SPONSOR EXECUTIVE SUMMARY

JUNE 23, 2014

EDAP Ablatherm® Integrated Imaging High Intensity Focused Ultrasound (HIFU) Indicated For The Treatment Of Low Risk, Localized Prostate Cancer

PREMARKET APPROVAL APPLICATION P130003

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EDAP ABLATHERM® INTEGRATED IMAGING PMA

EXECUTIVE SUMMARY

1 SUMMARY

1.1 PMA Introduction

This PMA introduces transrectal high-intensity focused ultrasound (HIFU) treatment with the Ablatherm® Integrated Imaging device, a minimally invasive treatment for low-risk, localized prostate cancer. HIFU is a minimally invasive treatment during which the Ablatherm® device precisely focuses ablative energy on the prostate gland while avoiding damage to sensitive adjacent anatomy.

This PMA application is based on IDE G050103 which was designed to demonstrate non-inferiority of Ablatherm® HIFU in comparison to Endocare CRYOcare cryotherapy for the treatment of low-risk localized prostate cancer. The primary effectiveness endpoint is achievement of PSA nadir ≤ 0.5 ng/ml and stability of PSA according to ASTRO criteria through 24 months follow up without a positive biopsy. The non-inferiority delta was 10 percentage points. Accrual difficulties were encountered in both arms of this investigation. In response to these difficulties, extraordinary efforts were undertaken to increase accrual which ultimately proved fruitless for the control arm. Additional scientifically valid means were then utilized to generate a meaningful control with endpoints and analysis based as closely as possible on the original study design.

Within the PMA Application, multiple cohorts of HIFU data and comparator data are presented and compared. There are several ways in which this body of evidence can be presented. The approach taken in the EDAP Executive Summary is different from that presented in the FDA Executive Summary. EDAP bases the arguments of reasonable safety and effectiveness of the device on the totality of the data presented in the PMA. This approach is consistent with the EDAP's approach in the original PMA and PMA Amendments. FDA focuses on the long-term data as the primary evidence of safety and effectiveness.

The data presented in this PMA include clinical trial data collected in an IDE study conducted in the U.S. and Canada over a period of six years, as well as data collected in Europe over a period exceeding 15 years.

1.2 Disease Background

Prostate cancer is a disease that spans a wide prognostic spectrum, from indolent to lethal and the entire range in between these extremes. Prostate cancer can be stratified by risk into three groups: low risk, intermediate risk and high risk. The proposed intended use of the device that is the subject of this PMA is to treat localized, low risk prostate cancer. Therefore, this discussion will be limited to low risk disease.

Low risk prostate cancer is defined as a PSA of 10 ng/mL or less, and a Gleason score of 6 or less, and a clinical stage T1a to T2a (Thompson et al 2007[1]). Standard treatments within the United States for localized low risk disease have remained binary: active surveillance or definitive local therapy. The latter is associated with significant morbidity and detrimental impact on quality of life. The current American Urological Association's guidance for the treatment of low risk localized prostate cancer is as follows (Thompson et al 2007[1]):

> "Active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy are appropriate monotherapy treatment options for the patient with low-risk localized prostate cancer."

The juxtaposition of active surveillance and definitive local therapy exists in part due to the inability to accurately determine the risk classification of the individual patient due to upgrading and upstaging (Jalloh et al 2014[2], Busch et al 2014[3]) and the real threat that low-risk prostate cancer poses in the long term (Thomsen et al 2014[4]).

1.3 Challenges in Conducting Prostate Cancer Research

Conducting research on treatments for low risk prostate cancer is challenging. A difficulty frequently encountered when conducting prostate cancer trials comparing fundamentally different definitive local therapies is accruing the target number of subjects as determined in the statistical analysis plan. Several widely supported and well-funded attempts have been made. The percentage of the accrual target actually enrolled was <1% for SWOG8890 (USA), 3% for SPIRIT (USA), 9% for START (USA), and 51% for Calgary (Canada) which were randomized clinical trials comparing radical prostatectomy versus external beam radiation therapy, radical prostatectomy versus brachytherapy, active surveillance versus definitive treatment and external beam radiation therapy versus cryotherapy, respectively.

Also, it is necessary to use surrogate endpoints, most often PSA, when studying the treatment of low risk prostate cancer in the short and intermediate term due to the low occurrence of definitive clinical events such as metastasis and mortality in the 2-5 year time period.

