



**SONABLATE® 450**

**FOR THE TREATMENT OF LOCALLY RECURRENT  
PROSTATE CANCER**

**PMA P130002**

**SPONSOR EXECUTIVE SUMMARY**

FDA Advisory Committee Meeting  
Gastroenterology and Urology Devices Panel

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SonaCare Medical, LLC  
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## LIST OF ACRONYMS

AE	Adverse Event
BT	Brachytherapy
CTCAE	Common Terminology Criteria for Adverse Events
EBRT	External Beam Radiation Therapy
ED	Erectile Dysfunction
EPIC-36	Expanded Prostate Cancer Index Composite
FDA	Food and Drug Administration
HIFU	High Intensity Focused Ultrasound
IDE	Investigational Device Exemption
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
ITT	Intent to Treat
PMA	Pre-Market Approval Application
PP	Per Protocol
PSA	Prostate Specific Antigen
RF	Radiofrequency Ablation
RT	Radiotherapy
SAE	Serious Adverse Event
SCM	SonaCare Medical, LLC
SRP	Salvage Radical Prostatectomy
UADE	Unanticipated Adverse Device Effect
UTI	Urinary Tract Infection

## 1 EXECUTIVE SUMMARY

Although prostate cancer is one of the most commonly diagnosed cancers in men, the ideal treatment for localized disease remains unclear. The accepted treatments include radical prostatectomy, external beam radiation therapy (EBRT), interstitial radioactive seed placement (brachytherapy), cryotherapy, and active surveillance. The effort to treat prostate cancer is complicated by the diversity of the biologic behavior of the disease, the preoperative inability to accurately determine the extent of prostate cancer spread within and beyond the capsule, and the strategic location of the prostate relative to other pelvic structures. Definitive prostate cancer treatment is often a lifestyle-inhibiting proposition with associated high rates of incontinence and impotence. Although many accepted cancer treatments are associated with a good success rate, recurrence of prostate cancer can occur in a high percentage of treated patients. Despite continuous implementation of novel radiotherapy (RT) techniques such as three-dimensional (3D), conventional RT, and intensity-modulated RT providing more targeted and higher doses of radiation to the prostate as a definitive primary treatment, the risk of local recurrence after RT is still quite high. Kuban et al, for instance, reported 4,839 patients who underwent EBRT for clinically localized prostate cancer. Of these, 1,582 (33%) had biochemical failure by prostate-specific antigen (PSA) criteria; 416 (9%) had clinical local failure; and 329 (7%) had distant failure (Kuban et al., *Int J Radiat Oncol Biol Phys*, 2003)<sup>1</sup>.

Since the prognosis for patients with biochemical recurrence is poor, there remains a need for curative salvage therapy for these patients.

Salvage treatment options include radical prostatectomy, cryotherapy, and brachytherapy. Regardless of approach, biochemical control rates have been reported to be around 50% at five years with a 2-3% incidence of rectal fistula, 5-20% risk of bladder neck stricture, 10 – 50% risk of urinary incontinence, and very high incidence of impotency. In many cases, patients are also on adjuvant androgen deprivation therapy, so the true response rate from the definitive local salvage intervention alone is not clear.

Another option that has been explored in the treatment of recurrent prostate cancer is high intensity focused ultrasound (HIFU). The Sonablate® 450 (Sonablate) uses high intensity focused ultrasound (HIFU) to elevate the tissue temperature within the focal zone resulting in coagulative tissue necrosis while the intervening tissue between the focal zone and the probe is kept at physiologically safe temperatures. Treatment with the Sonablate is performed as a minimally invasive, outpatient procedure, lasting 2-4 hours on average depending on the size of the prostate. A feasibility trial was undertaken with the Sonablate in 11 subjects who failed radiation therapy (10 in the EBRT arm and 1 in the Brachytherapy arm). The primary endpoints were PSA nadir of  $\leq 0.5$  ng/mL and a negative biopsy at 180 days post treatment. Nine of the 11 subjects (81.8%) achieved PSA nadir of  $\leq 0.5$  ng/mL. Ten of the 11 subjects (90.9%) had a negative biopsy at 180 days post-treatment. The overall success rate (PSA nadir + negative biopsy) was 9/11 (81.8%). No device or procedure related Serious Adverse Events (SAEs) were reported in this trial.

The pivotal trial data submitted in this premarket application studied 100 subjects who experienced local recurrence after failed EBRT for prostate cancer. This was a single arm, non-randomized trial. A combined endpoint was defined as absence of biochemical failure (achieving PSA nadir of  $\leq 0.5$  ng/mL during 12 months post-treatment) and a negative 12 month biopsy. Seventy-eight subjects completed the 12 month follow-up period, including the 12 month biopsy. Of these 78 subjects, 50 (64%) were treatment successes (PSA nadir + negative biopsy). Any subjects that did not have a 12 month biopsy and PSA, for any reason, are considered failures under the study design. Adjuvant androgen deprivation hormones were not allowed during the study period.

Clinical side effects of the treatment included ongoing incontinence requiring pads in twenty one (21%) of all treated subjects. Urinary tract infections and post-voiding symptoms were expected and typically resolved within 3-6 months post-treatment. Rectal fistulas were divided into 2 categories based on the type of intervention needed: 3 subjects (3%) required medical intervention only (catheter and antibiotics), and 2 (2%) were treated with surgical intervention. A retraining program was conducted in 2011, after 61 subjects had been treated, to retrain all clinical trial proctors and clinical trial investigators on treatment techniques and post-HIFU care. Only one rectal fistula has occurred post-training. In this single case, surgical intervention was initiated by a non-HIFU physician and was contraindicated based on the subjects presenting symptoms and the recommended post-treatment care training guidelines. Fourteen subjects (14%) experienced device or procedure related serious adverse events (SAEs); all SAEs had been resolved by the time of this submission. There were no device or procedure related deaths or life-threatening events reported in this trial.

Treatment with Sonablate HIFU offers a minimally invasive procedure with favorable disease control in the absence of hormone deprivation and with a lower risk of certain adverse events than other therapy options for recurrent prostate cancer. It is expected that the outcome and complication rates will continue to improve as HIFU is integrated into the market place, training methodologies are refined, and post approval data is collected.

## 2 BACKGROUND

Approximately 30% of all patients treated with definitive radiation therapy for localized prostate cancer experience recurrence of disease (Chen et al., *Urology*, 2003)<sup>2</sup>. Relapse of prostate cancer occurs in two forms: local (confined to the prostate gland) or loco-regional/metastatic (disease is identified outside of the anatomic boundaries of the prostate gland). The former is amenable to local salvage intervention while the latter is treated customarily with systemic therapy.

Contemporary definitions of local disease recurrence include a rise in the prostate specific antigen level (PSA) detected during post-treatment monitoring and histologic confirmation of viable tumor upon prostate biopsy. The role of imaging in the identification of recurrent disease remains a subject of research and debate. The ideal candidate for salvage intervention appears to be the patient with a PSA below 10 ng/mL at the time of recurrence and no evidence of

metastatic disease on pre-salvage imaging. The patient should also have a life expectancy sufficient to offset the risks that attend salvage interventions.

## 2.1 Current Treatment Options

### 2.1.1 Salvage Radical Prostatectomy (SRP)

SRP has been practiced for decades by urologic oncologists. SRP was historically performed infrequently because of the significant morbidity that attended the procedure even in the hands of experienced, high-volume surgeons. Detailing clinical information accumulated between 1985 and 2000, Chen et al. provide a sobering picture of the historical experience with SRP.<sup>2</sup>

**Table 1. Contemporary Results of Salvage Therapy<sup>2</sup>**

Study	Period Reported	Patients, N*	Patients with ADT <sup>†</sup>	Organ Confined (%)	Seminal Vesicle Invasion (%)	Lymph Node Involvement (%)	Positive Surgical Margins (%)	Disease-Free Survival (%) <sup>‡</sup>	Mean Follow-Up Time (mo)
Mador <i>et al.</i> <sup>90</sup> (1985)	1981–1984	7 (3)	3	29	NA	NA	NA	NA	3–22
Thompson <i>et al.</i> <sup>16</sup> (1988)	1984–1985	5	NA	40	0	0	20	NA	NA
Neerhut <i>et al.</i> <sup>15</sup> (1988)	1984–1987	16	0	25	63	6	38	88	20 (3–39)
Link and Freiha <sup>17</sup> (1991)	1984–1988	14	2	36	50	0	43	43	18 (1–52)
Moul and Paulson <sup>18</sup> (1991)	1975–1988	12 (8)	NA	25	25	33	33	33	49 (9–139)
Ahlering <i>et al.</i> <sup>19</sup> (1992)	1977–1987	34 (24)	27	35	NA	NA	NA	65	53 (25–93)
Stein <i>et al.</i> <sup>14</sup> (1992)	NA	13 (2)	NA	36	46	15	15	NA	NA
Pontes <i>et al.</i> <sup>20</sup> (1993)	1982–1991	43 (8)	26	30	26	12	70	29	12–120
Brenner <i>et al.</i> <sup>67</sup> (1995)	1989–1991	10	5	30	40	NA	40	30	35 (14–51)
Rogers <i>et al.</i> <sup>27</sup> (1995)	1984–1992	40	1	20	49	5	38	47	39 (2–97)
Garzotto and Wajsman <sup>24</sup> (1998)	1985–1993	29 (20)	29	28	34	7	31	79	61.2
Gheiler <i>et al.</i> <sup>25</sup> (1998)	1992–1997	40 (10)	4	42	28	15	13	47	36.1 (2–65)
Amling <i>et al.</i> <sup>29</sup> (1999)	1966–1996	108	71	39	28	18	36	44 <sup>§</sup>	NA
Vaidya and Soloway <sup>28</sup> (2000)	1995–2000	6	5	NA	33	0	17	83	27 (2–48)

NA = not available.  
<sup>\*</sup> Number of included cystoprostatectomies is given in parentheses when different from the total number of patients.  
<sup>†</sup> Neoadjuvant or adjuvant androgen deprivation therapy.  
<sup>‡</sup> Includes biochemical progression-free survival.  
<sup>§</sup> 10-year progression-free survival.

Of note, in a patient population where only one third of those treated were found to have organ-confined disease, disease-free survival ranged from 29–88%. Complications were frequent and included incontinence (0–67%), bladder neck contracture (0–28%), and rectal injury (0–29%). Table 2 from Memorial Sloan Kettering illustrates the morbidity of SRP and details the experience with incontinence in the post SRP population during two different eras (Eastham et al. *Curr Urol Rep*, 2003, Stephenson et al., *J Urol*, 2004).<sup>3,4</sup>

**Table 2. Continence after Salvage Radical Prostatectomy<sup>3,4</sup>**

	Early group (1984–1994; n = 46)*	Contemporary group (1995–2002; n = 43)*
Continent (0 pads)	11 (23.9%)	11 (25.6%)
Mild incontinence (one to two pads)	2 (4.3%)	12 (27.9%)
Moderate incontinence (three to four pads)	9 (19.6%)	6 (14.0%)
Severe incontinence (more than four pads)	13 (28.3%)	5 (11.6%)
Total incontinence (+/- artificial sphincter)	11 (23.9%)	9 (20.9%)

\*The level of continence was unavailable for six patients in the early group and for 11 patients in the contemporary group.

As more detailed evaluations of the outcomes of SRP were performed, it became apparent that although advances in surgical technique improved, certain morbidity parameters such as rectal injury rate, incontinence, and bladder neck contracture continued to occur in approximately 1/3 of those treated.<sup>5,6</sup> Chade and colleagues have reviewed extensively the literature and the collaborative work of an international consortium to evaluate the most contemporary data on SRP available. Their findings appear in Tables 3 and 4, reproduced below (Chade et al. *Eur Urol*, 2012):<sup>7,8</sup>

**Table 3. Clinical and Pathologic Outcomes after Salvage Radical Prostatectomy<sup>8</sup>**

First author	Yr	No.#	RT type, % (EBRT/BT/ Comb)	RT + ADT, %	Follow-up, median mo (range)	Pathologic organ confined, %	PSM, %	Lymph node involvement, %	BCR-free probability, %	CSS, %	Time probability, yr <sup>r</sup>
Link	1991	14	71/29/0	0	18 (1–52)	27	43	NA	57	–	1.5
Ahlering	1992	11	NA	100	–	–	–	NA	71	71	4
Zincke	1992	32	100/0/0	0	44	–	–	NA	82	–	5
Pontes	1993	35	88/12/0	NA	(12–120)	30	70	14	28	79	10
Brenner	1995	10	0/100/0	0	30	30	40	NA	30	–	4
Lerner	1995	79	90/10/0	0	50 (24–260)	39	–	8	53	72	10
Rogers	1995	40	35/65/0	2.5	39 (2–97)	22	37	5	55	95	5
Cheng	1998	86	92/7/1	0	70 (12–180)	–	–	16	–	64	–
Gheiler	1998	30	90/10/0	0	36 (2–65)	53	13	16	47	87	3
Amling	1999	108	98/2/0	0	–	39	36	18	34	70	10
Stephenson	2004	100	58/42/0	0	–	21/50	38/10 <sup>***</sup>	9	42/66	–	5
Bianco	2005	100	29/42/29	16	60 (12–240)	35	21	9	55	73	5
Ward	2005	138	NA	NA	84	39	–	NA	–	77	10
Darras	2006	11	90/10/0	27	83 (27–158)	81	0	0	55	91	7
Sanderson	2006	51	58/24/18	18	–	25	36	28	47	–	5
Boris <sup>***</sup>	2009	11	36/55/9	NA	20 (1–77)	–	–	18	73	–	2
Leonardo	2009	32	100/0	0	35	53	34	0	75	–	3
Paparel	2009	146	NA	NA	45	44	16	13	54	–	5
Eandi <sup>***</sup>	2010	18	NA	17	18 (4–40)	50	28	5.5	67	–	1.5
Heidenreich	2010	55	35/38/27	22	23 (2–56)	73	11	20	87	–	2
Chade	2011	404	65/18/3	NA	55	55	25	16	37	83	10

RT = radiation therapy; EBRT = external-beam radiation therapy; BT = brachytherapy; Comb = combination; ADT = adjuvant-androgen deprivation therapy; PSM = positive surgical margin; BCR = biochemical recurrence; CSS = cancer-specific survival; NA = not available; SRP = salvage radical prostatectomy.  
<sup>#</sup> Number of patients after SRP only (excluding other salvage surgeries).  
<sup>r</sup> For both oncologic outcomes (BCR-free and CSS).  
<sup>\*\*</sup> SRP before or after 1993.  
<sup>\*\*\*</sup> Robotic SRP series.

