and certified clinicians specializing in Urology, Radiology and/or Radiation Oncology.** **THE DEVICE IS RESTRICTED TO THE USE OF FULLY QUALIFIED, PROPERLY TRAINED AND CERTIFIED PERSONNEL ACCORDING TO THE TRAINING PROGRAM OF THIS DEVICE.**

Read all instructions, including CONTRAINDICATIONS, WARNINGS and PRECAUTIONS, prior to use. Failure to follow these instructions could result in serious patient injury. Specialized training in both magnetic resonance imaging and use of the Exablate are critical to ensure proper performance and safe use of this device.

Physicians should contact their local INSIGHTEC representative prior to initial use of the Exablate to obtain information about training and receive the required certification. Collaboration with a physician trained in urology for patient evaluation is strongly recommended.

This document and instructions are not to be used in the United States of America.

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CHAPTER 1: OVERVIEW

1.1. Device Description

The Exablate Prostate system, Model 2100V1 Type-3, is a non-invasive thermal ablation medical device that has been used for ablation of prostate cancer tissue. This system combines a focused ultrasound surgery (FUS) delivery system and a conventional diagnostic 1.5T or 3T MRI scanner. The Exablate system provides real-time therapy planning algorithm, thermal dosimetry, and closed-loop therapy control. Treatment is achieved by utilizing the unique interactive MRI scan control features of 1.5/3T MRI system. The Exablate Prostate system comprises the following integrated components: Operating console, Patient table, Equipment cabinet with Control PC, Water system and a Cleaning and High-Level Disinfection cart.

The full name and configuration of the device are summarized in the table below:

Table 1: Exablate system configuration	
Generic name	MRgFUS
System	Exablate
Model	2100V1
Cradle Type	3.0
Application	Prostate

1.2. Intended Use / Indication for Use

Exablate 2100V1 (Type 3.0) MR guided focused ultrasound is intended for the treatment of locally-confined prostate cancer.

1.3. Clinical Benefit

Insightec's prospective, single arm, multicenter study for Focal MR-Guided Focused Ultrasound Treatment of Localized Intermediate Risk Prostate Lesions (IDE G100108, described in Chapter 4 of this document) was designed to assess safety and effectiveness of Exablate MRgFUS in the treatment of subjects with intermediate risk, localized (organ confined) prostate lesions.

Study effectiveness data, based on biopsy results, showed that of 101 patients, 91% had no cancer within the area of treatment after 6 months. Patients showed a 91% decrease in their PSA levels after 6 months. As for safety, there were no unanticipated events, and no serious adverse events reported.

CHAPTER 2: PATIENT SELECTION CRITERIA

2.1. Patient Selection Criteria

1. Adult males
2. Biopsy proven diagnosis of prostate cancer
3. Patient with organ-confined prostate cancer
4. No evidence of extracapsular extension or seminal invasion as seen on MRI
5. Patient should be eligible for the chosen anesthesia (e.g. epidural or general anesthesia)

2.2. Contraindications

1. ASA status > 2.
2. Any Contraindication to MRI, or contrast agent
3. Severely abnormal coagulation (INR>1.5).
4. Patient with unstable cardiovascular
5. Any rectal disease, pathology, anomaly, injury, previous treatment, or scarring which could change acoustic properties of the rectal wall, or might prevent safe probe insertion (e.g., inflammatory bowel disease, fistula, stenosis, fibrosis, or symptomatic hemorrhoids).
6. Existing urethral or bladder neck contracture/stricture.
7. Implant near (<1cm) the prostate.
8. Calcification of 2 mm or more in largest diameter neighboring the rectal wall (less than 5 mm from the rectal wall) that is in the acoustic beam path.

2.3. Warnings and Precautions

1. Prolonged immobilization may lead to increased risk of deep venous thrombosis (DVT) or pulmonary embolism (PE). The physician should obtain a detailed medical history of the patient prior to treatment. Due to the period of immobilization required for the Exablate treatment, this should include factors that may impact the risk of clotting and assess the use of measures to minimize the risk of deep venous thrombosis. Patients with risk of DVT or PE should not be candidates for the treatment. To reduce any such risk, treatment time (in which patient is positioned without movement) should be limited.
2. The endorectal balloon must be in complete contact with the rectal wall, without any air gaps, trapped air bubbles (larger than 2mm) or residual feces that either absorb or reflect ultrasound energy and might result in rectal wall injury.