1.4 Overview of Clinical Studies

EDAP has collected a comprehensive set of both intermediate-term (biochemical survival at 2 years) and long-term (freedom from metastasis and prostate cancer specific survival at 8 and 10 years) effectiveness data on Ablatherm® HIFU. Safety data for the HIFU procedure was collected through 24 months in the IDE study. Due to difficulties in enrolling prospective control cohorts, described in Section 6, these data are presented in comparison with relevant literature data on cryotherapy and radical prostatectomy that provide context and appropriate comparators for the observed HIFU results.

A significant body of intermediate term data has been collected on patients treated with Ablatherm® HIFU including. This includes data from the prospective pivotal HIFU IDE study conducted in the U.S. and Canada (the HIFU IDE Cohort), a systematic review and meta-analysis of the HIFU literature (HIFU MA) as well as data from a registry and three studies of HIFU patients treated outside of the United States.

Section 6 summarizes in detail the original IDE study, challenges encountered in its execution, and changes made in light of these challenges, including the development of a HIFU performance goal (HIFU PG) based on systematic review and meta-analysis of the cryotherapy literature As well, it describes the supporting data (HIFU Registry HIFU Meta-Analysis) that demonstrate the consistency of the results observed in the HIFU IDE study in terms of biochemical survival and safety and comparability of these different cohorts is addressed. Finally, long-term data on clinical outcomes with HIFU is also presented, in comparison to long-term data reported in the literature for radical prostatectomy. Long-term Ablatherm® HIFU clinical data (8-10 year freedom from metastasis data) from three European studies was collected. Three HIFU cohorts were derived from this dataset.

Inclusion and exclusion criteria similar to those used in the HIFU IDE study were applied to enroll subjects in the HIFU Long Term cohort. Based on discussions with FDA, the HIFU Long Term Refined cohort, a subset of the HIFU Long Term cohort, further excludes subjects with previous hormone therapy, previous TURP and incidental prostate cancer (Stages Ta and T1b). The

HIFU Long Term Refined cohort was selected for the principal analysis of long-term effectiveness. The HIFU Long Term cohort results were included in the PMA as supportive evidence but are not discussed here since it includes subjects with previous hormone therapy, previous TURP and incidental prostate cancer (Stages Ta and T1b) which are not comparable to the HIFU IDE Cohort or consistent with the proposed product intended use. The third cohort, the HIFU Prospective Safety cohort, is a subset of the subjects in the HIFU Long Term cohort who had also been followed in one of three previously conducted prospective studies and, as a result, had prospectively collected safety data available.

The radical prostatectomy results in low risk cases were taken from publications of two randomized controlled studies:

- The radical prostatectomy arm of the Prostate Cancer Intervention Versus Observation Trial (PIVOT)[5]
- The radical prostatectomy arm of the Scandinavian Prostate Cancer Research Group-4 Trial (SPCG-4)[6]

These prostate cancer studies were chosen as literature controls due to their prospective controlled randomized trial design. The PIVOT trial was chosen as the primary comparator as it was a study conducted in the USA during the PSA era.

Table 1 summarizes the data sources used to evaluate the safety and effectiveness of Ablatherm® HIFU compared to cryotherapy for the treatment of low-risk localized prostate cancer in the intermediate term. The table also summarizes the long term Ablatherm® HIFU safety and effectiveness cohorts as well as the literature controls used for comparative purposes.

Table 1: Clinical Data Sources in Support of Ablatherm® Integrated Imaging HIFU

Treat-ment	Cohorts	Description	Sample Size	Role	Principal Endpoints	Comparator
Intermediate-Term Results						
HIFU	HIFU IDE	Prospective, multicenter, collected in US IDE G050103	135	Principal Effectiveness, Safety	Phoenix Biochemical Survival Rate and adverse events	CRYO PG
	HIFU MA	Prospectively defined systematic review and meta-analysis of HIFU studies	13 articles 623 subjects	Principal Safety Supporting Effectiveness	Adverse event rates	CRYO MA
	HIFU Registry	Prospectively defined data abstraction, multicenter, collected in Europe from prospectively managed registry	115[1]	Internal Consistency	n/a	n/a