**Table 4. Surgical Complications after Salvage Surgery<sup>8</sup>**

First author	Yr	No.	Technique	Operating time, min, median	Rectal injury, %	Anastomotic stricture, %	Clavien 3–5, %	Blood loss, ml, mean, range	Blood transfusion, %
<i>Open</i>									
Neerhut	1988	16	SRP	–	19	25	6	–	–
Rainwater	1988	30	27 SRP; 3 SCP	–	0	17	–	–	–
Link	1991	14	SRP	185	0	7	–	1000* (300–8000)	–
Moul	1991	22	4 SPP; 18 SCP/RCP	480 (SPP 260)	–	–	–	800* (200–1800)	–
Stein	1992	13	11 SRP; 2 SCP	211	8	15	0	1100 (500–2350)	–
Pontes	1993	43	35 SRP; 8 SCP	180–360	9	11	–	–	–
Lerner	1995	132	79 SRP; 53 Ex/PLND	–	6	12	–	–	–
Rogers	1995	40	40 SRP	270	15	27.5	22.5	910 (350–2200)	–
Gheiler	1998	40	30 SRP; 10 SCP	220	–	–	–	1100*	–
Amling	1999	108	108 SRP	–	6	21	–	–	43
Pisters	2000	13	13 SRP/cath	–	0	–	30	1850 (800–2800)	–
Stephenson	2004	100	100 SRP <sup>†</sup>	264 vs 222	15 vs 2	30	33 vs 13	–	–
Ward	2005	199	138 SRP; 61 SCP	–	5 vs 10	22	–	–	–
Darras	2006	11	SRP	119	–	18	–	494 (300–800)	–
Sanderson	2006	51	SRP	–	2	41	6	–	–
Leonardo	2009	32	SRP	122	0	12	0	550 (350–1200)	–
Gotto	2010	98	SRP	–	9	41	25	–	–
Heidenreich	2010	55	SRP	120	2	11	3.6	360 (150–1450)	4
<i>Laparoscopic</i>									
Vallencien	2003	7	Transperitoneal	190	0	0	0	387 (50–1100)	0
Stolzenburg	2007	9	Extraperitoneal	148	0	0	11	238 (100–400)	0
Nunez-Mora	2009	9	Transperitoneal	170	0	0	11	260 (100–500)	0
<i>Robotic</i>									
Kaouk	2008	4	Robotic SRP	125	0	–	0	117 (50–250)	–
Boris	2009	11	Robotic SRP	183	9	9	9	113 (50–300)	–
Eandi	2010	18	Robotic SRP	160	0	17	17	150 (50–350)	0
Strope	2010	6	Robotic SRP	356	0	33	33	280 (50–800)	–
Chauhan	2011	15	Robotic SRP	140	0	–	6	75* (50–100)	0

SRP = salvage radical prostatectomy; SCP = salvage cystoprostatectomy; RCP = radical cystoprostatectomy; SPP = salvage perineal prostatectomy; Ex = exenteration; PLND = pelvic lymph node dissection; SRPcath = SRP with urinary catheterizable reconstruction.  
<sup>†</sup> SRP performed before vs after 1993.  
\* Median.

From these data, one could conclude that increased surgical experience with SRP has resulted in decreased morbidity in some areas such as rectal toxicity. It is also apparent that due to limitations of contemporary early detection and non-invasive staging technology, a significant proportion of patients undergoing salvage surgery have extraprostatic disease at the time of intervention and therefore may not be candidates for local salvage therapy.

More recently, robot-assisted SRP has become an additional option. Jamal et al. reported the first robotic SRP in 2008, while Kaouk et al. described the first robotic series of four cases. From 2008 to 2011, five robotic SRP series showed median operating times ranging from 125 to 356 min, 0–9% of patients experiencing rectal injury, and 9–33% of patients developing anastomotic stricture after surgery. Major complications (Clavien 3–5) occurred in 9–33% of patients, and estimated blood loss varied from 75 to 280 ml. In comparison between surgical approaches, major complications ranged from 0% to 25% in open SRP series, from 0% to 11% in laparoscopic series, and from 0% to 33% in robotic SRP series (see Table 4).<sup>8</sup>

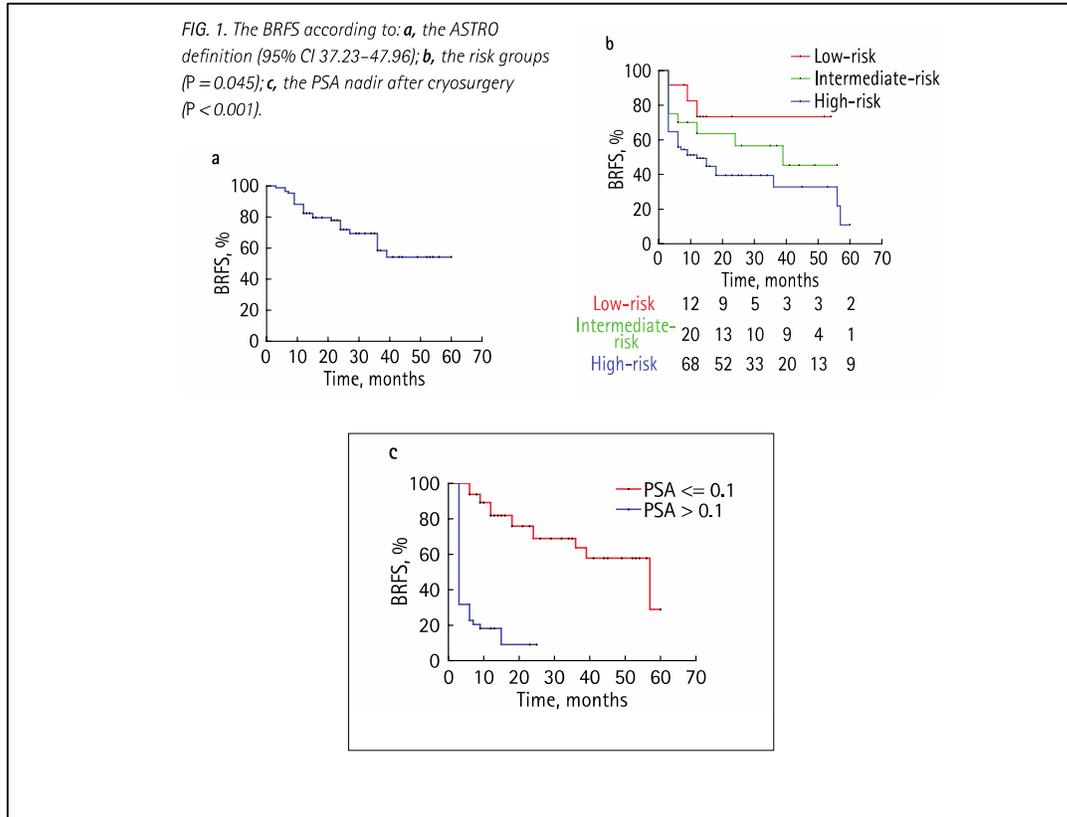
Finally, in a systemic review paper on salvage local therapy after failure of radiotherapy for prostate cancer, morbidity for SRP was reviewed in 1329 patients in 24 series, by Parekh. The following complication rates were noted: 50% incontinence, 26% bladder stricture, 5% rectal

injury, and 2.4% fistula. Urinary incontinence was noted as the most common complication with SRP. Rectal injury ranged from 0-11%.<sup>9</sup>

### **2.1.2 Cryotherapy**

Cryotherapy (cryo) for the treatment of prostate cancer was introduced in the 1980s as a minimally invasive approach to whole gland treatment. The use of first generation technology was associated with unacceptably high rates of morbidity resulting in its abandonment as a primary treatment strategy. With the development of more refined cooling systems and better instrumentation, cryo has received renewed attention as a salvage treatment for prostate cancer following radiation therapy.

Long-term disease control, assessed by freedom from biochemical recurrence, is achieved most frequently in patients with low risk pre-cryotherapy parameters, as illustrated in Figure 1 (Ismail et al., *BJU Int.*, 2007).<sup>10</sup> The experience of Katz and colleagues indicates that PSA nadir after salvage cryo is an important predictor of recurrence free survival.<sup>11</sup> Complications of treatment include rectal pain, hematuria, incontinence and scrotal edema.<sup>11, 12</sup> Other investigators have noted that, like patients who are candidates for SRP, certain patient-specific characteristics predict long-term freedom from disease recurrence following salvage cryo. These characteristics include a greater than 10-year life expectancy, initial clinical stage of T1-2, N0M0, and a pre-cryotherapy PSA of <10 ng/ml.<sup>13</sup> This group also reported that few patients appear to be cured by salvage cryotherapy and that patient selection is the key to treatment success.<sup>14</sup> Quality of life studies on patients undergoing cryotherapy suggest that results are comparable to other therapies in appropriately selected individuals.<sup>15</sup>



**Figure 1. Long Term Disease Control – Cryotherapy<sup>10</sup>**

The morbidity of salvage cryo includes incontinence, rectal injury, bladder neck contracture, and erectile dysfunction.<sup>15</sup> In a comparison of patients undergoing salvage cryo and SRP at MD Anderson Cancer Center, Pisters et al. concluded that, for younger patients with good life expectancy who are surgical candidates, SRP provides better long-term disease control than salvage cryo.<sup>16</sup> In a review of the published literature on salvage cryo, Finley and Beldegrun note that while complication rates have declined with experience, prospective trials of salvage cryotherapy are needed to better define the oncologic efficacy of this therapeutic approach (Finley and Beldegrun, *Curr Urol Rep*, 2011) (see Table 5).<sup>17</sup>

**Table 5. Oncologic Outcomes of Recent Whole Gland Salvage Cryotherapy Trials<sup>17</sup>**

Study	Patients, n	Follow-up, mo	Cryonit/cycles	cStage at RT	Gleason at cryo	Med pre-RT, and post-cryo PSA, ng/mL	Failure definition	ADT	Post-treatment biopsy, % +	bNED, %
Williams et al. [16 <sup>a</sup> ]	187	90	Candella, cryocare, FT 2x	≤ T2: 86.1%; ≥ T3: 13.9%	GS 6-7: 60.7%; GS ≥ 8: 39.3%	11.0, 4.9	Phoenix	71% neo, 32% adjuvant	6, 12, 24 mo (n=178): 16.7	64 DSS (10 y); 39 DFS; 87 OS
Pieters et al. [37]	279	21.6	Cryocare	NR	GS 6-7: 51.2%; GS ≥ 8: 43.7%	NR, 7.6	ASTRO & Phoenix	50.9% neo, 8.2% adjuvant	MD discretion, (n=46, 16.5%); 32.6	58.9 & 54.5 (5 y)
Donnelly et al. [38]	46	NR	Multi	≤ T2: 86.9%; ≥ T3: 13%	GS 6-7: 58.7%; GS ≥ 8: 41.3%	19.2, 5.6	Nadir +0.2 2x or >1.0	15.2% neo	MD discretion (n=NR)	-50 (3.3 y)
Ismaïl et al. [36]	100	33.5	Cryocare, SeedNet <sup>b</sup>	≤ T2: 70%; ≥ T3: 30%	GS 6-7: 63.0%; GS ≥ 8: 37.0%	NR, 5.4	ASTRO & PSA <0.5 ng/mL	22% neo, 24% adjuvant	PSA progression	59 (3 y)
Cheetham et al. [23]	51	121	2nd or 3rd generation FT 2x	Unknown in 90.2%	GS 6-7: 53.2%; GS ≥ 8: 46.8%	NR, 6.4	ASTRO & Phoenix	NR	NR	NR
Spess et al. [21]	450	40.8	NR	≤ T2: 67%; ≥ T3: 33%	GS 6-7: 82.7%; GS ≥ 8: 17.3%	2.2 (mean), 7.8 (mean)	PSA >0.5 ng/mL	38.1% neo, 0% adjuvant	NR	34
Bahn et al. [22]	59	82.3	NR, FT 2x	≤ T2: 69%; ≥ T3: 29%	GS 6-7: 71%; GS ≥ 8: 29%	NR, 5.6	Increase in PSA ≥0.5 ng/mL; 1.0 ng/mL	0% adjuvant	6, 12, 24, 60 mo if PSA rise or PSA >0.5 ng/mL (n=38, 64.4%); 0	59 (0.5 ng/mL), 69 (PSA 1.0 ng/mL)
Han and Beldegrun [39]	29	NR	SeedNet, FT 2x	NR	NR	NR, NR	PSA ≤0.4	NR	12 mo	72.2
Eisenberg et al. [27] <sup>a</sup>	15	18	SeedNet, FT 2-4x	≤ T2: 82.4%; ≥ T3: 17.6%	GS 6-7: 63.2%; GS ≥ 8: 36.8%	NR, 3.3	ASTRO & Phoenix	NR	12 mo (n=66.7%); 10	50, 79 (3 y)

<sup>a</sup> Hemibladder

<sup>b</sup> Manufactured by Galil Medical, Arden Hills, MN

ADT androgen deprivation therapy, ASTRO American Society for Therapeutic Radiology and Oncology, bNED biochemical no evidence of disease, cryo cryotherapy, DFS disease-free survival, DSS disease-specific survival, FT freeze/thaw, GS Gleason score, MD medical doctor, NR not reported, OS overall survival, PSA prostate-specific antigen, RT radiotherapy

Other centers have reported contemporary experience with salvage cryo and document recurrence free survival rates of approximately 40% at 10 years post salvage intervention, with complication rates similar to those documented by earlier reports.<sup>18,19</sup> The results from an analysis of the Cryo On-line Database (COLD) registry suggest that short term continence and biochemical control can be achieved in approximately 75% of patients but long-term follow-up data on large groups of prospectively studied patients will be required to better understand the role of salvage cryo in the treatment of patients with recurrent prostate cancer.<sup>20, 21</sup>

The further evolution of third generation cryotherapy technology, including the use of ultrathin cryoneedles (17G) and more guided pressurized, gas-exchange system using argon (to freeze) and helium (to thaw) gases, decreased dramatically the reported incidence of major complications with cryosurgery. For example, a group from Columbia University recently reported a relatively low rate of complications including incontinence (9.7%), voiding complications (5.8%), rectal pain (12.8%), and urinary retention (1.9%). Cohen compared the complications of salvage cryo between first, second, and third-generation devices showing tremendous improvements with each subsequent generation of devices, with a substantial decrease in serious side effects such as incontinence and rectourethral fistulas reported in a large, single institutional patient cohort.<sup>21</sup>

Mouraviev et al. summarize the reported rates of acute and late complications associated with SCA in Table 6.<sup>21</sup> Although the incidence of erectile dysfunction (ED) remains exceedingly high (72-86%) after salvage cryo (Table 6), recent studies would suggest a lower incidence of previous commonly occurring complications after salvage cryo such as perineal pain (8-39.5%), mild-moderate incontinence (4-40%), severe incontinence (2-4%), urinary retention (2-21%), and rectourethral fistula formation (0-3%). The major risk of salvage cryo even with contemporary third generation cryotherapy devices remains incontinence, but this risk is significantly lower than with salvage radical prostatectomy.