3. To reduce the probability of rectal wall injury due to residual feces in the beam path, the following patient preparations should be performed:
    - Patient should be fasting prior to the procedure: 12 hours without food or fluids other than water, and 6 hours without drinking water.
    - Before patient positioning, he should undergo bowel preparation (similar to preparation for colonoscopy) according to the hospital standard of care.
    - In case MR imaging still shows residual feces in the rectum (in the potential beam path), extract the probe and apply a cleansing enema. Do not treat the patient in case feces cannot be moved away from the ultrasound beam path.
4. To reduce the probability of rectal wall injury due to air bubbles in the interface, carefully check the "Bubble Detection" MR series. In case air bubbles are identified:
    - Further inflate the endorectal balloon with an additional 30cc of water in an attempt to push any air bubbles away from the acoustic treatment path.
    - While the probe is still connected with the motion unit, unlock the motion unit and the positioner and gently rotate it from side to side / back and forth in an attempt to sweep remaining air bubbles aside.
    - As a last resort, deflate the balloon to reference volume, completely extract the probe, clean it, re-apply ultrasound gel (attempt to remove as many air bubbles from the gel as possible) and re-insert the probe. Inflate the balloon back to 60cc.
    - Do not treat the patient in case of an air bubble in the beam path (larger than 2mm) or in case of multiple (>5) smaller air bubbles.
5. Patient or organ movements during the treatment can result in serious injury to non-targeted tissue. In order to reduce risks of the movement the following should be applied:
    - Patient movement should be minimized using proper anesthesia, either by epidural with conscious sedation or by general anesthesia. Spinal anesthesia is not recommended as depth of anesthesia cannot be controlled throughout the procedure, and the treatment requires constant muscle relaxation and analgesia.
    - Urinary bladder movement should be avoided by drainage, either using a Foley catheter or Supra-pubic catheter.
    - Use system restraints to minimize the risk of patient movement
6. The patient must be monitored throughout the treatment, according to the given anesthesia. MR-compatible anesthesia and monitoring equipment are required, depending on the type of anesthesia used (i.e. ventilation machine; or monitor [HR, BP, SpO2] + infusion pump).
7. In case the treatment is performed under epidural and conscious sedation, ensure that the patient can activate the MR Stop Scan button before initiating treatment.

8. Accurate alignment of the thermal spot location at the start of the treatment is critical to proper tissue targeting and to avoid injury to non-targeted tissue. Perform geometrical verification prior to treatment to ensure proper alignment.
9. Unintended cavitation can result in serious injury to non-targeted tissue. Cavitation should be constantly monitored throughout the treatment using the spectrum graph.
10. Thermal injury may occur outside the intended treatment volume. To minimize this risk, the following instructions should be followed:
    - Real time thermal and anatomical images must be carefully reviewed throughout the treatment.
    - Do not treat beyond or above the apex, as this may increase the risk of urinary incontinence, urethral strictures, or osteitis pubis.
    - Do not treat the rectal wall or Denonvilliers' fascia, as this may result in a rectal injury.
11. Failure to monitor the MR thermal maps during the procedure may result in unintended heating of non-targeted tissues, which may cause permanent injury. Cancel/abort the procedure if MR thermometry data are not available or do not give reliable or adequate imaging.
12. The patient should be instructed regarding appropriate oral prophylactic antibiotics intake prior to the treatment in order to minimize the risk of UTI.

Refer to the Operator's Manual for the Exablate and for the GE MR system for more detailed warnings and precautions regarding safe use of these systems.

CHAPTER 3: ANTICIPATED TREATMENT-RELATED RISKS

Based on PCa003 study protocol (G100108) literature review. See references at the end of this chapter.

3.1. MR Imaging Related Risks

1. Gadolinium DTPA (Magnevist, Omniscan) is an intravenously injectable contrast medium for MRI. The package inserts note 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%.
2. 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 an 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.