Treat-ment	Cohorts	Description	Sample Size	Role	Principal Endpoints	Comparator
Control	HIFU PG	Based on systematic review and meta-analysis of cryotherapy studies	25 articles 687 subjects	Principal Effectiveness	Biochemical Survival Rate	HIFU IDE
	CRYO MA	Systematic review and meta-analysis of cryotherapy studies	25 articles 687 subjects	Principal Safety Supporting Effectiveness	Adverse event rates	HIFU MA
	CRYO Retro	Prospectively defined retrospective collection of cryotherapy data	67	n/a	n/a	n/a
	CRYO IDE	Prospective, multicenter, collected in US IDE G050103	5	n/a	n/a	n/a
Long-Term Results						
HIFU	HIFU Long Term Refined	Prospective protocol for retrospective data abstraction, multicenter, collected in Europe; Sub-cohort of the HIFU Long-Term Cohort	227	Principal Effectiveness	Freedom from Metastasis Rate	PIVOT RP
	HIFU Prospective Safety	Prospective protocol for retrospective data abstraction, multicenter, collected in Europe; Sub-cohort of the HIFU Long-Term Cohort	62	Safety	Adverse events	PIVOT RP
Control	PIVOT RP	Prospective, multi-center, randomized trial comparing radical prostatectomy to	148	Principal Effectiveness Safety	Freedom from Metastasis Rate and adverse events	HIFU IDE

Treat-ment	Cohorts	Description	Sample Size	Role	Principal Endpoints	Comparator
		observation				
	SPCG-4 RP	Prospective, multi-center, randomized trial comparing radical prostatectomy to observation	166	Supporting effectiveness	-	HIFU IDE
[1] Some of the subjects in this cohort may be included in the HIFU Long-Term Cohort.						

1.4.1 Methodology and Analyses

The principal safety and effectiveness evaluations of the Ablatherm® HIFU based on the data sources described above are summarized below in Table 2 and further described in Section 6.

Table 2: Principal Safety and Effectiveness Evaluations

Evaluations	Principal Endpoint	Principal Comparison	Supporting Data
Intermediate-term effectiveness	Phoenix Biochemical Survival rate at 24 months	HIFU IDE Cohort vs. HIFU PG	Comparisons of HIFU IDE cohort with: • HIFU Registry Cohort • HIFU Meta-analysis • CRYO Meta-analysis
Long-term effectiveness	Freedom from metastasis at 8 years	HIFU Long Term Refined Cohort vs. PIVOT RP	Comparisons of freedom from metastasis at 10 years in the HIFU Long Term Refined Cohort with SPCG-4 RP arm
Safety	Adverse events	HIFU meta-analysis vs. CRYO meta-analysis	Comparisons of HIFU IDE Cohort and HIFU Prospective Safety Cohort with PIVOT RP arm

1.5 Effectiveness Results

1.5.1 Intermediate-Term Clinical Outcomes

The principal effectiveness endpoint for the intermediate-term clinical assessment was the Phoenix definition of biochemical survival (PSA nadir + 2.0 ng/ml) at 24 months in the HIFU IDE cohort compared to the HIFU PG, which is shown in Table 3. The observed 24-month Phoenix biochemical survival rate is compared to the HIFU PG of 82% using a one-sided, asymptotic binomial test of proportion. The HIFU PG was derived from the CRYO MA by Phoenix Biochemical Survival rate (87%). Adjusting for the non-inferiority margin of 5%, the lower bound of the HIFU IDE must be at least 82% to be considered non-inferior to cryotherapy. The Phoenix Biochemical Survival rate in the HIFU IDE cohort is 90.5% with a lower bound confidence limit of 85.2%, demonstrating that a biochemical survival rate of 82% or less can be ruled out (p=0.009).

Table 3: Principal Effectiveness Comparison of Phoenix Biochemical Survival at 24 Months

Cohort	Phoenix Biochemical Survival Rate (95% CI)	Performance Goal	Performance Goal Met?
HIFU IDE	90.5% (85.2%, 95.8%)	82%	Yes

The estimated Phoenix Biochemical Survival Rate for the Ablatherm® HIFU subjects in the HIFU IDE cohort was consistent with the biochemical survival in other study cohorts analyzed (HIFU Registry, HIFU MA) (Table 4). Thus, this evaluation is indicative of the effectiveness of the Ablatherm® HIFU for the treatment of low-risk, localized prostate cancer.

Table 4: Biochemical Survival at 24 Months in other Study Cohorts

Cohort	Biochemical Survival Rate	95% CL or Range[1]
HIFU Registry	94.4%	90.0, 98.8%
HIFU MA	92%	74 – 98%
CRYO MA	87%	69 - 96%
[1] Range of biochemical success estimates given for the HIFU MA and CRYO MA results.		

1.5.2 Long-Term Clinical Outcomes

The primary endpoint for long-term assessment of the effectiveness of the Ablatherm® HIFU was freedom from metastasis which is not a surrogate endpoint and, given the nature of the long-term evaluation (8 years), provides an excellent indication of the effectiveness of the Ablatherm® HIFU device.