**Table 6. Complications of Salvage Cryoablation<sup>21</sup>**

References	No. of patients	Cryodevice	Incontinence, %	Obstruction/retention, %	Perineal pain, %	Rectourethral fistula, %	LUTS, %	UTI, %	ED, %
Pisters et al. [45]	150	Cryocare	73	67	8	1	NA	NA	72
Chin et al. [36]	118	Candela Cryocare	33.3	8.5	NA	3.3	NA	NA	NA
Bahn et al. [46]	59	Cryocare	8	NA	NA	3.4	NA	NA	NA
Han et al. [47]	18	Seednet	11	11	5.6	0	0	NA	86
Cresswell et al. [34]	20	Seednet	4	4	NA	0	0	NA	86
Ismail et al. [42]	100	Seednet	13	4	NA	1	16	NA	NA
Ghafar et al. [25]	38	Cryocare Seednet	7.9	0	39.5	0	15.8	2.6	NA
Pisters et al. [48]	279	Cryocare	4.4	3.2	NA	1.2	NA	NA	NA
Ng et al. [24]	187	Candela Cryocare	40	21	14	2	90	10	NA

LUTS = lower urinary tract symptoms; UTI = urinary tract infection; ED = erectile dysfunction; NA = not available.

In their systemic review paper on salvage local therapy after failure of radiotherapy for prostate cancer, Parekh found overall morbidity rates with salvage cryo to be: 16.4% incontinence, 15% perineal pain, 11.7% bladder neck strictures/retention, and 8.2% experienced tissue sloughing, and a 1.61% fistula rate.<sup>9</sup>

### 2.1.3 Brachytherapy

Brachytherapy - the insertion of individual radiation sources into a target organ - has been used for decades as an initial treatment for patients with organ-confined disease, and open implantation of I-125 radiation sources was employed initially in the 1980s for the management of recurrent disease.<sup>22</sup> The observed rate of local complications, including rectal fistula and ulcer formation, suggested that large volume implantation and the use of high energy sources were associated with greater morbidity in this small initial experience. Subsequent attempts at salvage brachytherapy using improved dosimetry, percutaneous access, and CT-guided source placement resulted in cancer control rates similar to those reported using other salvage techniques with transient minimal morbidity.<sup>23</sup>

More contemporary series, utilizing both salvage brachytherapy and androgen ablation, report intermediate term (4-year) freedom from biochemical recurrence in 75% of patients studied, but with local complication rates of 40%.<sup>24</sup> A review of the published literature on salvage brachytherapy following radiation therapy by Allen et al. reveals that salvage brachytherapy appears to achieve similar freedom from biochemical recurrence as other salvage modalities, albeit based on the study of small numbers of patients.<sup>25</sup>

**Table 7. Postradiotherapy Brachytherapy Salvage Series<sup>25</sup>**

Postradiotherapy Brachytherapy Salvage Series						
Year reported	Modality	Institution	Reference	Patients	Median follow-up, mo	DFS
1992	Prostatectomy	UCLA	Stein, et al. <sup>10</sup>	13	65.4	NA
1992	Prostatectomy + AD	City of Hope	Ahlering, et al. <sup>16</sup>	34	53	71% @ 4 y
1998	Prostatectomy	Mayo	Cheng, et al. <sup>18</sup>	86	69.6	CSS 64% @ 10 y
1998	Prostatectomy	Wayne State Univ	Gheiler, et al. <sup>15</sup>	40	36.1	47% @ 3 yrs
1998	Prostatectomy + AA*	Florida	Garzotto, et al. <sup>20</sup>	29	63.6	44-80% @ 5 y
1998	Prostatectomy	USC	Bochner, et al. <sup>11</sup>	18	N/A	NA
2000	Prostatectomy + AD <sup>†</sup>	Miami	Vaidya, et al. <sup>14</sup>	6	27	83% @ 2 y
2003	Prostatectomy	Paris	Vallancien, et al. <sup>21</sup>	7	11.2	71% @ 1 y
2005	Prostatectomy	MSKCC	Bianco, et al. <sup>22</sup>	100	60	55% @ 5 y
				<b>333</b>		
2000	Cryotherapy	Allegheny Genl Hosp	Benoit et al. <sup>27</sup>	87	60	58% @ 5 y
2001	Cryotherapy + AD <sup>‡</sup>	Columbia	Ghafar, et al. <sup>31</sup>	38	24	74% @ 2 y
2001	Cryotherapy	Ontario	Chin, et al. <sup>28</sup>	118	18.6	34-68% @ 3 y
2002	Cryotherapy	MDACC	Izawa, et al. <sup>35</sup>	131	57.6	23-57% @ 5 y
2003	Cryotherapy	Ventura	Bahn, et al. <sup>33</sup>	59	84	50-62% @ 7 y
2005	Cryotherapy	Calgary	Donnelly, et al. <sup>34</sup>	46	N/A	51% @ 1 y
				<b>479</b>		
1980	Brachytherapy	Stanford	Goffinet, et al. <sup>36</sup>	14	N/A	57% @ <3 y
1990	Brachytherapy	MSKCC	Wallner, et al. <sup>37</sup>	13	N/A	51% @ 5 y
1993	Brachytherapy	Iowa	Loening, et al. <sup>38</sup>	31	N/A	40% @ <5 y
1999	Brachytherapy	Mayo Scottsdale	Grado, et al. <sup>41</sup>	49	64.1	34% @ 5 y
2003	Brachytherapy	Milan	Losa, et al. <sup>42</sup>	10	20.6	~70% @ 2 y
2004	Brachytherapy	Arizona Oncology	Beyer <sup>40</sup>	30	46	~25% (high risk), ~67% (low risk) @ 3 y
2005	Brachytherapy	Brigham and Women's	Suh, et al. <sup>44</sup>	20	27.6	88% @ 3 y
2005	Brachytherapy	Mount Sinai	Lo, et al. <sup>43</sup>	30	59.3	48% @ 8 y
2005	Brachytherapy + AD <sup>‡</sup>	Mayo Scottsdale	Wong, et al. <sup>45</sup>	17	30	79% @ 4 y
2006	Brachytherapy + AD <sup>‡</sup>	Wisconsin	Allen, et al.	12	45	67% @ 4 y
				<b>226</b>		

DFS indicates disease-free survival; NA, not available; AD, androgen deprivation; AA, androgen ablation.  
\* 24 patients underwent 3 months neoadjuvant androgen ablation or orchiectomy.  
<sup>†</sup> Five patients underwent neoadjuvant androgen ablation for a mean of 6.3 months.  
<sup>‡</sup> All patients underwent 3 months neoadjuvant androgen ablation.

**Table 8. Oncological Results of Salvage Brachytherapy<sup>26</sup>**

References	No. pts	Median follow-up (months)	Adjuvant hormonal manipulation (%)	bDFS (%)	Definition of failure
Wallner et al.[57]	13	36	NA	51 (5yr)	Metastasis
Loening et al.[60]	31	23	NA	67 (5yr)	Overall survival
Grado et al.[54]	49	64	NA	34 (5yr)	2 rises above nadir
Nguyan et al.[30]	25	47	0	70 (4yr)	Phoenix[18]
Koutrouvelis et al.[55]	31	30	97	87 (5yr)	ASTRO[13]
Beyer et al.[56]	17	62	47	53 (5yr)	ASTRO[13]
Wong et al.[58]	17	44	71	57 (4yr)	ASTRO[13]
Lee et al.[59]	21	19	52	89 (2yr)	ASTRO[13]

bDFS = biochemical disease free survival, NA = not available

Other investigators have reported similar rates of short-term biochemical disease control in small series.<sup>27-30</sup> Quality of life studies on patients undergoing salvage brachytherapy suggest that return to baseline urinary and bowel function occurs slowly and may take more than two years to achieve in this population.<sup>31</sup>

**Table 9. Complications of Salvage Brachytherapy<sup>26</sup>**

References	No. pts	Incontinence (%)	Grade 1-2 GU toxicity (%)	Grade 3-4 GU toxicity (%)	Grade 1-2 GI toxicity (%)	Grade 3-4 GI toxicity (%)	ED (%)
Wallner et al.[57]	13	31	36	NA	NA	15	NA
Loening et al.[60]	31	0	23	NA	NA	NA	NA
Grado et al.[54]	49	6	12	14 (TURP)	4	2	NA
Nguyan et al.[30]	25	0	NA	16	NA	24	NA
Koutrouvelis et al.[55]	31	0	NA	NA	NA	5	NA
Beyer et al.[56]	17	24	NA	24	NA	0	NA
Wong et al.[58]	17	6	NA	47	29	6	NA

Lee et al.[59]	21	0	86	14	14	0	100 (Grade 2)
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NA- not available; GU-genitourinary; GI- gastrointestinal; TURP- tranurethral resection of prostate; ED- erectile dysfunction

#### 2.1.4 Early Hormone Therapy (HT)

In spite of the conflicting data in the literature addressing the issue of the role of HT in salvage settings, it is still considered the standard of care and thus an historical control for patients presenting biochemical and systemic failure after primary definitive therapy of localized prostate cancer. It remains controversial whether early-salvage HT (i.e., at the time of biochemical failure) has better outcomes than either late-salvage HT (i.e., at the development of clinically evident distant metastases) or observation. Data from non-randomized studies comparing early-versus late-salvage HT after RT are summarized in Table 10.<sup>32</sup> These studies showed improved overall survival (OS) with HT according to PSA level (<10 ng/mL, ≤ 15ng/mL, or < 20 ng/mL). This improvement is limited only to patients with a low PSA, M0 patients and/or to patients with longer PSA-DT (>7 months and >12 months). Conversely, a retrospective cohort analysis of 248 men with biochemical failure after EBRT showed no advantage for HT (versus “watchful waiting”) in the subgroup of men with a PSA-DT >12 months (P =0.74), leading to the conclusions that patients with signs of local recurrence only (low-risk patients with late recurrence signs and a slow PSA rise) are best managed by observation alone.<sup>32</sup> A recent secondary analysis of patients enrolled in the ICORG 97-01 randomized trial (comparing 4 months versus 8 months of neoadjuvant HT before RT for intermediate-to high-risk prostate cancer) showed that early salvage HT, based on PSA ≤ 10 ng/mL and the absence of distant metastases, improved OS. Besides the limitations of the retrospective analysis, these reports evidenced the positive impact on OS of starting HT at the earliest sign of recurrence. These advantages must be weighed against potential impact on quality of life or on age-related health problems, especially for young men and for long-term schedules. Therefore, the optimal management and prescription of HT in patients with localized prostate cancer developing biochemical failure after primary definitive therapy still remains controversial, and some alternative schedules have been proposed. Two randomized trials are currently ongoing, addressing the relevant issue of early HT in patients who relapse after initial curative RT.<sup>32</sup>

**Table 10. Studies Comparing Early vs. Late Salvage Androgen Deprivation Therapy (ADT) After Radical Radiotherapy (RT) With or Without ADT for Prostate Cancer<sup>32</sup>**

Ref	Study design	Population	Number of patients	Median follow-up (years)	Outcomes after salvage AD
34	Retrospective analysis	Clinically localized prostate cancer (all risk) treated with RT alone	381	3.8–4.2	PCSS and OS improved with early-salvage ADT (PSA < 10 ng/mL BS-negative versus PSA > 10 ng/mL BS-negative versus BS-positive)
35	Secondary analysis of RTOG 8610	Bulky stage T2–T4 prostate cancer, N0/N1, randomized to RT + 4 mo ADT versus RT alone	247	9	OS improved with early-salvage ADT (M0 versus M1, and PSA level < 20 versus > 20 ng/mL)
36	Retrospective analysis	Clinically localized prostate cancer (all risk) treated with RT ± ADT, includes post-prostatectomy RT for rising PSA	124	6.2	OS improved with early-salvage ADT (PSA < 15 ng/mL versus > 15 ng/mL [HR 2.15] and PSADT > 7 versus < 7 mo [HR 2.63])
37	Secondary analysis of RTOG 8531	Unfavorable-prognosis prostate cancer (i.e., T3 or N1), includes post-prostatectomy pT3, randomized to RT + adjuvant life-long ADT versus RT alone	243 (RT-alone arm)	8.5	OS improved with early-salvage ADT (PSA < 10 ng/mL versus ≥ 10 ng/mL [HR 1.5])

Ref, reference; ADT, androgen deprivation therapy; BS, bone scan; DSS, disease-specific survival; HR, hazard ratio; LF, local failure; M0, distant metastasis absent; M1, distant metastasis present; N0, pelvic node negative; N1, pelvic node positive; OS, overall survival; PCSS, prostate cancer-specific survival; RTOG, Radiation Therapy Oncology Group; PSADT, PSA doubling time.

### 2.1.5 Summary

Patients with locally recurrent prostate cancer following definitive radiation therapy have been treated by SRP, cryo, brachytherapy, and HIFU. Hormone therapy is sometimes used as an adjuvant therapy to these salvage treatments. The available data on the efficacy and safety of these modalities of care are limited. Most reports document single institutional, retrospective experiences in small groups of patients. Randomized, controlled studies have not been performed. To the extent that the available data can be summarized, it can be concluded that approximately 50% of patients treated by any of the above-referenced methods will achieve short-to intermediate-term biochemical control of disease. Local toxicity from therapy is significant and includes erectile dysfunction, voiding dysfunction, and a relatively small but real risk of serious gastro-intestinal morbidity.

A recent review of salvage therapies by Peters et al., shown in Table 11, underscores the morbidity of salvage therapy in general and the particular impact on sexual function in patients with a history of prior radiation therapy:<sup>33</sup> Erectile dysfunction at 72% with radical prostatectomy and 72-86% with cryotherapy; Incontinence at 20-68% for RP and 4-83% with cryotherapy; Bladder neck strictures at 22-24% for RP, 38% for BT, and 7-55% for cryo; GI toxicity at 2-7% rectal in jury for RP and 1-12% BT, 6-37% perineal pain and 1-11% fisula for cryo.

**Table 11. Review of Salvage Therapies<sup>33</sup>**

Table 4 Comparison with results from previous literature—toxicity	Salvage procedure	Radical prostatectomy	125-I implantation	Cryosurgery
	<i>Literature</i>			
	No. studies [references]	5 [9, 11, 20, 22, 27]	3 [9, 23, 24]	6 [9, 25, 28–31]
	<i>N</i>	308	66	707
	% GU toxicity	20–68 % incontinence 22–41 % bladder neck stricture	12 % grade 1–2 38 % grade 3–4	4–83 % incontinence 7–55 % bladder neck stricture/retention
	% GI toxicity	2–7 % rectal injury	0–12 % grade 1–2 0–2 % grade 3–4	6–37 % perineal pain 1–11 % fistula
	Erectile dysfunction	72 %—Nearly uniform	NA	72–86 %
<i>Present study</i>				
	% GU toxicity	23 % grade 3	23 % grade 3	22 % grade 3
	% GI toxicity	9 % grade 3	6 % grade 3	7 % grade 3
	Erectile dysfunction	86 %	45 %	93 % <sup>a</sup>

*GU* genitourinary; *GI* gastrointestinal; *NA* not available  
<sup>a</sup> 44 % of patients had pre-existent erectile dysfunction

In Cancer Control and Complication of Salvage Local Therapy After Failure of Radiotherapy for Prostate Cancer: A Systematic Review<sup>9</sup>, by Parekh, a direct comparison between therapeutic interventions had strikingly similar biochemical disease free survival rates at 5 years: 55.6% for brachytherapy, 52% for prostatectomy, 56% for cryotherapy, and 52% for HIFU. Incontinence rates were found to be the highest for SRP at 49.7%, and lowest with brachytherapy at 6%.