3.2. Risks Related to The Use of Urinary Catheter

1. Pain and irritation of the urethra and miatus and immediate dysuria due to the Foley catheter used during and or after the procedure may occur. Dysuria can last up to one week, but usually resolves in a couple of days.
2. Urinary tract infection (UTI) is reported in 5-48% of whole gland HIFU treatments due to the prolonged catheterization that is frequently required after whole gland treatments, and non-sterile handling.
3. Occasionally, infection may persist and lead to prostatitis (<2%), epididymo-orchitis (5-7.5% if using SPC, 8.5% if using urethra catheter), epididymitis, cystitis, pyelonephritis.

4. Suprapubic catheter (SPC) may also cause urinary bladder infection and infection at the insertion site in the skin; insertion of the catheter is sterile and handling of a SPC should be under clean conditions to avoid infection.
5. Urethral stenosis due to prolonged catheterization may occur. Thus, in cases where catheter is expected to be left in situ for more than a week, an SPC (suprapubic catheter) should be preferred for bladder drainage.
6. The procedure of inserting a SPC is done under anesthesia and sterile conditions; therefore, it may involve risks of bleeding, infection, and potential risk of small bowel injury.
7. Hematuria due to catheter irritation may occur and is spontaneously resolved when catheter is removed.

3.3. Risks Related to Regional Anesthesia

1. Low blood pressure, which is the reason the patient is routinely hydrated prior to the placement of either of these forms of anesthesia.
2. Post-dural 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.
3. Backache is an infrequent problem. It most likely is due to ligament strain due to profound muscle relaxation or surgical positioning.
4. 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.

3.4. Risks Related to General Anesthesia (GA):

1. 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. Estimated death rate 1:200,000-250,000 cases; and overall complication rate is <3%.
2. Aspiration - GA suppresses the normal throat reflexes that prevent aspiration, such as swallowing, coughing, or gagging.
3. Changes in blood pressure or heart rate or rhythm.
4. Cardiac event or stroke.
5. Damage to teeth and lips.

6. Swelling in the larynx.
7. Sore throat and/or hoarseness caused by injury or irritation of the larynx.
8. Allergic reactions to medications are rare – potential allergies will be evaluated by the anesthetist before anesthesia.
9. Nausea and vomiting after anesthesia – occur in less than 10% of the patients.

3.5. Anticipated Risks Incidental to The Exablate Prostate Treatment

1. There are potential risks from the intravenous catheter used during the treatment. These may include pain and/or bleeding/bruising at the IV site, phlebitis (local hardening of the vein) or infection.
2. There is a potential risk of deep venous thrombosis (DVT) from lying stationary for several hours.
3. 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.

3.6. Risks Associated with Exablate Prostate MRgFUS Procedure

1. Pain or discomfort requiring oral analgesia is expected to occur in almost all patients after treatment.
2. 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 whole gland ablation treatments.
3. Swelling of the prostate and surrounding soft tissues is likely to occur which, may result in urinary obstructive symptoms new occurrence or aggravation and even in urinary retention when ablation is in vicinity to the urethra, or in patients with baseline symptoms of BPH (Benign Prostate Hyperplasia).
4. Permanent urinary incontinence was reported in 7-35% of the patients following whole gland Ultrasound-guided HIFU treatments.
5. Bladder neck stricture or stenosis of the prostatic urethra may cause urinary retention/obstruction requiring intervention. It has been described in up to 17% in whole gland US-guided HIFU treatment.
6. Urethral sloughing should be expected in about 10-20% of the cases where the urethra is involved in the treated volume.
7. Erectile dysfunction in previously potent men is reported to range between 40 and 50% after ultrasound-guided HIFU treatments

8. Retrograde/dry ejaculation - since the treatment frequently includes the ejaculatory ducts and their orifices into the urethra, retrograde ejaculation can occur and may be permanent.
9. Epididymitis and epididymo-orchytis may occur in up to 9% of the cases due to post-treatment obstruction of the ejaculatory ducts.
10. Hematuria.
11. Proteinuria.
12. Hematospermia.
13. Unintended ablation of vulnerable structures outside the planned treatment volume due to improper targeting of the focal point may occur.
14. There is a risk of damage to the anal sphincter from the insertion, extraction or repositioning of the rectal probe.
15. Risk of mechanical damage to the rectal wall by sonication or the insertion, extraction or repositioning of the transducer.

Actual safety events that occurred during the PCa003 Focal Therapy trial (G100108) are summarized in section 4.5.2 below.