The 8-year cumulative risk estimates for the primary endpoint of cancer metastasis are shown in Table 5 for the HIFU Long Term Refined Cohort and the PIVOT RP Cohort. The estimates show similar rates of metastasis between the HIFU treated subjects and those with radical prostatectomy with overlapping confidence limits (1.1% with 95% CI: 0.1% to 2.0% vs. 1.4% with 95% CI: 0.4%, 4.8%). Therefore, the results of HIFU treatment are similar to those of radical prostatectomy.

This finding is supported by the secondary analyses of the rates of metastasis and death from prostate cancer in the HIFU Long Term and Long Term Refined Cohorts compared to the PIVOT and Scandinavian Prostate Cancer Group Study-4 (SPCG-4) RP Cohorts. A summary of the secondary endpoints by cohorts is also shown in Table 5.

Table 5: Competing Risk Estimates for Metastasis and Death due to Prostate Cancer from HIFU Long-Term Refined, PIVOT RP and SPCG-4 RP Cohorts

Effectiveness Endpoints	Cohort	Metastasis		Death from Prostate Cancer	
		Cumulative Incidence (%)	95% CI	Cumulative Incidence (%)	95% CI

Effectiveness Endpoints	Cohort	Metastasis		Death from Prostate Cancer	
		Cumulative Incidence (%)	95% CI	Cumulative Incidence (%)	95% CI
Primary					
8 Years	HIFU Long Term Refined	1.1	(0.1, 2.0)	Supporting Effectiveness	
	PIVOT RP	1.4	(0.4, 4.8)		
Secondary					
8 Years	HIFU Long Term Refined	Principal Effectiveness		0.4	(0.0, 1.0)
	PIVOT RP			1.4	(0.4, 4.8)
10 Years	HIFU Long Term Refined	1.5	(0.3, 2.7)	0.4	(0.0, 1.0)
	SPCG-4 RP	4.9	(2.0, 11.6)	4.1	(1.5, 11.0)

The comparison of the freedom of metastasis rate of the HIFU Long Term and Long Term Refined Cohorts to the PIVOT RP and SPCG-4 RP Cohorts provides reasonable assurance of the long-term effectiveness of HIFU treatment of low-risk, localized prostate cancer.

1.6 Safety Results

1.6.1 Adverse Events Reported in the Literature

The safety profile for the HIFU IDE cohort represents the most comprehensive profile for the HIFU treatment. A complete summary of adverse events collected in the Ablatherm® HIFU IDE study was presented in the PMA and is summarized in section 7.1.6 of this report. However, due to the lack of an appropriate control, no comparison to a prospective cryotherapy control treatment is provided.

The most appropriate safety comparison for the intermediate-term clinical assessment is between the HIFU MA and CRYO MA results since the estimates for both cohorts were obtained using the same approach (Table 6). Most of the adverse event rates were similar between the cohorts. The incidence of retention and stricture, which are clinically manageable and usually transient events, was higher in the HIFU MA cohort while the incidence of erectile dysfunction was higher in the CRYO MA cohort. The lower rate of erectile dysfunction following HIFU is a compelling factor in support of Ablatherm® HIFU treatment, especially for younger, sexually active men.

Table 6: Comparison of Adverse Event Rates, HIFU MA vs. CRYO MA

Adverse Events	HIFU MA			CRYO MA		
	Median [IQR] Rate (%)	Range	Articles Included	Median [IQR] Rate (%)	Range	Articles Included
Erectile Dysfunction	43.2 [36.3, 50.0]	13.0 – 77.1	9	70.0 [53.0, 89.8]	25.2 – 100	17
Incontinence	8.5 [6.2, 15.6]	0.0 – 20.0	12	7.5 [3.9, 17.2]	0.9 – 32.0	23

Adverse Events	HIFU MA			CRYO MA		
	Median [IQR] Rate (%)	Range	Articles Included	Median [IQR] Rate (%)	Range	Articles Included
Retention	13.9 [7.4 – 19.3]	3.6 – 20.0	4	4.2 [2.2, 9.5]	0.0 – 22.0	12
Obstruction	17.3 [12.9, 20.2]	4.0 – 24.5	4	14.8 [11.9, 21.8]	9.0 – 28.7	3
Stricture	10.8 [7.3, 14.7]	3.2 – 21.7	6	0.0 [0.0, 5.2]	0.0 – 17.0	5
Fistula	0.0 [0.0, 0.6]	0.0 – 1.2	3	0.1 [0.0, 0.5]	0.0 – 1.9	15