Stricture rates were most common with SRP at 26%, and least common with cryo at 4.2%. Fistula rates were quite low across all series and technologies, ranging from 1-4%, while rectal injury ranged from 2-5%.<sup>9</sup>

## **2.2 Proposed Indications for Use**

The Sonablate® 450 (Sonablate) is indicated for the treatment of biopsy proven recurrent prostate cancer, stage T1c- T2, in patients who have failed primary External Beam Radiation Therapy and have a PSA < 10 ng/mL.

## **2.3 Regulatory and Marketing History**

The Sonablate system received CE mark in July 2001. It is commercially available in over 30 countries throughout Europe, South America, Central America, Australia, Canada, Mexico, Bermuda, and the Caribbean.

Focus Surgery, Inc. received approval for the feasibility study (IDE G000280) in November 2000. The first subject was treated in 2002, and the IDE Final Report was submitted in October 2007.

Focus Surgery, Inc. received conditional approval for the pivotal study (IDE G080057), which supports this Premarket Application (PMA) in May 2008, with final approval in December 2008. The first subject was treated in February 2009. IDE Supplement 10 was approved by the FDA in July 2009 to allow for an interim analysis on the first 100 subjects treated in the study.

Focus Surgery became a fully-owned subsidiary of USHIFU, LLC (US HIFU) on 01 July 2008. Effective 21 February 2013, the company changed its name from USHIFU, LLC to SonaCare Medical, LLC (SonaCare Medical).

SonaCare Medical submitted an application for Premarket Approval to the FDA in January 2013 which included data on 100 enrolled subjects. The FDA response letter, dated 28 February 2013, indicated our application was granted expedited review, as the “device represents a significant clinically meaningful advantage over existing alternatives”. An amendment to the PMA was submitted in July 2013 which included updated clinical trial data to include 12-month follow-up data on all 100 subjects treated in the study.

The clinical trial (IDE G080057) supporting this PMA is ongoing. Subjects continue to be enrolled and continue to be followed and evaluated for study endpoint criteria at 12 months. Subjects that meet the study endpoints continue to be followed to year 5 post-treatment in order to assess for long-term effectiveness. Subjects who do not meet the 12 months endpoint criteria of biopsy and PSA are not carried forward into the long-term analysis (post approval study).

### 3 SONABLATE® 450 OVERVIEW

#### 3.1 Device Description

The Sonablate® 450 (Sonablate) is a computer-controlled device designed for transrectal delivery of high intensity focused ultrasound (HIFU) energy to the prostate for treatment of prostate cancer via thermal ablation. The device makes use of integrated biplanar ultrasound imaging for real-time treatment monitoring, treatment planning, and pre- and post-treatment imaging of the prostate.

The Sonablate system consists of the following basic components and accessories (see Figure 2 below):

- Sonasource Console with an integrated digital thermal printer and a flat screen monitor
- Sonablate Probe 30/40 (two per system)
- Sonachill™ Chiller
- Sonablate Two-Axis Stepper
- Sonablate Probe Arm
- Accessories (O-Ring Applicator and O-Ring, Probe Tip, Sonachill Cleaning Kit, Probe Cleaning Tubing Kit, and Procedure Treatment Kit)



**Figure 2. Sonablate® 450 System**

(Sonasource Console, Sonablate Probe 30/40, Sonachill and Sonablate Probe Arm shown)

### 3.1.1 Sonasource Console

The Sonasource Console is an assembly of various components and sub-assemblies, which include a Windows-based computer with Sonablate software, as well as, power, imaging, and transducer control assemblies.

The high-resolution flat panel color monitor displays all system, patient, imaging, and treatment information via a graphical user interface (GUI). During the treatment session, updated (live) images of the prostate are acquired and displayed on the screen immediately after each HIFU exposure, helping the user to monitor changes in the tissue being treated. The GUI information guides the user through the treatment planning and execution process.

### 3.1.2 Sonablate Probe 30/40

The Sonablate Probe 30/40 (Probe) incorporates proprietary transducer technology that is designed to provide gray-scale ultrasound images of the prostate and also deliver high-intensity focused ultrasound (HIFU) to targeted tissue without damaging intervening tissue.

### 3.1.3 Sonachill Chiller

The Sonachill Chiller provides a constant flow of cold water to the Probe in order to provide coupling between the transducer and tissue, help remove heat from the transducer surface, and aid in keeping the rectal wall temperature at safe levels.

### 3.1.4 Sonablate Two-Axis Stepper and Probe Arm

The Two-Axis Stepper is used to make fine adjustments to optimize probe positioning in relation to the prostate. The Probe Arm is used to stabilize the Probe while it is in the patient's rectum during the Sonablate HIFU procedure.

## 3.2 Principles of Operation

The main mechanism of action with HIFU therapy is the thermal destruction of tissue, referred to as thermal ablation. Tissue absorption of ultrasound energy results in the buildup of heat, which increases rapidly to the point where cell death via coagulative necrosis occurs. Coagulative necrosis is a process by which cellular changes lead to cell death - coagulation of proteins.

During treatment with the Sonablate, the temperature of the prostate tissue in the focal zone is elevated above 60 degrees Celsius (140 degrees Fahrenheit) in a short duration (< 3 seconds) while the intervening tissue between the transducer and the focal zone is kept at physiologically safe temperatures. The HIFU beam is kept on for 3 seconds resulting in an elementary thermal lesion of larger volume by the process of *tissue heat conduction*. The high temperature results in thermal coagulative necrosis of the prostate tissue. The site intensity in the focal zone is in the

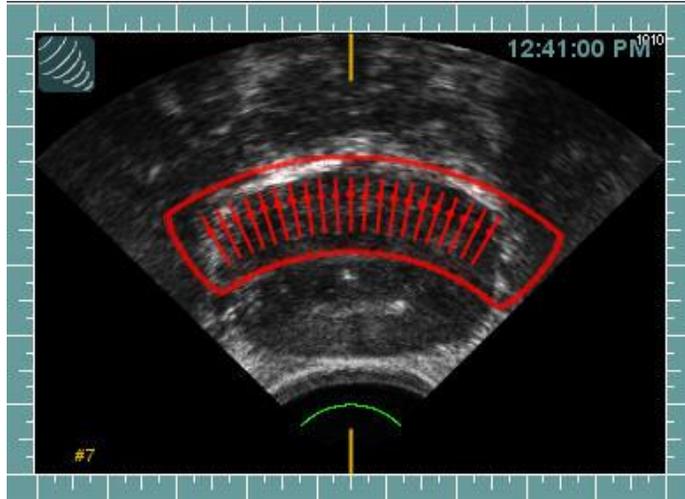
range of 1200 to 2000 W/cm<sup>2</sup> depending on the dosage setting, probe focal length, and the tissue depth. The resulting elementary lesion volume is approximately 108 mm<sup>3</sup>. The HIFU ON time of 3 seconds is followed by an OFF time of 6 seconds to cool down the transducer surface and to avoid overheating of the tissue outside the targeted zone. Larger tissue lesion volume is generated by placing several overlapping elementary lesions adjacent to each other through precise mechanical movements of the transducer in two perpendicular planes (longitudinal and transverse planes) controlled by the Sonablate's computer. During the OFF time, the transducer is positioned to the next treatment site. The system takes updated real-time ultrasound images of the prostate in both longitudinal and transverse planes and displays them on the screen for the purpose of real-time treatment monitoring. Multiple elementary lesions are created to treat the entire selected tissue volume of the prostate.

### 3.3 Clinical Use

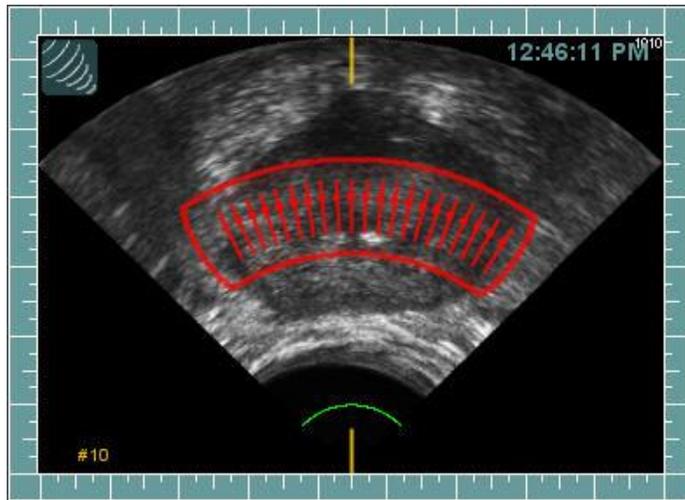
The Sonablate software is started, and a series of system tests are performed. Prior to treatment the patient is placed in a supine position and anesthesia is administered. The type of anesthesia chosen should, as far as possible, eliminate potential patient movement. Use of nitrous oxide is contraindicated due to the risk of the introduction of an unintended gas effect in the treatment area. A suprapubic and urethral catheter are placed prior to insertion of the Sonablate Probe (probe). The urethral catheter is used to assist with positioning of the probe and to identify anatomical landmarks (bladder neck, apex, etc.), as well as an aid in the placement of the suprapubic catheter. The urethral catheter is removed prior to beginning actual HIFU treatment. The suprapubic catheter remains in place for an average of 2-4 weeks, until the patient is able to void on his own.

The probe tip is covered with a latex sheath (non-latex sheath is also available) and primed with degassed water. The patient's anus is dilated prior to inserting the probe. The Stepper is attached to the surgical bed, the Probe Arm is attached to the Stepper for stabilization, and the probe is inserted into the probe arm. The probe is then inserted into the patient's rectum using ultrasound coupling gel. Ultrasound images of the prostate in sagittal and transverse planes are obtained to ensure that the treatment is technically feasible (i.e. anterior gland is accessible, absence of acoustic shadowing, etc.) and to aid in the final placement of the probe. Reference Images are created and are used as a point of reference throughout the treatment in order to show treatment effect and possible gland movement. Next, a treatment plan is created and treatment commenced.

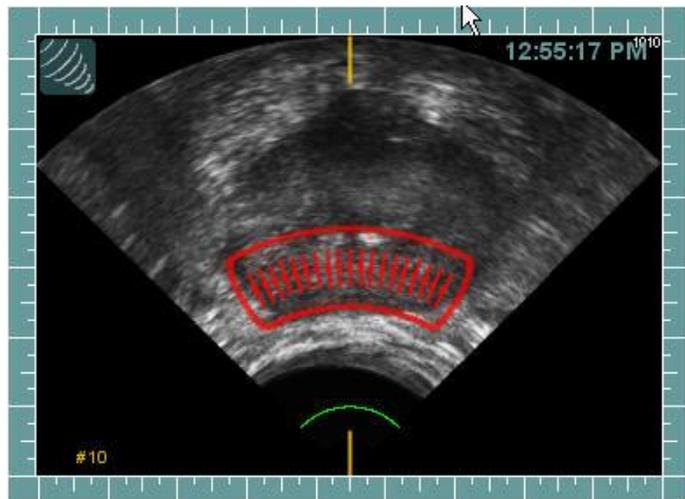
As illustrated in Figures 3, 4, and 5, the prostate is divided into multiple zones to treat the whole prostate. The first zone is always along the anterior portion of the prostate with the subsequent zones placed to treat towards the rectal wall (middle and posterior portions) to ensure that all parts of the prostate are treated. The 4.0 cm transducer is used to treat the anterior zone and the mid-gland of the prostate. The 3.0 cm transducer may be used to treat the middle zone if the rectal wall is beyond 2.0 cm with the use of the 4.0 cm transducer. Lastly, the 3.0 cm transducer is used to treat along the posterior side of the prostate.



**Figure 3. Anterior Treatment Zone**



**Figure 4. Middle Treatment Zone**



**Figure 5. Posterior Treatment Zone**

The apex and external urinary sphincter are imaged using the sector (transverse view) and the linear (sagittal view) imaging capabilities of the Sonablate. This real-time imaging of the apex of the prostate enables clear recognition of the urogenital diaphragm and the apex of the prostate, thereby defining the external urinary sphincter. This region is avoided during treatment planning, and the images are updated during HIFU treatment to permit the user to interrupt treatment if the external urinary sphincter moves into the treatment zone as a result of patient or prostatic gland movement. Power is set with User Manual recommendations based on rectal wall distance and then the user has the ability to increase or decrease the power based on tissue changes observed during the HIFU treatment. The total treatment time is approximately 2-4 hours based on the size of the prostate. On average, 10 cc of prostate tissue is ablated per hour of treatment.

Once treatment is completed, the patient is recovered per hospital protocol, which typically takes 2-3 hours. Upon discharge the patient is given catheter care instructions, an Emergency Care Card, and trained via demonstration/return demonstration method.

### 3.4 Safety Features

Sonablate® 450 safety features include hardware, software, procedure planning, and imaging. Below is a list of key safety features:

- **Emergency stop button:**
  - Can be used in emergency situations to stop the delivery of HIFU and the Sonachill unit. The planned treatment or program is not changed, which allows for continuing the process as soon as the issue is corrected.
  
- **Reference and Actual Images:**
  - The set (stack) of images used to plan the treatment are maintained as “Reference Images” so the user can compare them against the “Actual Images” (real time treatment images) during treatment to ensure that treatment is being delivered as planned.
  
- **RIM (Reflectivity Index Monitor) Box:**
  - This is used to monitor rectal wall heating. Using both the Reference Images and Actual Images, the brightness of the rectal wall is compared. A brighter rectal wall on the Actual Image versus the Reference Image indicates increased heat absorption.
  
- **Probe Tip Temperature Indicator:**
  - Displayed on the screen of the console is the temperature of the water inside the probe tip. In addition, a color coded reference for temperature (green - within range; yellow - upper end of range; red - above of normal range) is included for ease of reference.