References for Chapter 3:

- Resnick MJ, Koyama T, Fan KH, Albertsen PC, Goodman M, Hamilton AS,et al. Long-term functional outcomes after treatment for localized prostate cancer. N Engl J Med 2013;368:436–45.
- Barret E, Ahallal Y, Sanchez-Salas R, Galiano M, Cosset JM, Validire P, et al. Morbidity of focal therapy in the treatment of localized prostate cancer. Eur Urol 2013;63:618–22.
- Sanda MG, Dunn RL, Michalski J, Sandler HM, Northouse L, Hembroff L, et al. Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008;358:1250–61.
- Kunin, C. M., Urinary tract infections. Detection, prevention, and management. Baltimore, Williams & Wilkins (1997).

CHAPTER 4: CLINICAL TRIAL SUMMARY: FOCAL MR-GUIDED FOCUSED ULTRASOUND TREATMENT OF LOCALIZED INTERMEDIATE RISK PROSTATE LESIONS (US FDA IDE G100108)

4.1. Executive Summary

Title:	PCa003: Focal MR-Guided Focused Ultrasound Treatment of Localized Intermediate Risk Prostate Lesions (IDE G100108)
Study Devices:	Exablate Prostate system, model 2100 Type-3
Sponsor:	Insightec
Statement of Compliance:	This clinical study was conducted in accordance with Good Clinical Practice and FDA 21 CFR 50, 54, 56 and 812
Objectives and Subject Population:	To assess safety and effectiveness of Exablate MRgFUS in the treatment of subjects with intermediate risk, localized (organ confined) prostate lesions
Population Size:	101 subjects at 8 sites
Structure:	The study is a prospective, single arm, multicenter study. Subjects that meet eligibility will undergo Exablate treatment 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. Primary effectiveness will compare 6-month follow-up results to baseline measures, with safety assessed at 12 months.
Method of Assignment:	All subjects who complied with the inclusion/exclusion criteria are enrolled chronologically. Subjects are considered enrolled after completion of Exablate treatment.
Results:	The first subject was consented under this IDE (G100108) on July 22, 2013. The data snapshot for this report occurred on October 31, 2019. No Serious Adverse Events (SAEs) reported. Effectiveness at 6 months follow-up with biopsy results showed that of 101 patients, 91% had negative result within the area of treatment. Patients showed a 91% decrease in their PSA levels after 6 months.
Conclusions:	This clinical study demonstrates safety and effectiveness equivalence of Exablate in the treatment of intermediate risk, localized prostate lesions.

4.2. Study Design and Objectives

This is a multi-center, prospective, single arm study to evaluate MRgFUS treatment of intermediate risk, organ-confined prostate lesions. All subjects are treated and followed for up to 24 months for safety and efficacy. The objective of this trial is to assess safety and effectiveness of the Exablate MRgFUS in the treatment of intermediate risk, localized (organ confined) prostate lesions.

4.3. Study Population

4.3.1. Inclusion Criteria

1. Male patients 50 and older.
2. Biopsy proven adenocarcinoma of the prostate (using an image-guided 14+ core mapping biopsy) and targeting cores as needed obtained up to 6 months prior to scheduled treatment.
3. Patients 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 of 7 (4+3/GGG 3 or 3+4/GGG 2), based on mapping prostate biopsy, with no more than 15mm cancer in maximal linear dimension in any single core.
6. Single unilateral index Gleason 7 (GGG 2 or 3) lesion, identified in the prostate based on biopsy mapping with supporting MRI; may have secondary Gleason 6 (GGG 1) lesion on ipsilateral or contralateral side confirmed with biopsy and/or MRI.
7. Gleason 7 (GGG 2 or 3) 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 ≤ 5mm, on axial images.
    b. Largest imaging dimension of cancerous finding < 20mm.
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 to 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.