1.6.2 HIFU Prospective Safety Cohort

For the long-term clinical assessment, the safety of the HIFU Prospective Safety cohort was compared to the PIVOT RP cohort. Additionally, the HIFU IDE cohort was compared to the PIVOT RP cohort. A total of 43 procedure-related adverse events, including wound infection, sepsis, transfusion, myocardial infarction and bowel injury requiring surgical repair as well as 1 death were reported only in the radical prostatectomy cohort. The rates of the perioperative adverse events such as urinary tract infection, urinary catheter, urinary retention, dysuria and hematuria were higher in one or both of the HIFU Prospective Safety and HIFU IDE Cohorts than the PIVOT RP. In fact, there were no reports of urinary retention, dysuria and hematuria in the in the PIVOT RP Cohort even though these are commonly occurring events following prostate cancer treatment. The rates of the 2-year postoperative adverse events of erectile dysfunction and urinary incontinence were lower in the HIFU IDE Cohorts than the PIVOT RP Cohort. Thus, the HIFU Prospective Safety and HIFU IDE Cohort demonstrated none of the potentially life threatening surgical adverse events associated with radical prostatectomy and the HIFU IDE Cohort had a lower incidence of 2 year postoperative adverse events than the PIVOT RP Cohort.

1.7 Safety And Effectiveness Comments

EDAP has presented the results of treatment with the Ablatherm® HIFU from prospective clinical trials, retrospective data collected from real world experience and a meta-analysis of published data. The HIFU IDE cohort met the performance goal of an 82% lower 95% confidence bound for Phoenix biochemical survival at 24 months, with an observed Phoenix biochemical survival of 90.5% (85.2%, 95.8%). These results are supported by the similarity of the HIFU Registry and HIFU MA results with the HIFU IDE results. Furthermore, the results of the HIFU Registry cohort and the HIFU meta-analysis provide real world evidence of the effectiveness of the device at 2 and 5 years post-treatment.

Long-term clinical evaluation of the European experience with the EDAP Ablatherm® Integrated Imaging HIFU device showed a 99.5% freedom from metastasis rate at 2 years and 98.2% at 5, 8 and 10 years post-HIFU, respectively. These freedom from metastasis rates are excellent, and their proximity to 100% suggests that they would compare favorably to any other treatment for low risk prostate cancer. The 8-year cumulative risk estimates for the primary endpoint of cancer metastasis show similar rates of metastasis between the HIFU treated subjects and those with radical prostatectomy from the PIVOT study with overlapping confidence limits (1.1% with 95% CI: 0.1% to 2.0% vs. 1.4% with 95% CI: 0.4%, 4.8%). Therefore, the results of HIFU treatment are similar to those of a significantly more invasive procedure, radical prostatectomy. Secondary effectiveness endpoints were consistent with and supported the findings of the principal effectiveness endpoints.

All subjects analyzed in the prospective and retrospective cohorts were selected according to predefined inclusion and exclusion criteria without consideration of results. The analyses were conducted in accordance with predefined statistical analysis plans by independent statisticians following best statistical practices.

The consistency in the types of adverse events collected in the HIFU Cohorts affords assurance that the risks of the Ablatherm® HIFU are known. There are a few differences in the safety profile of HIFU compared to cryotherapy and radical prostatectomy. HIFU has a higher potential risk of short-term, clinically manageable urinary events and a lower potential risk of long-term, more permanent erectile dysfunction than cryotherapy and radical prostatectomy. In addition, multiple severe adverse events were observed following radical prostatectomy that are not observed following HIFU treatment.

1.8 Risk Benefit Analysis

The data sets presented within this Executive Summary and their analyses form an internally consistent body of evidence supporting the safety and effectiveness of Ablatherm® HIFU upon which an assessment of risk-benefit can be made. There are several benefits associated with the treatment of low-risk prostate cancer with the Ablatherm Integrated Imaging HIFU device including:

- **Benefit of Minimally-Invasive Procedure:** The Ablatherm® Integrated Imaging HIFU treatment is not associated with the relatively rare but severe perioperative adverse events that are observed following radical prostatectomy. These include perioperative wound infection, sepsis, transfusion, myocardial infarction, bowel injury requiring surgical repair and death which were only observed in the radical prostatectomy cohort. There were no HIFU treatment or procedure related deaths reported in any of the data sources included in the PMA.

- **Benefit of Precise Energy Delivery and Automated Safety Features:** The Ablatherm® Integrated Imaging Device incorporates novel technology to treat localized, low-risk prostate cancer. Its design allows for the preservation of the intervening tissue between the rectum and prostate. Energy delivery is precise resulting in immediate, sharp delineation between treated and untreated tissue. It has several safety features which include automatic detection of unintended probe movement prior to each ultrasound delivery, a patient movement detector and software driven controls.