- **Rectal Wall Distance:**
  - Rectal wall height is constantly monitored by tracking chevrons (reference points). The chevrons indicate the position of the rectal wall on the screen and change colors (green - within range; yellow - upper end of range; red - above of normal range) as the rectal wall becomes closer to the treatment zone. In the event the chevrons become red, the software will alarm and treatment stops automatically.
- **Reverberation:**
  - The software will identify reverberation (loss of acoustic coupling) conditions on the screen. If this occurs, the software will show an alarm, treatment will stop automatically, and treatment cannot continue until the condition is corrected.
- **Forward and Reverse Power Monitoring:**
  - The output of the HIFU transducer is constantly monitored. If the output falls below the alarm setting (threshold) the software will stop treatment.
- **Watchdog Circuit:**
  - The software monitors the duty cycle of HIFU treatment. The watchdog circuit confirms that the ON and OFF times are met during HIFU treatment.
- **Screen Grid:**
  - To aid identifying displacement of the gland (patient movement, swelling, edema) there is a Grid Toll. This allows for easy comparison of the position of the gland before (Reference Images) and after the current treatment (Actual Images).
- **Transducer Current Limits:**
  - If there is any obstruction in the movement of the transducer (Linear/Sector) the software will alarm and treatment automatically stop until the condition is resolved.

### 3.5 Contraindications

Contraindications to treatment include the following:

- The operator must avoid regions in tissue through which the treatment beam will pass that might alter the beam focus. Varying attenuation (tissue absorption) among these tissues may cause an unpredictable lesion size. For instance, patients with significant (>10mm) fluid-filled cavities (cysts), large reflective surfaces (significant calcifications >10mm or a urethral stent) in the treatment zone are excluded from treatment.

- Treatment with the Sonablate requires that the transrectal probe be covered with a sheath (latex or latex-free) prior to insertion.
- Clinical or histological evidence of urinary bladder cancer.
- Urethral stricture.
- Metal implants or stents in the urethra.
- History of prostatitis within the past 6 months.
- Men with brachytherapy seeds adjacent to the posterior prostate capsule, the Denonvilliers' fascia, or the rectal wall.
- Men who have had their prostate removed surgically.
- Men with evidence of metastatic disease.
- Men with an inability to tolerate a transrectal ultrasound.
- Men with active urinary tract infection.
- Men with functional bladder problems.
- Men who have undergone prior significant rectal surgery.

## **4 NON-CLINICAL STUDIES**

The Sonablate® 450 (Sonablate) has undergone comprehensive non-clinical testing to demonstrate that its performance properties are appropriate for clinical use. A list of tests is included in Table 12 below.

### **4.1 Electrical Safety**

The Sonablate system was tested to demonstrate compliance with applicable IEC 60601 collateral and particular standards. The essential performance and safety testing was conducted in accordance with requirements set forth by the 60601-1 (3rd Edition) standard. The EMC compliance testing was conducted in accordance with requirements set forth in 60601-1-2 standard. The Sonablate system passed all applicable tests from 60601-1 and 60601-1-2.

The particular standard applicable to the Sonablate system is the 60601-2-37 that provides the necessary requirements for basic safety and essential performance of ultrasonic diagnostic equipment. The Sonablate system passed all applicable tests from 60601-2-37.

## **4.2 Bench Testing**

### **4.2.1 Imaging Verification**

Imaging testing was performed to verify the imaging functionality of the Sonablate system. Imaging functions such as resolution and contrast for tissue differentiation, ability to acquire and display transverse and longitudinal images, and image acquisition frame rate were verified using the protocol described in “Imaging Resolution and Scanning.”

### **4.2.2 Therapy Verification**

Therapy testing included verification of physical and functional aspects of the Sonablate and the probe arm accessories. The primary functions related to HIFU treatment that were verified included acoustic power output, focal site intensity, prostate volume being treated, and average temperature outside the treatment zone. The physical and functional aspects of the probe, chiller, probe arm, and stepper also were verified. This testing assessed the ability of the subsystems to perform as an integrated system.

### **4.2.3 User Interface Verification**

The user interface verification testing was performed to verify the hardware and software interface of the Sonablate system. These tests covered user interface aspects that are critical for the safe operation and control of the power being delivered during the treatment.

### **4.2.4 Coupling Verification**

The coupling verification test verifies adequate coupling between the HIFU transducer and the patient’s body. This includes testing with a phantom to verify that there are no reverberations in the visible image when the probe is prepared as instructed in the User’s Manual.

### **4.2.5 Digital Recordkeeping Verification**

The digital recordkeeping verification test verifies that the Sonablate system provides a means for archiving patient data onto a removable media such as a CD or DVD. The test also verifies that the user is able to save data during the treatment onto an optical disk.

### **4.2.6 Reliability Testing**

The Sonablate system reliability estimation was performed using field service data from devices installed in the USA (clinical trial) and outside the USA (which are approved for use in the countries in which they are located). The reliability data was calculated for each sub-system and for each sub-assembly within a sub-system. Reliability estimation establishes system performance over an extended period of time in a real user environment.

#### 4.2.7 Distribution and Storage Verification

The Sonablate device will be transported by air (internationally) and by ground (within the USA). The Sonablate system, with all accessories, is shipped in a wooden crate. Shipping verification tests were performed to demonstrate compliance with ISTA 3E for shipping the entire crate that holds all the sub-systems and accessories and ISTA 3A for shipping an individual probe.

The shipping test for the entire crate was also conducted in compliance with the ASTM D4169 standard. The requirements for the tests specified in the ASTM D4169 for shipping a crate are significantly more rigorous as compared to the ISTA 3E.

The procedure treatment kit has been validated for a six-month shelf life through accelerated age conditioning and real time age testing. Shipping verification tests were performed to demonstrate compliance with the ASTM D4169 standard.

**Table 12. Sonablate® 450 Non-Clinical Testing**

<b>Objective</b>	<b>Summary Results</b>
Imaging Verification	Meets required acceptance criteria.
Acoustic Power Output, Focal Site Intensity, and Depth	Meets power Design Input Requirements.
Verification of HIFU Redundancy	System can effectively stop therapy and indicate a system error with an alarm with acceptable system of redundancy.
Prostate Volume Verification	System is capable of treating a tissue volume of up to 40 cm <sup>3</sup> with tissue thickness up to 40 mm.
Probe Dimension Verification	Probe dimensions are within recommended limits.
Lesion Size and Lesion Volume Verification	System is capable of creating single and volume lesions in x,y, and z dimensions that meet acceptance criteria.
Focal Zone and Non-Focal Zone Temperature Verification	Temperature levels are sufficient to induce coagulative necrosis without damaging rectal wall.
HIFU ON time/OFF time Verification	System meets ON-time/OFF-time requirements.
Verification of Two-Axis Stepper	Meets required acceptance criteria.
Verification of Probe Arm	The probe arm meets the acceptance criteria.
Verification of Treatment Consumables	Treatment consumables related to the water path meet required acceptance criteria and fulfill Design Input Requirements.

<b>Objective</b>	<b>Summary Results</b>
Verification of Sonachill Chiller	Able to cool and degas the water according to Design Input Requirements.
Verification of TAP Meter	Meets sub-system requirements.
Verification of Probe Arm Attachment Clamp	Probe arm attachment clamp meets required acceptance criteria and fulfills Design Input Requirements.
Cleaning and Sterilization	Reprocessing methods were validated by Nelson Laboratories. The reusable components of the system, probe arm and two-axis stepper, are cleaned and steam sterilized achieving a sterility assurance level of $10^{-6}$ according to the instructions for use. The Sonasource console and Sonachill are non-critical environmental surfaces which meet the cleaning requirements of TIR12:2010 when reprocessed according to the instructions for use.
Energy Control Verification	Passed all acceptance criteria.
User Interface Verification	Meets all acceptance criteria.
Shipping Verification	Meets acceptance criteria outlined in ASTM D4169-09.
Probe Cleaning and Sterilization	The probe reprocessing methods were validated by Nelson Laboratories and the cleaning and ethylene oxide sterilization process is effective, achieving a sterility assurance level of $10^{-6}$ .
Disposable Sterilization	The procedure treatment kit is sterilized using gamma radiation using the VDmax (27.5 kGy) method (ANSI/AAMI/ISO 11137-2:2012), achieving a sterility assurance level of $10^{-6}$ .
Power Supply Verification	Meets required acceptance criteria and Design Input Requirements.
Verification of Remote Access	System does not connect to any outside communication network.

### 4.3 Biocompatibility

Biocompatibility testing included:

- Cytotoxicity (ISO 10993-5)
- Sensitization (ISO 10993-10)
- Rectal Irritation
- Hemocompatibility

## 4.4 Pre-Clinical Animal Evaluations

In order to assess the fundamental performance characteristics of the Sonablate, a series of *in vivo* experiments were carried out in a canine model. The canine prostate is similar in anatomic location and physical configuration to the human prostate.

Two animal studies (Study 1 and Study 2) were performed in support of Investigational Device Exemptions G000280 and G080057.

A series of laboratory and animal tests also were performed that tested the safety and effectiveness of the Sonablate device. These tests included testing the system ON and OFF times, ability to ablate tissue within the planned treatment zone, and verification of the active Sonachill chiller system. Tests were performed using turkey tissue and an in-vivo canine model. Test results indicated a less than 0.6% difference in planned versus treated volumes, the ability to correctly raise the temperature of targeted tissue to above 70 degrees and the ability to limit the dose delivered to tissue outside the targeted zone to less than 60 degrees. In tests where the entire animal's prostate was targeted, histopathological examination revealed coagulative necrosis in the treated prostate tissue. The rectal wall was shown to be free of pathologic change in all cases and the bladder was spared pathologic changes in all but one dog where review of the plan indicated poor target identification. The results of these animal studies demonstrate the ability of the Sonablate to destroy prostate tissue while sparing surrounding non-target tissue.

All patient-contacting materials have demonstrated appropriate biological safety profiles for the nature and duration of tissue contact through extensive testing performed in compliance with ISO 10993-1 and FDA Blue Book memorandum G-95.

## 5 CLINICAL STUDY: IDE G000280

The system was studied initially in humans with recurrent prostate cancer under a feasibility trial (IDE G000280).

### 5.1 Study Design

The trial was designed to study the Sonablate device in the context of treating recurrent prostate cancer in two groups of 10 subjects each: Group 1 – subjects with locally recurrent prostate cancer following external beam radiation therapy (EBRT); and Group 2 – subjects with locally recurrent prostate cancer following primary brachytherapy (Brachy). Eleven subjects were enrolled (10 in the EBRT arm and 1 in the Brachy arm) from 2002 to 2006.

Study success was defined as PSA nadir  $\leq 0.5$  ng/mL AND a negative biopsy at 180 days post-treatment.

## 5.2 Summary of Results

Nine of the 11 subjects (81.8%) achieved PSA nadir of  $\leq 0.5$  ng/mL. Ten of the 11 subjects (90.9%) had a negative biopsy at 180 days post-treatment.

The overall success rate (nadir + negative biopsy) at 180 days was 81.8% (9/11).

No serious adverse events associated with the device or procedure were reported.

Assessment of voiding and sexual dysfunction following therapy was performed using the International Prostate Symptom Score (IPSS) and International Index of Erectile Function (IIEF) questionnaires. Data from this trial indicated that treatment was associated with worsening of both voiding and sexual function compared to baseline in the patients studied. Short-term treatment associated voiding and sexual dysfunction were noted in this trial but improved as expected over the 180 day follow-up period.

## 6 CLINICAL STUDY: IDE G080057 (STAR Trial)

The study objective for the pivotal IDE G080057, *A Multicenter Clinical Study of the Sonablate<sup>®</sup> 450 for the Treatment of Locally Recurrent Prostate Cancer with HIFU* (FSI-003 STAR Trial), is to determine the safety and effectiveness of the Sonablate using data from pre-treatment screenings, treatment records, and scheduled follow-up visits through 12 months post-treatment.

### 6.1 Primary Objective

Local control of prostate cancer  $\geq 40\%$ . Local control is defined as achieving:

- Absence of biochemical failure – PSA nadir of  $\leq 0.5$  ng/mL within 12 months post-treatment; and
- Negative biopsy at 12 months post-treatment

### 6.2 Study Design

The study is a non-randomized, prospective, single arm study. The safety and effectiveness of the Sonablate treatment in subjects with locally recurrent prostate cancer was evaluated with regard to freedom from biochemical failure and disease recurrence following HIFU treatment.

#### 6.2.1 Study Population

The study population was composed of men (40-85 years of age) with histologically confirmed, organ-confined, recurrent, non-metastatic prostatic adenocarcinoma. All participants had documented disease relapse two or more years following external beam radiation therapy

(EBRT). All participants had a prostate specific antigen (PSA) level  $\geq 0.5$  ng/mL and  $\leq 10$  ng/mL, and clinical stage T1c-T2 prior to radiation. Participants were candidates for salvage therapy on the basis of an assessment of general health and inter-current comorbidities.

### 6.2.2 Number of Trial Sites and Subjects Planned

A maximum of 200 subjects could be enrolled and up to 20 clinical trial sites were planned for this study. The first study cohort includes 100 subjects enrolled at 16 clinical trial sites.

**Table 13. IDE G080057 Clinical Trial Investigators**

Investigator Name	Site Name	Location
Earl Gurevitch	Specialists in Urology	Naples, FL
David Jarrard	University of Wisconsin	Madison, WI
William Huang	New York University	New York, NY
Leonard Marks/Allan Pantuck	UCLA	Los Angeles, CA
Lee Ponsky/Robert Abouassaly	University Hospitals	Cleveland, OH
David McLeod	Walter Reed National Military Medical Center	Bethesda, MD
Joseph Chin	London Health Sciences Center	London, ON
James Bailen	Metropolitan Urology	Jeffersonville, IN
Jack Barkin	Can-Am	Toronto, ON
John Ward	MD Anderson Cancer Center	Houston, TX
Laurence Belkoff	Urologic Consultants of SE PA	Bala Cynwyd, PA
Benjamin Lee	Tulane University	New Orleans, LA
David Chen	Fox Chase Cancer Center	Philadelphia, PA
Michael Koch/Thomas Gardner	Indiana University	Indianapolis, IN
James Donovan	University of Cincinnati	Cincinnati, OH
Edward Uchio/Matthew Bui	Tower Urology	Los Angeles, CA

### 6.2.3 Endpoint Definitions and Analysis Plan

Primary endpoint is local control of prostate cancer. Local control is achieved if both of the criteria in the combined endpoint are met:

1. Achieving a PSA nadir of  $\leq 0.5$  ng/mL within 12 months of treatment, and
2. Negative prostate biopsy at 12 months.

Secondary endpoints are evaluated at 12 months post-treatment and compared to baseline values:

- Mean change in the International Index of Erectile Function (IIEF-5) score
- Mean change in the International Prostate Symptom Score (IPSS) score
- Mean changes in the Expanded Prostate Cancer Index Composite (EPIC)-26 values
- Overall and cause specific survival rates

The freedom from prostate cancer rate (as defined by a nadir PSA within 12 months of  $\leq 0.5$  ng/mL and a negative prostate biopsy at 12 months following therapy) will be compared to an objective performance goal of 40% using a Chi Square scores test, as per the protocol.