4.3.2. Exclusion Criteria

1. ASA status >2.
2. Contraindications to MRI:
    a. Claustrophobia.
    b. Implanted ferromagnetic materials or foreign objects.
    c. Known intolerance to the MRI contrast agent.
3. Severely abnormal coagulation (INR >1.5).
4. Patients with unstable cardiac status including:
    a. Unstable angina pectoris on medication.
    b. Patients with documented myocardial infarction within 40 days prior to enrollment.
    c. Congestive heart failure NYHA class IV.
    d. Patients with unstable arrhythmia status, already on anti-arrhythmic drugs.
5. Severe hypertension (diastolic BP >100 on medication).
6. Severe cerebrovascular disease (multiple CVAs 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 (GGG 2 or 3) 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 2mm or more in largest diameter neighboring the rectal wall (in a distance of less than 5mm) and interfering with the acoustic beam path.
14. Lower limb musculoskeletal fixed deformities preventing safe probe insertion or patient positioning during procedure.
15. Prostate with multiple cystic lesions.
16. Evidence of distance 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 (≤ 1cm) the prostate.
23. Interest in future fertility.
24. Current participation in another clinical investigation of a medical device or drug or has participated in such a study within 30 days prior to study enrollment.

4.4. Study Endpoints

4.4.1. Safety Endpoints

Adverse Events are documented and reported by the investigational sites throughout the subject's participation in the study. The safety endpoints are:

- Adverse Events (AEs)
- Serious Adverse Events (SAEs)
- Evaluation of incidence and severity of complications from treatment day visit through the 12-month follow-up

4.4.2. Effectiveness Endpoints

The primary effectiveness endpoints in this study are the analysis of "*targeted lesion control*" per-protocol, post-treatment. The key efficacy endpoints are:

- Biopsy result (positive/negative) at 6-months (confirmed by core lab) – No GGG tissue within the planned ROT, i.e. negative biopsy within planned ROT
- Reduction in PSA value at 6 months compared to baseline, reported as ng/mL
- Patient-reported clinical outcomes:
    - FACT-P (Version 4) – Quality of life for chronic illness
    - ICIQ-SF – Urinary incontinence
    - IPSS – Prostate symptom
    - IIEF-15 – Erectile function
    - NRS – Pain Numeric Rating Scale
- Biopsy results at 6 months outside the planned ROT

4.5. Study Results

One-hundred and one (101) subjects treated are included in the analysis.

4.5.1. Demographics

The average age of subjects at the time of treatment was 62.9 years (±6.7, 47.5-81.9). Average BMI was 28.5 (±4.5, 20.6-43.3), indicating population as being overweight by average BMI. 89% of subjects were white Caucasian and 7% were Black/African American.

Subjects had either 1 or 2 (average 1.2 ± 0.4) MRI visible foci identified at baseline with an average lesion volume of 3cc. Baseline biopsy data shows 1 or 2 (average 1.4 ± 0.5) lesions present, with the lesion planned for treatment being Gleason 7, either (3+4)/Gleason Grade Group 2 (n=79, 78.2%) or (4+3)/Gleason Grade Group 3 (n=22, 21.8%).

4.5.2. Safety results

Total of 200 adverse events were reported. There were no Life-threatening Adverse Events (AEs) reported, and only 1 AE was categorized as Severe for an UTI event resolving in less than a week. The vast majority of AEs reported were Mild (n=173, 86.5%). Of all AEs reported, only 4 occurred at a frequency of 5% or higher: penile/testicular pain (5.0%, 9 of 10 were mild), mild erectile dysfunction (9.5%, 16 of 19 were mild), hematuria (10.5%, 20 of 21 were mild), and mild urinary incontinence (9.0%, 15 of 18 were mild). 127 (63.5%) events resolved in 90 days or less, with 46 (23%) resolving within a week. 38 (19%) events took more than 90 days to resolve.

Thirty-five (17.5%) events were ongoing at the time of this report (the data snapshot for this report occurred on October 31, 2019). Of those 35 events, 32 were related to either the Exablate device or procedure, and 26 (26/35=74%) were mild and coded within the reproductive or urinary/renal body systems. There were no ongoing AEs noted as severe or life threatening.

Safety results are presented below in **Table 2** below.