- **Benefit of Definitive Local Therapy:** There is debate with regards to the need to treat low-risk prostate cancer. However, prostate cancer is often understaged and/or undergraded and although active surveillance may be an attractive treatment option for men with low risk prostate cancer, its choice carries the risk of not treating a cancer that is actually more aggressive than was diagnosed. HIFU is a definitive local therapy.

- **Benefit of Controlling Cancer:** HIFU showed a biochemical survival comparable to cryotherapy in the intermediate-term assessment and a high freedom from metastasis rate comparable to radical prostatectomy in the long-term. Results from the analyses and comparisons of secondary endpoints demonstrate consistency with the principal analyses. Thus, the EDAP Ablatherm® Integrated Imaging HIFU device is effective in providing control of cancer, as compared to a control procedure or the standard of care, for the treatment of low-risk localized prostate cancer.

- **Benefit of Preserving Erectile Function:** The data presented demonstrates the incidence of erectile dysfunction following HIFU to be lower than the incidence following cryotherapy and radical prostatectomy. The lower rate of erectile dysfunction following HIFU is a compelling factor in support of Ablatherm® HIFU treatment, especially for younger, sexually active men.

- **Benefit of Preservation of Treatment Options:** Treatment with HIFU does not result in a therapeutic "impasse" as subsequent definitive local therapy with other standard of care treatments such as cryotherapy, brachytherapy, external beam radiation therapy and radical prostatectomy remain viable options in the event of local failure.

Ablatherm HIFU has been used outside of the U.S. for over 15 years with more than 40,000 HIFU treatments administered. The literature search conducted for the HIFU MA cohort found 13 peer-reviewed articles regarding well-controlled studies of HIFU treatment in men with localized, low-risk prostate cancer. The safety profile of this device is well documented and understood.

All therapeutic procedures for the treatment of prostate cancer have their own set of risks. There was a higher potential risk of urinary events, such as incontinence, retention, obstruction and stricture reported with the use of Ablatherm® HIFU device when compared to the use of a control device (cryotherapy) and a standard of care procedure (radical prostatectomy). However, these urinary events are clinically manageable and usually transient. The increased urinary adverse events following HIFU in comparison to cryotherapy are likely related to the ablation of the urethra and adjacent tissue. During cryotherapy, the urethra is preserved with a warming device which may also preserve periurethral tissue which often harbors cancer. As with any prostate cancer treatment, there is also a potential risk of long-term erectile dysfunction associated with Ablatherm, but the rates observed were lower following HIFU treatment than for cryotherapy or radical prostatectomy.

1.9 Conclusion

In the intermediate-term, the Phoenix biochemical survival rate in subjects treated with HIFU was comparable to cryotherapy. Additionally, the HIFU results from the IDE study were found to be consistent with the results from a literature review and meta-analysis of HIFU treatment, as well as a European HIFU registry. The longer-term freedom from metastasis rate of subjects treated with HIFU is similar to that of radical prostatectomy. Based on the totality of evidence, the EDAP Ablatherm® Integrated Imaging HIFU device is effective in providing control of cancer, as compared to a control procedure or the standard of care, for the treatment of low-risk localized prostate cancer. There are several benefits to HIFU which include the preservation of future treatment options if needed due to local recurrence, the precise energy delivery and automated safety features of the Ablatherm® HIFU device, the minimally invasive nature of the procedure resulting in an avoidance of serious surgical adverse events, and the reduced rates of erectile dysfunction.

The potential risks of HIFU include higher rates of clinically manageable, usually transient urinary events. There is also a potential risk of long-term erectile dysfunction, but this was lower following HIFU treatment compared with cryotherapy and radical prostatectomy.

The consistency in the types of adverse events collected in the HIFU IDE and HIFU Prospective Safety cohorts with those reported in the literature affords assurance that the risks of the Ablatherm® HIFU are known.

There is a need for a treatment for low-risk prostate cancer that provides equivalent effectiveness to standard treatments, avoids serious perioperative surgical adverse events and preserves erectile function. The Ablatherm® HIFU is a minimally-invasive treatment option for low risk prostate cancer that compares favorably in terms of erectile dysfunction to both cryotherapy and radical prostatectomy. For men for whom surgery is too risky or for whom the potential side effects of the currently available treatments are not attractive, the Ablatherm® HIFU provides an alternative treatment that is safe and effective. Therefore, the probable benefits of Ablatherm® HIFU outweigh the probable risks.