#### 6.2.4 Inclusion Criteria

- subjects with initial presentation of organ confined recurrent prostate cancer (Stages T1c and T2 only) who have been treated with EBRT (conventional, 3D conformal, or IMRT) or proton therapy, two or more years prior, and currently have biopsy proven local recurrence. Previous radiation therapy must be to a documented therapeutic dose of 60 to 81Gy or GyE (gray equivalent) for proton therapy;
- negative bone scan within 6 months prior to enrollment to rule out metastases;
- negative CT scans of the chest, abdomen, and pelvis within 6 months prior to enrollment to rule out metastases;
- age  $\geq 40$  years through  $\leq 85$  years of age;
- prostate biopsy with  $\geq 10$  core biopsies demonstrating 1 or more cores positive for cancer cells within 6 months prior to treatment;
- prostate volume  $\leq 40$  gm(cc) (HIFU subject prostate volume will be initially calculated utilizing TRUS measurements during screening and verified with the use of the Sonablate before initiating the HIFU procedure. Patients with prostate volumes greater than 40 gm(cc) as determined by either measurement will not be enrolled in the study);
- AP diameter of the prostate  $\leq 4.0$  cm;
- serum prostate specific antigen (PSA)  $\geq 0.5$  ng/mL and  $\leq 10$  ng/mL;
- $> 90$  days post hormone therapy usages (Subjects who have had or are currently undergoing hormone therapy (GnRH agonist/antagonist) must discontinue hormone therapy and go through a 90 day washout period prior to consideration for study participation, and must remain off hormone therapy throughout the duration of the follow-up period (5 years));
- signed informed consent for the HIFU treatment through the 12-month follow-up visit (7 visits) and then through the extended follow-up period of 5 years (4 additional visits); and
- life expectancy  $> 12$  months.

#### 6.2.5 Exclusion Criteria

- American Society of Anesthesiologists (ASA) criteria of IV or higher;
- intra-prostatic calcifications  $> 1.0$  cm (single or continuous grouping) on 2 or more consecutive images along the same plane by either the TRUS or Sonablate 450 measurement will not be enrolled;

- active, uncorrected bleeding disorder as determined by abnormal prothrombin time, partial thromboplastin time, or INR at the time of HIFU (use institutional lab normal ranges for parameters);
- use of coumadin or any other anticoagulant, unless anticoagulation can be temporarily reversed or stopped;
- active urinary tract infection;
- interest in future fertility;
- body weight which would preclude proper suprapubic catheter functioning, per investigator's discretion;
- inability to visualize the prostatic tissue adequately on transrectal ultrasound imaging;
- use of any 5ARI drugs within 3 months prior to enrollment such as Finasteride (Proscar) or Dutasteride (Avodart);
- a debulking transurethral resection of the prostate (TURP) is not acceptable once the screening biopsy for patient selection has been conducted;
- prior treatment for prostate cancer, other than EBRT or hormone therapy;
- history of urethral stent or urethral surgery (urethral dilation, urethroplasty); a Uroflow exam may be conducted at the investigators discretion;
- prior significant rectal surgery (hemorrhoidectomy is acceptable; rectal resection/fissure repair are excluded);
- history of inflammatory bowel disease of the rectum;
- history of any other malignancy treated within the last 5 years, other than squamous or basal cell skin cancer;
- functional bladder problems defined as IPSS > 19;
- current bladder cancer, urethral stricture, or bladder neck contracture; a cystoscopy may be performed at the investigator's discretion to rule out these conditions;
- urinary tract or rectal fistula;
- rectal fibrosis/stenosis; anoscopy or proctoscopy may be performed at the investigator's discretion;
- anomaly of the rectal anatomy or mucus membrane; anoscopy or proctoscopy may be performed at the investigator's discretion;
- prostate seroma/abscess;
- current symptomatic radiation proctitis requiring creams; and
- participation in other investigational studies, unless approved in writing by the study sponsor.

### 6.2.6 Visit Schedule, Procedures, and Assessments

The subjects are enrolled in the study if they meet inclusion/exclusion criteria, including providing consent to participate in the treatment and the extended follow-up study (5 years).

The subject is contacted on the second day after treatment for a phone screening assessment to evaluate the subject's comprehension of suprapubic catheter care and assess for signs of infection. Subjects are instructed as needed, based on their situation.

Subjects are seen for suprapubic catheter removal usually between 2-4 weeks post-treatment (determined when the post-void residual urine volume is < 100 cc).

Follow-up visits are conducted at the following intervals: 6 weeks, 3 months, 6 months, 9 months, and 12 months. Subjects that meet both primary study endpoints will continue into the extension study and participate in annual follow-up visits to assess for long-term effectiveness.

The follow-up visits include:

- Physical exam
- Urinalysis and urine culture
- PSA test
- Completion of study questionnaires (IIEF, IPSS, Sexual Aid Use, EPIC-26)
- Concomitant medication evaluation (adjuvant therapy with hormones is not permitted at any point in the trial)
- Adverse event evaluation
- Trans-rectal ultrasound (TRUS) and biopsy (12-month visit only; or may be performed on or after the 3 month visit if the PSA value is greater than 10.0 ng/mL).

Annual follow-up visits from 2-5 years of the extension study will involve a PSA level test, urinalysis/urine culture, an assessment of the change in subject health (evaluation of adverse events and concomitant medications), and inclusion of any biopsy data collected.

### 6.2.7 Statistical Methodology

The study is a two stage group sequential design with group size  $N = 100$ . An interim analysis was conducted after the first 100 subjects enrolled were followed for 12 months or withdrew. The FDA has approved using the Pocock criteria to obtain an overall  $\alpha=0.05$  significance level,  $\alpha=0.0294$  must be used at each stage. Therefore, two-sided tests must use  $\alpha=0.0294$  and one-sided tests must use  $\alpha=0.0147$  to show significance.

The primary analyses required for the primary and secondary endpoints were performed on the intent to treat (ITT) study population, including all subjects who met the inclusion/exclusion criteria, provided written informed consent, were enrolled, and received treatment. Additional analyses of study endpoints was performed in the per protocol (PP) study population. The PP study population consists of all study subjects who met the ITT requirements, and who completed the entire 12 months of the study (to include a 12 month PSA and biopsy). Subjects

who failed to have a 12 month biopsy were assumed to be failures for the primary endpoint. Likewise other missing data was treated using “Last Value Carried Forward” (LVCF).

The primary hypothesis tested is that HIFU treatment with the Sonablate results in at least a 40% rate of local control of prostate cancer, where local control is defined as achieving a PSA nadir of  $\leq 0.5$  ng/ml within 12 months of treatment and a negative prostate biopsy at 12 months. The primary hypothesis can be stated as follows:

$H_0$ : PLC < 40%                       $H_a$ : PLC  $\geq$  40%

where PLC is the proportion of subjects who achieve local control. This hypothesis was tested using a Chi-square scores test. Statistical power of at least 90% was reported, with a performance goal of 40% local control of prostate cancer. Using the Pocock criteria, the results are declared statistically significant if the p-value is less than 0.0294 on two-sided tests and 0.0147 on one-sided tests in either the interim or final analysis.

The primary safety analysis of the study reported the rate of adverse event occurrence by type and severity.

Three quality of life questionnaires (IIEF-5, IPSS, and EPIC-26) were graded for each follow-up visit and compared to the pre-treatment results for each subject to determine if there is a significant difference from pre-treatment to post-treatment. Standard summary statistics (mean, median, standard deviation, range, 95% confidence intervals) were used to characterize the changes. Pre/post changes were examined with paired Student’s t-test, Wilcoxon Signed Rank tests, and repeated measures analyses of variance.

## **6.3 Subject Accountability and Demographics**

### **6.3.1 Subject Accountability**

This trial is a non-randomized, single-arm study. All subjects who provided informed consent and met all eligibility criteria were treated with the Sonablate. One hundred (100) subjects were enrolled into the first study cohort and are included in this interim analysis. Twenty-two (22) subjects did not complete the 12 month follow-up period due to withdrawing of consent prior to 12 months or refusal of the 12 month prostate biopsy. For the purposes of this evaluation, the Intent-to-Treat (ITT) group includes all subjects who received HIFU, and the Per Protocol (PP) group includes all subjects who had both a biopsy and PSA at 12 months post-HIFU.

Safety data has been presented in the form of adverse event tabulations for all 100 enrolled subjects. Subject Accountability describes the status of all participants in the trial at the time of the interim statistical analysis, including information on vital status, disease progression, study exit, and biopsies not performed; these data are outlined in Tables 14, 15, and 16.

**Table 14. Subject Accountability (N=100)**

	<b>Enrolled</b>	<b>Completed Month 12, biopsy and PSA (PP Group)</b>	<b>Dropped or Biopsy Not Done</b>	<b>Included in Analysis (ITT Group)</b>
Number of subjects	100	78	22	100 = 78+22

**Table 15. Subjects Removed from Study or Biopsy Not Performed (N=22)**

	<b>Subjects</b>	<b>Met PSA Nadir</b>
Completed 12-Month visit but refused biopsy	7	5
Did not have a 12-Month visit	15	5
<b>Total</b>	<b>22</b>	<b>10</b>

**Table 16. Subjects had a 12 Month Visit but No Biopsy (N=7)**

Did not meet the nadir criteria	2
Did meet the nadir criteria, but had a rising PSA at 12 Months (0.8 ng/mL at 12M)	1
Did meet the nadir criteria, but had 2 missing values (0.2 ng/mL at 12M)	1
Did meet the nadir criteria, had no missing values, and all PSAs < 0.2ng/mL	3
<b>Total</b>	<b>7</b>

### 6.3.2 Baseline Demographics

Demographic data is provided in Table 17.

**Table 17. Demographic Characteristics**

	Intent-to-treat group (N=100)	Per-protocol group (N=78)
Age	Range: 53 – 83 Mean: 69.7	Range: 53 – 83 Mean: 69.7
Race	American Indian - 0 Asian - 0 Black - 16 Hawaiian - 0 White - 76 Hispanic - 5 Other – 3	American Indian - 0 Asian - 0 Black - 13 Hawaiian - 0 White - 58 Hispanic - 5 Other – 2
Pretreatment PSA	Range: 0.4 – 14* Mean: 4.90	Range: 0.4* – 10.1* Mean: 4.74
*Although the criteria for study entry is a pretreatment PSA of $\geq 0.5$ ng/mL and $\leq 10$ ng/mL, three subjects were found to have pretreatment PSAs outside that range (0.4, 10.1, and 14 ng/mL) when the results were received from the central lab. These are reported as protocol deviations.		

## 6.4 Effectiveness

The effectiveness of salvage HIFU administered using the Sonablate for the purposes of treating locally recurrent prostate cancer was examined in this study. One hundred participants were enrolled and all 100 subjects have been followed for 12 months (with exception of those who withdrew prior). An analysis suggests that the study's primary endpoint (greater than 40% success in achievement of local control; local control is defined as a nadir PSA  $\leq 0.5$  ng/ml and a negative prostate biopsy at 12 months) has been met by the Per Protocol group.

### 6.4.1 Primary Endpoint: Analysis of ITT & PP Groups

In the interim analysis of this pivotal trial, the intent to treat (ITT) group and the per protocol (PP) group are evaluated separately. A significant enough number of patients in the PP population achieved the primary endpoint to indicate that salvage therapy as administered and performed according to sponsor expectation exceeded the standard set in the protocol. For the PP group there were 50 subjects that obtained local control ( $50/78 = 64\%$ ). The study was successful for this group. The 97.06% confidence interval is (0.5227, 0.7593), and the p-value was 0.0001, which is less than 0.0147, therefore statistically significant. The PP group clearly exceeds the specified objective standard of local control set in the protocol and implies that the true success rate is between 52% and 75%.

**Table 18. Summary of Tests for Local Control for ITT and PP Groups**

Group Sample Size		Number of Successes	Estimate of P_{LC}	p-value	95% CI
<b>ITT</b>	100	50	0.5000	0.0206	(0.3911, 0.6089)
<b>PP</b>	78	50	0.6410	0.0001	(0.5227, 0.7593)

**Table 19. Breakdown of Subject Outcomes in PP Group (N=78)**

PP Group (N=78)	Negative Biopsy	Positive Biopsy
<b>Nadir <math>\leq</math> 0.5 ng/mL</b>	50	10
<b>Nadir <math>&gt;</math> 0.5 ng/mL</b>	13	5

There were 60 subjects in the PP group with a successful nadir. Fifty subjects (83%) had a negative biopsy; ten subjects (16.6%) had a positive biopsy.

Of the 22 subjects who did not complete the 12 month follow-up period per protocol (Table 15):

- 7 subjects completed the Month 12 visit but did not have a final biopsy
- 15 subjects did not have a Month 12 visit

Of the 7 subjects above that had a Month 12 visit but did not have a final biopsy (Table 16):

- 2 did not meet the nadir criteria
- 1 did meet the nadir criteria, but had a rising PSA at Month 12 (M12 PSA = 0.8 ng/mL)
- 1 did meet the nadir criteria, but had 2 missing values (M12 PSA = 0.2 ng/mL)
- 3 did meet the nadir criteria, had no missing values, and all PSAs  $\leq$  0.2 ng/mL

For the ITT group there were 50 subjects that obtained local control (50/100=50%). This group was just on the edge of success at the 97.06% confidence interval (0.3911, 0.6089) which barely includes the 40% success rate. The p-value was 0.0206, which is greater than 0.0147, so therefore did not meet statistical significance.

**Table 20. Breakdown of Subject Outcomes in ITT Group (N=100)**

Intent to Treat (ITT) Group (N=100)	Negative Biopsy	Positive Biopsy	No 12 Month Biopsy
Nadir $\leq$ 0.5 ng/mL	50	10	10
Nadir $>$ 0.5 ng/mL	13	5	12

The combined result of this interim analysis report implies the true success rate of Sonablate HIFU is between 52% and 75%, which is consistent with other salvage therapy options' success rates observed in the literature.

#### 6.4.2 Secondary Endpoints: Quality of Life Questionnaires

Post HIFU there are statistically significant changes from baseline in the IPSS and IIEF-5. There are not statistically significant changes in the other quality of life indicators. These are summarized in Table 21 below.

Note that only 44 subjects were included in the analysis of the EPIC-36 questionnaire. Forty-nine subjects had already been treated when use of the EPIC-36 was added to the protocol. An additional 7 subjects had incomplete Baseline EPIC-36 questionnaires that did not allow domain scores to be calculated.