Table 2: AEs by Grouping, Body System, Severity and Resolution Time

					Severity			Resolution Time [Days]				
Grouping	**Coded Body System**	**Coded AE Term**	**No. of Events**	**No. of Subjects**	**Mild**	**Moderate**	**Severe**	**≤7 Days**	**7 < Days ≤29**	**30≤ Days ≤90**	**>90 Days**	**Ongoing**
Procedure (Exablate)	Gastro-intestinal	Constipation / bloating	2	2 (2%)	2	0	0	0	2	0	0	0
		Diarrhea	1	1 (1%)	1	0	0	0	1	0	0	0
		Hemorrhoidal hemorrhage	1	1 (1%)	1	0	0	0	1	0	0	0
	General	Edema limbs	1	1 (1%)	1	0	0	0	0	1	0	0
		Fatigue	3	3 (3%)	2	1	0	0	2	1	0	0
	Infection	Testicular infection	1	1 (1%)	0	1	0	0	1	0	0	0
		Urinary tract infection	1	1 (1%)	1	0	0	0	1	0	0	0
	Pain / Discomfort	Anal/rectal pain	2	2 (2%)	1	1	0	0	2	0	0	0
		Groin / pelvic / suprapubic pain	3	3 (3%)	2	1	0	0	1	0	2	0
		Penile / testicular pain	10	10 (9.9%)	9	1	0	0	6	4	0	0
		Urinary tract pain	5	5 (5%)	5	0	0	0	2	1	2	0
	Reproductive	Ejaculation disorder	9	9 (8.9%)	8	1	0	0	0	1	6	2
		Erectile dysfunction	19	19 (18.8%)	16	3	0	0	0	0	3	16
		Hematospermia	9	9 (8.9%)	9	0	0	0	1	5	2	1
	Urinary / Renal	Bladder spasm	1	1 (1%)	1	0	0	0	1	0	0	0
		Hematuria	21	21 (20.8%)	20	1	0	0	8	13	0	0
		Urethral stricture	1	1 (1%)	0	1	0	0	0	0	0	1
		Urinary frequency	8	8 (7.9%)	8	0	0	0	1	3	2	2
		Urinary hesitancy	6	6 (5.9%)	5	1		0	0	3	2	1
		Urinary incontinence	18	18 (17.8%)	15	3	0	0	1	1	9	7
		Urinary retention	9	8 (7.9%)	8	1	0	0	1	4	4	0
		Urinary urgency	5	5 (5%)	5	0	0	0	1	1	2	1
Device (Exablate)	Reproductive	Prostatic cyst	1	1 (1%)	1	0	0	0	0	0	0	1
Procedure (Biopsy)	Gastro-intestinal	Constipation / bloating	1	1 (1%)	0	1	0	0	1	0	0	0
		Nausea/vomiting	1	1 (1%)	0	1	0	1	0	0	0	0
	Infection	Urinary tract infection	1	1 (1%)	1	0	0	0	0	0	1	0
	Pain / Discomfort	Groin / pelvic / suprapubic pain	1	1 (1%)	1	0	0	0	0	0	1	0
	Reproductive	Erectile dysfunction	1	1 (1%)	1	0	0	0	0	0	0	1
	Urinary / Renal	Hematuria	1	1 (1%)	1	0	0	0	0	0	1	0
		Urinary retention	2	2 (2%)	1	1	0	2	0	0	0	0
Transient	Gastro-intestinal	Constipation / bloating	1	1 (1%)	1	0	0	1	0	0	0	0