2 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Table 7: Abbreviations and Definitions

Abbreviation	Definition
AE	Adverse Event
CRYO IDE	Prospective cryotherapy control arm in IDE study
CRYO MA	Cryotherapy systematic literature review and meta-analysis
CRYO Retro	Retrospective cryotherapy cohort
DRE	Digital Rectal Exam
HIFU	High Intensity Focused Ultrasound
HIFU IDE	HIFU investigational cohort in IDE study
HIFU Long Term	HIFU Long Term cohort
HIFU MA	HIFU systematic literature review and meta-analysis
HIFU Registry	HIFU Registry cohort from European registry
OUS	Outside of United States
PCPT	Prostate Cancer Prevention Trial
PG	Performance Goal
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PSA	Prostate Specific Antigen
RP	Radical Prostatectomy
RCT	Randomized Controlled Trial
SPCG-4	Scandinavian Prostate Cancer Research Group-4 Trial
TURP	Trans Urethral Resection of the Prostate

3 DISEASE BACKGROUND

Prostate cancer is a disease that spans a wide prognostic spectrum, from indolent to lethal and the entire range in between these extremes. Prostate cancer can be stratified by risk into three groups: low risk, intermediate risk and high risk. The proposed intended use of the device that is the subject of this PMA is to treat localized, low risk prostate cancer. Therefore, this discussion will be limited to low risk disease.

A prostate-specific antigen (PSA) test and digital rectal examination (DRE) are used to screen men for prostate cancer. Abnormal or rising PSA or any detection of suspicious masses during a DRE is often followed by biopsy of the prostate gland. Samples of the biopsied prostate tissue are examined for cancer cells which if found, are graded and staged. Biopsy in the absence of other symptoms such as a rising PSA is not standard of care and a positive biopsy does not necessarily indicate disease significance, progression probability or threat to the patient. Likewise, a negative biopsy does not rule out prostate cancer.

3.1.1 Low Risk Prostate Cancer

Low risk prostate cancer is defined as a PSA of 10 ng/mL or less, a Gleason score of 6 or less, and a clinical stage T1a to T2a.[1] Standard treatments within the United States for localized low risk disease have remained binary: watchful waiting or active surveillance vs. aggressive radical whole-gland treatment (radical prostatectomy, radiation or cryotherapy). The latter is associated with significant morbidity and detrimental impact on quality of life.

Debate exists on whether or not low-risk prostate cancer should be managed with definitive local treatment. This debate is confounded by the inaccuracy of the grading and staging of prostate cancer at the time of diagnosis with approximately 30-50% of men diagnosed with low risk disease being undergraded and 10-13% being understaged (Jalloh et al 2014[7], Busch et al 2014[8]). The grade and stage of prostate cancer cannot be definitively known without pathologic inspection of a prostate specimen. Although active surveillance may be an attractive treatment option for men with low risk prostate cancer, its choice carries the risk of not treating a cancer that is actually more aggressive than was diagnosed.

A recent systematic review of the literature on Active Surveillance showed that the 5 and 10-year discontinuation rate for Active Surveillance ranged from 14 to 39% and 40 to 59%, respectively (Thomsen et al 2014[9]). Importantly, the trigger for discontinuing Active Surveillance was patient choice for only a limited number of cases in each study (1-8.7%) and the authors commented that the majority who discontinued Active Surveillance likely had underestimation of their disease at diagnosis.

In 2005 Albertsen et al published 20-year outcomes following conservative management of clinically localized prostate cancer.[10] This study of 767 men observed that 14% and 27% of men with Gleason scores of 5 and 6, respectively, died of prostate cancer. This study was conducted prior to the PSA era but certainly demonstrates a real risk of prostate cancer mortality for men with low risk pathological findings. The use of active surveillance with repeat biopsy may reduce the cancer specific mortality by detecting either understaged or undergraded disease as well as disease progression. However, repeat biopsy is not without risk.

A Memorial Sloan Kettering study[11] of 591 men on active surveillance who underwent repeat biopsy observed that fourteen patients (3.5%) had infectious complications including 13 requiring hospitalization. Five patients had positive urine cultures, and fluoroquinolone resistant isolates were identified in 4 patients, including 2 with extended spectrum beta-lactamase producing isolates. Only the number of previous prostate biopsies was significantly associated with an increased risk of infectious complications ($p = 0.041$). For every previous biopsy, the odds of an infection increased 1.3 times (OR 1.33, 95% CI 1.01-1.74).