**Table 21. Secondary Endpoint Outcomes**

Questionnaire	Cumulative Response (includes both ITT and PP groups)
IIEF-5	Subjects that retain potency of 29% and a 95% confidence interval of (16%, 42%). Forty-five subjects were potent pre-HIFU, and 13 were potent post-HIFU. Potency was defined as an IIEF score of 12 or greater.
IPSS	There is a 3.5 point improvement over baseline of the median at 12 months with a 95% confidence interval of (2.00, 6.00).
Sexual Aid Use	There was not a significant change in the number of sexual aid medications and/or devices at baseline, compared to each follow-up interval through Month 12.
EPIC-26	Only 44 subjects were included in this sample size, which is very small and should be weighed carefully. Three areas showed a drop post HIFU (Urinary Incontinence, Urinary Function, Sexual Function) and although the other three areas

	showed an initial drop, they returned to very near baseline by Month 12 (Urinary Irritative/Obstructive, Bowel, Hormonal).
Survival Rates	Two subjects died during their follow-up interval, neither related to HIFU. One died due to respiratory aspiration during elective esophageal surgery, and the other was being treated for uncontrolled hypertension and cause of death is not known. He was 10 months post his HIFU treatment and no significant AE/SAE's were recorded.

Defining potency as an IIEF score of 12 or more, the ITT group had 45 subjects that were potent at baseline. There were 13 subjects that were potent at 12 months; an estimate of the percentage of subjects that retain potency is 29% and a 95% confidence interval of subjects that retain potency of (16%, 42%). Erectile dysfunction is discussed further in Section 6.5.4.

## 6.5 Safety

The Common Terminology for Clinical Adverse Events (CTCAE) was utilized to categorize adverse events (AEs) within this clinical investigation. A grade of 1 through 5 was assigned for each AE based on this general guideline:

- Grade 1 – Mild AE
- Grade 2 – Moderate AE
- Grade 3 – Severe AE
- Grade 4 – Life-threatening or disabling AE
- Grade 5 – Death related to AE

Table 22 below represents the rate of device and/or procedure related events by severity.

**Table 22. Number of Subjects with Device/Procedure Related AEs (N=100)**

Total subjects with device/procedure related events	91
Mild	67
Moderate	80
Severe	20
Life-threatening	0
Death related	0

Tables 23, 24, and 25 represent all AEs (regardless of causality) by CTCAE Category for Renal & Urinary Disorders, Infections & Infestations, and Gastrointestinal Disorders, respectively.

**Table 23. CTCAE Class: Renal and Urinary Disorders by Category**

CTCAE Category	Number of Subjects with event (n)	Percent of subjects with event (n/100)*100	Intensity of event				Total events reported
			Mild	Moderate	Severe	Life threatening or death	
			Abnormal Urinalysis	1	1	1	
Benign Prostatic Hyperplasia	1	1	1	0	0	1	
Bladder Neck Contracture	5	5	0	5	0	5	
Bladder Neck/Urethral Stricture	8	8	0	7	2	9	
Bladder Spasm	15	15	2	15	0	17	
Bladder Stones	2	2	0	0	2	2	
Bruised Kidney	1	1	1	0	0	1	
Chronic Kidney Disease	1	1	1	0	0	1	
Cystitis Noninfective	4	4	2	2	0	4	
Dislodged S/P Catheter	1	1	1	0	0	1	
Dysuria	2	2	2	0	0	2	
Hematuria	48	48	44	14	5	63	
Incompetent Sphincter	1	1	1	0	0	1	
Inconsistent Stream	1	1	1	0	0	1	
Nocturia	1	1	0	1	0	1	
Odor to Urine	1	1	1	0	0	1	
Penile Discharge	1	1	1	0	0	1	
Pyuria	1	1	1	0	0	1	
Renal Calculi	1	1	0	0	1	1	
Renal Colic	1	1	0	1	0	1	
Urinary Fistula	3	3	0	0	3	3	
Urinary Frequency	37	37	12	28	0	40	
Urinary Incontinence	44	44	22	29	4	55	
Urinary Retention	47	47	3	65	5	73	
Urinary Tract Obstruction	18	18	6	11	3	20	
Urinary Tract Pain	18	18	7	14	0	21	
Urinary Urgency	26	26	7	19	0	26	
Urine Cytology	1	1	0	1	0	1	
Weak Urinary Stream	2	2	1	1	0	2	
Renal and Urinary Disorders - Totals	88	88	118	213	25	356	

**Table 24. CTCAE Class: Infections and Infestations by Category**

CTCAE Category	Number of Subjects with event (n)	Percent of subjects with event (n/100)*100	Intensity of event				Total events reported
			Mild	Moderate	Severe	Life threatening or death	
			Bacteremia	1	1	0	
Bladder Infection	1	1	0	1	0	0	1
Bone Infection	3	3	0	0	3	0	3
Catheter Related Infection	6	6	0	6	2	0	8
Clostridium difficile	1	1	0	1	0	0	1
Cold and Flu Symptoms	1	1	0	1	0	0	1
Epididymitis	1	1	0	1	0	0	1
Gastrointestinal Infection	1	1	0	1	0	0	1
Lung Infection	1	1	0	1	0	0	1
Nasal infection	1	1	0	1	0	0	1
Otitis Externa	1	1	0	1	0	0	1
Penile infection	1	1	0	1	0	0	1
Prostatitis / Prostate infection	2	2	0	2	0	0	2
Scrotal Infection	6	6	0	5	1	0	6
Skin Infection	3	3	1	1	1	0	3
Upper Respiratory Infection	2	2	1	1	0	0	2
Urinary Tract Infection	48	48	1	85	4	0	90
Infections and Infestations - Totals	58	58	3	109	12	0	124

**Table 25. CTCAE Class: Gastrointestinal Disorders by Category**

CTCAE Class	Number of subjects with event (n)	Percent of subjects with event (n/100)*100	Intensity of event				Total events reported
			Mild	Moderate	Severe	Life threatening or death	
Abdominal Pain	3	3.0	0	3	0	0	3
Anal Pain	9	9.0	6	4	0	0	10
Chipped Tooth	1	1.0	0	1	0	0	1
Colon polyp	1	1.0	1	0	0	0	1
Constipation	20	20.0	8	12	0	0	20
Dental Caries	1	1.0	0	1	0	0	1
Diarrhea	7	7.0	7	1	0	0	8
Diverticulitis	1	1.0	0	1	0	0	1
Dry Mouth	1	1.0	1	0	0	0	1
Dyspepsia	2	2.0	1	1	0	0	2
Fecal Incontinence	3	3.0	2	1	0	0	3
Flatulence	2	2.0	1	1	0	0	2
Gastric reflux	1	1.0	0	1	0	0	1
Hematochezia	1	1.0	1	0	0	0	1
Hemorrhoids	2	2.0	2	0	0	0	2
Lower Gastrointestinal Hemorrhage	3	3.0	1	1	1	0	3
Nausea	2	2.0	1	1	0	0	2
Oral Pain	1	1.0	0	1	0	0	1
Positive Fecal Leukocytes	1	1.0	0	1	0	0	1
Rectal Fistula	5	5.0	0	2	4	0	6
Rectal Hemorrhage	1	1.0	1	0	0	0	1
Rectal Mucositis	1	1.0	1	0	0	0	1
Rectal Pain	4	4.0	3	1	0	0	4
Rectal polyp	2	2.0	1	1	0	0	2
Small intestinal Obstruction	1	1.0	0	0	1	0	1
Stomach Pain	2	2.0	1	1	0	0	2
Vomiting	5	5.0	2	3	0	0	5
<b>Total</b>			<b>41</b>	<b>39</b>	<b>6</b>	<b>0</b>	<b>86</b>

Table 26 represents all device or procedure related SAEs reported and their outcome. Fourteen subjects (14%) experienced a cumulative total of 21 device or procedure related SAEs. All but two of these had resolved at the time of the PMA submission.

**Table 26. Serious Adverse Events**

CTCAE Class	CTCAE Category	Event start date	Resolution date	Intensity	Current Status	Interventions
Infections and Infestations	Bone Infection	4/5/2012	5/2/2012	Grade 3 - Severe AE	Resolved	Surgical, hospitalization, medication
Infections and Infestations	Urinary Tract Infection	10/5/2010	10/8/2010	Grade 3 - Severe AE	Resolved	Hospitalization, medication
Infections and Infestations	Bone Infection	11/19/2010	1/15/2013	Grade 3 - Severe AE	Resolved	Hospitalization, medication
Infections and Infestations	Bone Infection	4/1/12		Grade 3 – Severe AE	Ongoing at time of report	Hospitalization, surgical, prostatectomy on 12/14/12 with debridement
Infections and Infestations	Urinary Tract Infection	10/11/2010	11/12/2010	Grade 3 - Severe AE	Recovered	Hospitalization, medication
Renal and Urinary Disorders	Urinary Retention	8/2/2010	10/11/2010	Grade 2 - Moderate AE	Recovered	Hospitalization, medication
Renal and Urinary Disorders	Urinary Incontinence	11/30/12	5/17/13	Grade 3 - Severe AE	Resolved	Surgical, insertion of artificial sphincter
Renal and Urinary Disorders	Hematuria	9/23/2011	9/27/2011	Grade 2 - Moderate AE	Recovered	Foley catheter
Renal and Urinary Disorders	Hematuria	7/5/2012	7/17/2012	Grade 3 - Severe AE	Resolved	Medication, transfusion
Renal and Urinary Disorders	Urinary fistula	3/8/11	1/15/13	Grade 3 – Severe AE	Recovered	Medication, surgical

<b>CTCAE Class</b>	<b>CTCAE Category</b>	<b>Event start date</b>	<b>Resolution date</b>	<b>Intensity</b>	<b>Current Status</b>	<b>Interventions</b>
Renal and Urinary Disorders	Urinary Retention	3/16/2010	3/19/2010	Grade 3 - Severe AE	Recovered	Medication, surgical
Renal and Urinary Disorders	Urinary fistula	12/1/12		Grade 3 – Severe AE	Ongoing at time of report	Surgical
Renal and Urinary Disorders	Hematuria	12/27/2011	12/29/2011	Grade 3 - Severe AE	Recovered	Hospitalization, surgical
Renal and Urinary Disorders	Urinary Tract Obstruction	3/7/2012	3/23/2012	Grade 3 - Severe AE	Recovered	Surgical, hospitalization, cystoscopy
Renal and Urinary Disorders	Hematuria	5/17/2012	5/23/2012	Grade 3 - Severe AE	Recovered	Cystoscopy, medication, hospitalization
Cardiac Disorders	Myocardial Infarction	12/20/2010	12/24/2010	Grade 3 - Severe AE	Resolved	Hospitalization, medication
Gastrointestinal Disorders	Rectal Fistula	4/9/2009	11/3/2009	Grade 3 - Severe AE	Resolved	Surgical
Gastrointestinal Disorders	Rectal Fistula	1/20/2012	5/18/2012	Grade 3 - Severe AE	Resolved	Hospitalization, surgical, colonoscopy
Gastrointestinal Disorders	Rectal Fistula	6/4/2010		Grade 3 - Severe AE	Ongoing	Foley catheter and medication
Gastrointestinal Disorders	Rectal Fistula	8/2/2010	7/8/2011	Grade 3 - Severe AE	Recovered	Cystoscopy and medication
Gastrointestinal Disorders	Small Intestinal Obstruction	8/1/2010	8/4/2010	Grade 3 - Severe AE	Recovered	Hospitalization

There were two unrelated deaths. One subject died due to respiratory aspiration during elective esophageal surgery. The second subject was being treated for uncontrolled hypertension and cause of death is not known. He was 10 months post-HIFU treatment and had no significant AE/SAE recorded.

There were no life-threatening events related to the device or procedure.

### 6.5.1 Device/Procedure Related Adverse Events

Table 27 below represents the rates of the most frequently reported AEs associated with Sonablate HIFU for treatment of recurrent prostate cancer (inclusive of all device/procedure related AEs with a rate of 15% or higher). The table lists rates of common AEs experienced post-HIFU, including the rates for all events regardless of causality, device or procedure related events, related events by severity, rates of ongoing events, and median resolution time.

Additional information on incontinence, rectal fistulas, and erectile dysfunction in Section 6.5.2, 6.5.3, and 6.5.4 respectively, in order to provide a more detailed review.

**Table 27. Number of Subjects with the Most Frequently Reported Adverse Events (N=100)**

AE Category	Number of Subjects With Events (All)	Number of Subjects With Events (Related)	Number of Subjects With Mild Events	Number of Subjects With Moderate Events	Number of Subjects With Severe Events	Number of Subjects With Unresolved Events	Median Resolution Time (Days)
Incontinence	44	43	18	25	4	31	107
Stricture*	13	13	0	11	2	2	19
Urinary Retention	47	42	3	42	4	9	29
Urinary Tract Obstruction	18	16	6	8	3	3	31
Urinary Frequency**	38	36	12	26	0	18	50
Hematuria	48	41	33	6	3	3	23
Urinary Urgency	26	26	7	19	0	9	83
Urinary Tract Pain (Dysuria)	20	20	9	11	0	1	14
Bladder Spasms	15	15	2	13	0	5	16
Erectile Dysfunction	18	16	0	16	0	15	797
Urinary Tract Infection	48	45	1	44	4	2	17

\*Includes urethral stricture and bladder neck contracture

\*\*Includes urinary frequency and nocturia

The majority of these events were mild to moderate in severity. Many of these events were experienced within a few days after treatment and resolved gradually as the tissue healed. The median resolution time for resolved strictures, retention, obstruction, frequency, hematuria, dysuria, bladder spasms, and UTI was under 60 days. The median resolution time for resolved urgency events was under 90 days; and the median resolution time for resolved incontinence and was under 4 months.

### 6.5.2 Incontinence

Incontinence resulting from treatment with the Sonablate was experienced in 43% of patients (43 out of 100), ranging from mild to severe. The definitions of mild, moderate, and severe incontinence, per the CTCAE, include:

Mild Incontinence (Grade 1): Occasional (e.g., with coughing, sneezing, etc.), pads not indicated

Moderate Incontinence (Grade 2): Spontaneous; pads indicated; limiting instrumental ADL

Severe Incontinence (Grade 3): Intervention indicated (e.g. clamp, collagen injections); operative intervention indicated; limiting self-care ADL

Table 28 breaks down the events by severity and indicates the rates of ongoing events.

**Table 28. Incontinence Rates (N=100)**

Severity	Number of Subjects With Event (%)	Number of Subjects With Ongoing Events (%)
Mild	18	10
Moderate	25	19
Severe	4	2

Twenty-one subjects (21%) have ongoing incontinence requiring pads at 12 month post-HIFU.

The two cases of severe ongoing incontinence were experienced in subjects from the same clinical trial site. Both subjects had aggressive treatments for voiding symptoms within 6 months post-HIFU, which was not in line with the training recommendations. Subject details are included below and in Table 29.

Subject A experienced urinary retention for which a cystoscopy was performed (2 months post-HIFU) with resolution of the retention. Incontinence started shortly after the cystoscopy. The subject then underwent a transurethral resection of the prostate (TURP) for urethral stricture (less than 5 months post-HIFU); the subject underwent two additional TURPs within 10 months of the first; the stricture was ongoing at 12 month follow-up.

Subject B experienced urinary retention and obstruction for which a TURP was performed in March 2012 (4 months post-HIFU). Incontinence started within days of the TURP. The subject continued to experience retention and underwent 3 additional TURPs, all within approximately 8 months of the first procedure.