Table 2: AEs by Grouping, Body System, Severity and Resolution Time

					Severity			Resolution Time [Days]				
Grouping	**Coded Body System**	**Coded AE Term**	**No. of Events**	**No. of Subjects**	**Mild**	**Moderate**	**Severe**	**≤7 Days**	**7 < Days ≤29**	**30≤ Days ≤90**	**>90 Days**	**Ongoing**
		Diarrhea	2	2 (2%)	2	0	0	2	0	0	0	0
		Proctitis	1	1 (1%)	1	0	0	1	0	0	0	0
	General	Allergic reaction	1	1 (1%)	1	0	0	1	0	0	0	0
		Edema limbs	1	1 (1%)	1	0	0	1	0	0	0	0
		Fatigue	7	7 (6.9%)	6	1	0	5	2	0	0	0
		Vertigo	1	1 (1%)	1	0	0	1	0	0	0	0
	Infection	Urinary tract infection	1	1 (1%)	0	0	1	1	0	0	0	0
	Nervous	Paresthesia	1	1 (1%)	1	0	0	0	1	0	0	0
	Pain / Discomfort	Penile / testicular pain	5	5 (5%)	4	1	0	4	1	0	0	0
		Positional pain	1	1 (1%)	1	0	0	1	0	0	0	0
		Prostatic pain	1	1 (1%)	1	0	0	1	0	0	0	0
		Urinary tract pain	1	1 (1%)	1	0	0	1	0	0	0	0
	Reproductive	Hematospermia	4	4 (4%)	3	1	0	3	1	0	0	0
		Orchitis	1	1 (1%)	1	0	0	1	0	0	0	0
	Urinary / Renal	Bladder spasm	2	2 (2%)	2	0	0	2	0	0	0	0
		Hematuria	4	4 (4%)	4	0	0	3	1	0	0	0
		Urinary frequency	1	1 (1%)	1	0	0	1	0	0	0	0
		Urinary incontinence	3	3 (3%)	3	0	0	3	0	0	0	0
		Urinary retention	8	8 (7.9%)	5	3	0	7	1	0	0	0
		Urinary urgency	1	1 (1%)	1	0	0	1	0	0	0	0
	Vascular	Deep vein thrombosis	1	1 (1%)	1	0	0	1	0	0	0	0
Unrelated	Pain / Discomfort	Headache	1	1 (1%)	0	1	0	0	1	0	0	0
	Reproductive	Erectile dysfunction	1	1 (1%)	1	0	0	0	0	0	0	1
	Urinary / Renal	Proteinuria	1	1 (1%)	1	0	0	0	0	0	1	0
		Urinary frequency	1	1 (1%)	1	0	0	0	1	0	0	0
		Urinary hesitancy	1	1 (1%)	1	0	0	0	0	0	0	1
Totals			**200**	**70 (69.3%)**	**173**	**26**	**1**	**46**	**43**	**38**	**38**	**35**

4.5.3. Biopsy Results (Region of Treatment)

The first primary effectiveness endpoint is within area of treatment prostate biopsy occurring at 6-months post-treatment. Positive biopsy was defined as any Gleason Grade Group (GGG) tissue identified within the area of planned Exablate treatment. 92 (91%) of subject biopsies were negative within the area of treatment. There was no report of any GGG within the area of treatment at 6-months over the GGG 3 category. The frequency distribution of positive biopsy results within the ROT at 6-months can be found below in **Table 3**.
If reviewing positive biopsies within the area of planned Exablate treatment as any Gleason Grade Grouping higher than GGG 1/Gleason 6 (3+3), which is typically viewed as clinically significant, 96 were reported as negative (95.0%).

Table 3: Positive Biopsy Results Within the Planned ROT by Gleason Grade at 6 Months

Positive Biopsy Results Within the Planned ROT / Gleason Grade Group		**Exablate**	
		N	**%**
Yes	Gleason ≤ 6 (3+3) / GGG 1	4	4.0
	Gleason 7 (3+4) / GGG 2	4	4.0
	Gleason 7 (4+3) / GGG 3	1	1.0
	Total	9	8.9
No	Total	92	91.1
Totals	**Total**	**101**	**100.0**

4.5.4. Prostate Specific Antigen (PSA) results

The second primary effectiveness endpoint is reduction in PSA value from baseline to 6-months post-treatment. 92 (91%) subjects showed a decrease in PSA at 6-months.
The average PSA at baseline was 6.4 ng/mL (±3.1, 1.0-18.0), with a decrease to an average of 3.3 ng/mL (±2.9, 0.3-18.0) at 6-months. The average PSA remained lower through 12-months post-treatment with an average of 3.2 ng/mL (±2.5, 0.3-10.8).

4.5.5. Patient Reported Outcomes

The following clinical outcomes were collected based on patient self-evaluation. Outcomes were examined in 2 treatment groups: 57 patients with critical structures (i.e. neurovascular bundles and/or urethra) included in the treatment plan, and 44 patients with no critical structures in the treatment plan. No statistically significant differences were found between the two groups in any of the results presented below.

4.5.5.1. Functional Assessment of Cancer Therapy Prostate (FACT-P)

The FACT-P Trial Outcome Index (TOI) was included to assess health-related quality of life (HRQoL), with a higher score indicating higher HRQoL. There was no significant change from baseline to follow-up. Average scores were 90.3 (±9.2) at baseline, 88.0 (±10.4) at 6 months and 88.9 (±9.0) at 12-months.

4.5.5.2. International Consultation on Incontinence Questionnaire – Short Form (ICIQ-SF)

The ICIQ-SF was included to collect data on urinary incontinence, with a higher score indicating greater severity of symptoms. There was slight (but not significant) increase from baseline to follow-up. Average scores were 1.3 (±2.5) at baseline, 2.1 (±2.9) at 6-months and 1.9 (±2.6) at 12-months post-treatment.

4.5.5.3. International Prostate Symptom Score (IPSS)

The International Prostate Symptom Score (IPSS) was collected to capture the severity of urinary symptoms, with a higher score indicating greater urinary symptoms severity. IPSS urinary symptoms scores were 7.3 (±5.4) at baseline, indicating mild urinary symptoms, 6.8 (±5.4) at 6-months and 7.0 (±5.3) at 12-month post-treatment.

4.5.5.4. International Index of Erectile Function Questionnaire (IIEF-15)

The IIEF-15 questionnaire was collected to assess the following five dimensions: Erectile Function (EF), Orgasmic Function (OF), Sexual Desire (SD), Intercourse Satisfaction (IS), and Overall Satisfaction (OS). Lower scores indicate greater symptoms severity. The Erectile Function (EF) scores for both subgroups showed mild to moderate erectile dysfunction at baseline with average score of 21.2 (±9.2). Post-treatment, both groups were still categorized as having mild to moderate erectile function scores; however, the subgroup with no critical structures had a higher mean score by 2 points, which may indicate a clinical difference (although not statistically significant). The subgroup with critical structures included had 6- and 12-month post-treatment scores of 17.2 (±10.6) and 17.8 (±10.2), respectively. The subgroup with critical structures not included at 6- and 12-month post-treatment scores of 19.9 (±9.2) and 20.2 (±9.0), respectively.
There was no measurable difference seen from baseline to post-treatment for any of the other dimensions.

4.5.5.5. Pain Numeric Rating Scale (NRS)

The numeric rating scale (NRS) for pain was done immediately pre- and post-treatment as well as up to 1-month following the Exablate treatment. A higher score indicates a higher level of pain. Prior to treatment, the average score was 0.1 (±0.5). Immediately post treatment, there was a slight difference between subjects that had critical structures included reporting an average NRS of 1.0 (±1.9) verses those subjects that did not have critical structures included reporting 0.3 (±0.9). While this may indicate a clinical difference, statistically it was found non-significant. By 1-month post-treatment there was no significant difference between the subgroups and the average NRS was 0.5 (±1.0).

4.5.6. Biopsy (Outside Region of Treatment)

There were 52 subjects having a positive 6-month biopsy outside of the ROT. Of them, 34 (65%) had Gleason Grade Grouping (GGG) 1/Gleason 6 (3+3) as the highest GGG present. Fifteen subjects had Gleason 7, either GGG 2/Gleason 7 (3+4) or GGG 3/Gleason 7 (4+3) reported (n=12 and n=3, respectively). Two subjects were reported to have GGG 4/Gleason 8 and 1 subject had GGG 5/Gleason 9 outside the area of Exablate treatment. See **Table 4**.

Table 4: Gleason Grade Group (GGG) Positive Biopsy Results Outside the Planned ROT at 6 Months

GGG Positive Biopsy Results Outside the Planned ROT	Exablate	
	N	%
≤ 6 (3+3) / GGG 1	34	65.4
7 (3+4) / GGG 2	12	23.1
7 (4+3) / GGG 3	3	5.8
8 / GGG 4	2	3.8
9 - 10 / GGG 5	1	1.9
Total	52	100.0

4.6. Conclusions

The safety profile for this study was found favorable on its own as well as compared to the predicate devices. There were no life threatening nor unanticipated events, and no SAEs reported. Most events resolved within 90 days, and other than one “unrelated” severe AE, all of the AEs were either Mild or Moderate.

Effectiveness data based on 6 months biopsy results, showed that of 101 patients, 91% had a negative result within the area of treatment. PSA showed a decrease from baseline frequency of 91%.

The data that is presented in this report has undergone periodic review by a Data Safety Monitoring Board (DSMB). Based on the key safety and effectiveness data presented, it reports a positive risk to benefit ratio.

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