It is important to note that both incontinence events started after the first intervention was performed (within 6 months post-HIFU).

**Table 29. Severe Ongoing Incontinence - Subject History**

	<b>Subject A</b>	<b>Subject B</b>
<b>Date of HIFU Treatment</b>	08 January 2010	11 November 2011
<b>Post-HIFU Voiding Symptoms</b>	Urinary Retention (resolved) Urinary Stricture (ongoing)	Urinary Retention (ongoing) Obstruction (resolved)
<b>Post-Treatment Interventions</b>	Cystoscopy: March 2010 TURP: 28 May 2010 TURP: 20 July 2010 TURP: 22 March 2011	TURP: 22 March 2012 TURP: 01 June 2012 TURP: 04 August 2012 TURP: 30 November 2012
<b>Start Date of Incontinence</b>	06 April 2010	29 March 2012

Both subjects presented with urinary symptoms within one month of HIFU treatment. The recommendation of the Company is conservative management for the first 6 months post-HIFU, to allow enough time for tissue which has had previous radiation and HIFU to heal. Based on this information, it is unclear whether incontinence in these two subjects was experienced as a direct result of HIFU, a direct result of the post-HIFU surgical interventions, or a combination of the two. It is likely that, at minimum, the Grade 3 severity is a result of surgical intervention being performed too soon after HIFU while tissue is still healing and/or undergoing multiple TURP procedures within 10 months or less.

### **6.5.3 Rectal Fistulas**

Rectal fistulas occurred in two subjects (2%) who had Class III fistulas requiring surgical management and in three (3%) subjects who were treated with medical intervention only. The rectal fistula rate for those subjects requiring surgical intervention was 2%; the overall number of subjects experiencing rectal fistulas was 5 (5%).

In 2011, based on an interim review of the safety profile for the Sonablate treatments, all clinical proctors were retrained using the updated Physician's Instruction Manual and each clinical investigator was then individually trained by a clinical proctor in order to improve their technique. In addition, an experienced HIFU Proctor was added to the treatment team for all clinical trial cases conducted. As an example, a comparison of pre- and post-training results for recto-urethral fistulas, the most significant complication resulting from this treatment, is shown in Table 30.

**Table 30. Pre- and Post-Training Rectal Fistulas**

	<b>Pre-Training Program</b>	<b>Post-Training Program</b>
Class I – II Medical Management	3 (4.9%)	0
Class III Surgical Management	1 (1.6%)	1 (2.6%)
Subjects treated	61	39
Fistula rate combined (both medical and surgical together)	4 (6.6%)	1 (2.6%)

The one subject who experienced a rectal fistula post-training was not treated for the fistula by the clinical investigator, but rather by a physician not trained on post-HIFU management. It is believed that, per the subject's reported symptoms and based on the behavior of the previous medically treated fistulas in this trial, the fistula would have healed with medical intervention only (catheter placement).

#### **6.5.4 Erectile Dysfunction**

New onset erectile dysfunction (ED), resulting from treatment with the Sonablate, was reported as an AE in 16 subjects (16%). All were reported as moderate in severity. Subjects completed the Sexual Aid Use Questionnaire at each study visit. Fourteen subjects reported using a sexual aid (medication or device) at pre-treatment. Fifteen subjects reported using a sexual aide (medication or device) at 12 Months.

The International Index of Erectile Function (IIEF-5) questionnaire was used to monitor erectile function. The scores range from 5 to 25 and are partitioned into five categories of erectile dysfunction (ED) as follows:

**Table 31. IIEF Score Ranges**

Range	Description
22-25	No ED
17-21	Mild ED
12-16	Mild to Moderate ED
8-11	Moderate ED
5-7	Severe ED

Per the statistical analysis, freedom from impotence was defined as an IIEF score of 12 or greater. It is important to note that if a subject has not attempted sexual intercourse, the IIEF scores will be low; this is not necessarily indicative of impotence. Defining potency as an IIEF

score of 12 or more, the ITT group had 45 subjects that were potent at pre-treatment. Below is a breakdown of post-treatment potency:

- 13 subjects that reported potency at pre-treatment were still potent at 12 months
  - 3 of the 13 subjects did not complete a 12 month IIEF, but are considered potent due to last value carried forward (LVCF)
- 2 subjects who reported impotency at pre-treatment were potent at 12 months\*
  - 1 subject had a pre-treatment IIEF score of 10, just below the potency cut-off
  - 1 subject had a pre-treatment IIEF score of 1 due to no sexual intercourse attempts
- 2 additional subjects had low scores at 12 months indicating impotence; however intercourse was not attempted, per subject responses on IIEF\*\*
  - The subject's IIEF answers indicated moderate to high confidence levels
  - The total IIEF score is low due to no sexual intercourse attempts
  - It can be assumed that these subjects are potent, and that the low scores are due to no sexual activity (previous post-treatment IIEF scores indicate potency)

**Table 32. Breakdown of Potent Subjects**

	<b>Potency Per Protocol</b>	<b>Inclusive of Subject Factors Listed Above</b>
<b>Potent at Pre-Treatment</b>	45	(45 +2*) = 47
<b>Potent at 12 Months</b>	10	12
<b>Not Evaluated at 12 Months, Potent at Last Known Visit (LVCF)</b>	3	3
<b>Subjects with Moderate-High Confidence at 12 Months but no sexual activity</b>	NA	2**
<b>Total Subjects Potent</b>	13 out of 45	17 out of 47
<b>Post-Treatment Potency Rates</b>	29%	36%

### 6.5.5 Additional Risks

There were two unrelated deaths and no life threatening events associated with the procedure or use of the device in this study.

Three subjects experienced chronic urinary tract infections (UTI) which appeared to be resistant to antibiotics and were not properly managed during the 12 month post-treatment period. Chronic infections may be exacerbated by a reduced healing time in a post-radiated tissue. For these three subjects, their chronic infections led to urocutaneous fistula and osteomyelitis.

Two of these cases were resolved with surgical intervention; one resolved with medical intervention only.

One subject (Subject A, discussed above in Section 6.5.2) had several aggressive interventions for voiding symptoms including a cystoscopy 2 months post-treatment and 3 transurethral resection of the prostate (TURP) procedures within a 10 month period. Two of the TURPs were performed within 6 months post-HIFU. The training recommendation is to treat infections and voiding symptoms with conservative medical management (catheter, antibiotics) for the first 6 months post-treatment. The subject had an ongoing UTI at the time of the cystoscopy, which resolved, and the subject was infection free for five months. Chronic infection began after the second TURP procedure.

The investigator retraining conducted in September 2011 included instructions for post-treatment follow-up care, in addition to the treatment technique review. All clinical investigators and site coordinators completed additional post-treatment care training in August 2012, with specific attention to the treatment of infections and voiding symptoms. Infections are monitored closely by the clinical trial site and the sponsor's clinical trial management team. Each of the three cases of chronic infection discussed above occurred in subjects treated in 2010 and completed 12 month follow-up in January, May, and July of 2011 (prior to investigator/site retraining). Urinalysis and urine culture were added to the protocol as required study procedures at all visits, including annual visits in long-term follow-up, in order to identify and monitor chronic infections. There have been no other reported cases of urinary fistula or osteomyelitis since retraining.

## **7 POST APPROVAL PLAN**

### **7.1 Post-Approval Study**

The FSI-003 trial (IDE G080057) is ongoing and will serve as a post-approval study. The data supporting this PMA is based on an interim analysis on the first 100 subjects enrolled and followed through 12 months post-treatment. The post-approval plan is to continue enrollment to reach the goal of 200 subjects, per protocol, and follow all subjects to 12 months post-treatment. At that time, the second statistical analysis will be completed including the full study cohort to assess further the safety and effectiveness of treatment with the Sonablate.

Subjects that meet the primary study endpoints continue to be followed annually for 4 additional years post-treatment in the extension study (total follow-up time is 5 years). The extension study includes those subjects that were deemed treatment successes at 12 months (i.e. met primary

endpoint of local cancer control, defined as reaching PSA nadir of  $\leq 0.5$  ng/mL and a negative biopsy at 12 months). Long-term efficacy is evaluated by assessment of local cancer control (defined as absence of biochemical failure, per Phoenix criteria of nadir +2). Long-term safety will also be evaluated through reporting of all device or procedure related AEs.

The proposed Post-Approval Study protocol synopsis is included in Section 9 (Proposed Post-Approval Study).

## 7.2 Training Program

The planned post-approval physician training program includes four progressive levels of training. The training materials are presented through several different training mediums – voice-enriched video presentations, self-review of materials, lecture, and didactic (hands-on) experiences. All training is documented and the physician’s competency is verified through structured tests before progressing to the next level within the training program. Physicians are not expected to complete all four levels of the training program; however all are expected to progress to the point of practicing independently and competently (Level III).

Level I: Initial training includes an overview of HIFU, initial instructions for use of the Sonablate, the HIFU procedure, post-care instructions, and the post approval study requirements. Each physician is required to pass a competency assessment.

Level II: The second level of competency training is conducted onsite by a certified proctor. All physicians are required to go through this training program prior to conducting HIFU cases with the Sonablate device. Each physician is required to pass a competency assessment.

Level III: The third level of training is used to assess the new HIFU physician’s understanding of the mechanism and delivery of HIFU. The goal of this training is to progress the HIFU physician to an independent status, i.e., to conduct HIFU cases without the assistance of a certified proctor. As part of this training the new user is required to work through a computer-based library of as many as 20 clinical cases under the direction and guidance and with the participation of a remote trainer who will test the new user’s knowledge of the treatment planning system and its warning and screen function indicators, thereby indicating understanding of and comfort with the interventions required to insure an optimal delivery of care.

To be considered for independent status, the new HIFU physician is required to have completed at least five cases with a certified proctor on-site. The certified proctor must acknowledge that the physician is ready to complete cases independently. Sonablate HIFU cases are recorded on the Sonablate device’s hard drive and can be retrieved at a later date for review. The first five cases will each be reviewed by a minimum of two certified proctors who are blinded to the physician’s name. The on-site cases reviewed must indicate that the physician delivers HIFU safely as per the User’s Manual. If not, retraining will occur between the new HIFU physician and a certified proctor. Proctors will be available to conduct additional onsite training if needed.

### Level IV Proctor Training:

All HIFU physicians conducting HIFU cases will not be chosen as certified proctors. The Proctor Training program is reserved for those HIFU physicians who have significant experience using HIFU, work cohesively with the treatment team, and are viewed by the treatment team to be efficient communicators. Candidates for the proctor program are required to complete a minimum of 20 individual HIFU treatments without a certified proctor. A random sampling of 5 of their last 10 HIFU case videos will be blindly reviewed for compliance to the User's Manual by a minimum of two certified proctors. Candidates who pass the proctor screening program will be issued a Sonablate HIFU Proctor Certificate.

Candidates who do not pass will be required to undergo retraining. Candidates who do not pass their case reviews will be offered the opportunity to participate in a video conference with a certified proctor to review their HIFU cases together. If the candidate would like to continue to pursue becoming a certified proctor, an individualized training plan will be put into place. Once the candidate has conducted a minimum of 10 additional cases independently, 5 of those cases will be chosen at random for blinded review. The items listed below are utilized during the potential proctor screening process.

All treating HIFU physicians and certified proctors will have a minimum of two cases randomly selected for blinded review each year to ensure they are treating in compliance with the User Manual.

## **8 BENEFIT / RISK CONCLUSION**

In the interim analysis of this pivotal trial, the intent to treat (ITT) group and the per protocol (PP) group are evaluated separately. The percent of the PP population achieving the primary endpoint was sufficient to indicate that salvage therapy, as administered and performed according to sponsor expectation, exceeded the standard set in the protocol. For the PP group there were 50 subjects that obtained local control ( $50/78 = 64\%$ ). The study was successful for this group. The 97.06% confidence interval is (0.5227, 0.7593), and the p-value was 0.0001, which is less than 0.0147, noting statistical significance. The PP group clearly exceeds the standard set in the protocol for local control and implies that the true success rate is between 52% and 75%.

For the ITT group there were 50 subjects that obtained local control ( $50/100 = 50\%$ ). This group was just on the edge of success at the 97.06% confidence interval (0.3911, 0.6089). The p-value was 0.0206, which is greater than 0.0147, outside requirements for statistical significance. The combined result of this interim analysis report implies the true success rate of Sonablate HIFU is between 52% and 75%, which is consistent with observed success rate in the literature for salvage prostate cancer therapies.

There were two unrelated deaths and no life threatening events associated with the procedure or use of the device in this study. The CTCAE scale was used to categorize all adverse events. Two

subjects (2%) had Class III fistulas requiring surgical management and three subjects (3%) had fistulas that were treated with medical intervention only.

Incontinence was reported in a total of 43 subjects (43%). Some events resolved, leaving 31 subjects (31%) with ongoing incontinence at Month 12. Twenty one subjects (21%) have ongoing incontinence requiring pads.

Potency was defined as IIEF scores of 12 or greater. At pre-treatment, only 45 (45%) of subjects were potent; 1 of these subjects did not complete any post-treatment IIEF questionnaires (the planned Last Value Carried Forward (LVCF) populated this subjects subsequent visits with his initial value). At 12 months, 13 subjects were potent. Per the statistical analysis, an estimate of the percentage of subjects that retain potency is 29% and a 95% confidence interval of subjects that retain potency of (16%, 42%). Two subjects were had IIEF below 12 at pre-treatment, but scores were greater than 12 at 12 months. An additional two subjects indicated moderate and high levels of confidence; however these subjects indicated sexual intercourse was not attempted, resulting in IIEF scores below 12. With this additional information, it can be estimated that post-treatment freedom from impotence is observed in approximately 36% of subjects. New onset erectile dysfunction was reported as an AE related to treatment in 16 subjects (16%).

In summary, in a comparison of the results of this study with data from the systematic review of salvage local therapy after failure of radiotherapy for prostate cancer (Parekh) suggests that the biochemical freedom from disease with Sonablate is equivalent or superior to existing treatment modalities with a toxicity profile that is equivalent in terms of rectal fistula and superior in terms of incontinence, urethral and bladder neck strictures.

Salvage therapy is usually performed on an aging population with comorbidities that may preclude more rigorous interventions such as radical prostatectomy. Sonablate HIFU is minimally invasive and performed on an outpatient basis, making it a possible approach in the treatment of recurrent prostate cancer following radiotherapy in patients for whom more rigorous surgical interventions may not be clinically appropriate. We believe the trial data submitted supports the claim that the treatment benefits of Sonablate for the specific target population in which it has been studied outweigh the risks of illness or injury when used as indicated in accordance with the manufacturer's directions and that the device should be approved for the indicated use, namely, in the treatment of biopsy proven recurrent prostate cancer, stage T1c-T2, in patients who have failed primary External Beam Radiation Therapy and have a PSA < 10 ng/mL.

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