Thus, the scientific clinical literature on active surveillance confirms that the inability to accurately determine the risk classification of the individual patient and the real threat that low-risk prostate cancer has in the long term justifies the use of both active surveillance and definitive local therapies for the management of low-risk prostate cancer. As such, the current American Urological Association's guidance for the treatment of low and intermediate risk localized prostate cancer is as follows (Thompson et al 2007[1]):

> "Active surveillance, interstitial prostate brachytherapy, external beam radiotherapy, and radical prostatectomy are appropriate monotherapy treatment options for the patient with low-risk localized prostate cancer."

3.1.2 Current Standard Of Care In The US

Options currently available in the United States for the treatment of low risk localized prostate cancer are those listed in the AUA treatment guidelines. Focal radiation therapy and focal cryotherapy are under investigation but neither is considered standard of care. None of the devices that can deliver focal treatment are approved or cleared for this indication. Focal treatments are currently off-label.

3.1.3 Challenges In Conducting Prostate Cancer Research

Conducting research on treatments for low risk prostate cancer is challenging. The ability to interpret the effectiveness of new prostate cancer treatments in the short and intermediate term is confounded by the lack of robust, treatment specific surrogates. In the absence of longer-term clinical data on the treatment, surrogates cannot be correlated with long-term endpoints of either development of metastasis or prostate cancer specific survival. As such, validation of surrogates based on post treatment biochemical (PSA) patterns or pathological events is precluded. Biochemical events, specifically nadir and post treatment rising PSA, may prove to be valuable surrogates for clinical care as well as comparative purposes between similar therapies but they have not been validated and it is unknown how well they predict clinically significant disease progression. Biopsy, another surrogate sometimes used in clinical care, is not appropriate as a trial endpoint as a positive biopsy as a binary measure does not indicate disease significance, progression probability or threat to the patient. It is well recognized that small volume, low-grade disease is not clinically significant and that many men live with such disease without threat to their quality or quantity of life. The Prostate Cancer Prevention Trial (PCPT) found in a screening population that 17.5% men with PSA < 4.0 ng/ml and normal digital rectal exam had positive biopsy (Thompson et al 2003).[12] This is not surprising as the autopsy presence of prostate cancer is 30 % for men in their thirties and rises to 80% for men in their eighties (Sakr et al 1993).[13]

A recent active surveillance publication included 2494 subjects with very low risk disease defined as stage T1/T2, PSA ≤10 ng/ml, PSA density < 0.2 ng/ml^2, one or two positive biopsy cores, and Gleason score ≤ 6. A total of 1858 follow-up biopsies were performed of which 63.0% were positive.[14] Long-term follow-up was not presented as the median follow up was only 1.6 years. However, the long-term results will likely be similar to those recently published from the Rotterdam and Helsinki arms of the European Randomized Study of Screening for Prostate Cancer which used the same definition of low risk and found 10 year freedom from metastasis and cancer specific survival rates both > 99%.[15]

Another difficulty frequently encountered when conducting prostate cancer trials comparing definitive local therapies is accruing the target number of subjects as determined in the statistical analysis plan. Several widely supported and well-funded attempts have been made. The percentage of the accrual target actually enrolled was <1% for SWOG8890 (USA), 3% for SPIRIT (USA), 9% for START (USA), and 51% for Calgary (Canada) which were randomized clinical trials comparing radical prostatectomy versus external beam radiation therapy, radical prostatectomy versus brachytherapy, active surveillance versus definitive treatment and external beam radiation therapy versus cryotherapy, respectively. The only randomized clinical trial in the PSA era to accrue to target is SPCG-4 which was conducted in Sweden and compared radical prostatectomy to observation. None of the trials comparing fundamentally different definitive local therapies met accrual targets as men were unwilling to be randomized to treatment especially since most treatments were available outside of the trials. The most successful U.S. based randomized clinical trial comparing fundamentally different definitive local therapies was the START trial which accrued 9% of the target.

4 DEVICE DESCRIPTION

The Ablatherm® Integrated Imaging is a medical device intended to provide high intensity focused ultrasound (HIFU) treatment for prostate cancer. Under computer control, transrectal HIFU delivers high intensity ultrasound waves to the prostate which heats and ablates the tissue.

4.1.1 Intended Use/Indications

The Ablatherm® Integrated Imaging is intended for the primary treatment of localized prostate cancer in subjects with low risk, localized prostate cancer.

4.1.2 Scientific Basis Of Ablatherm® Imaging

The Ablatherm® Integrated Imaging uses high-intensity focused ultrasound (HIFU) to induce tissue lesions *in vivo* by focusing a high-energy ultrasound beam into the body. The absorption of ultrasound energy results in immediate thermal destruction of tissue at the focal point (i.e., the tumor). Intervening tissue between the ultrasound transducer and the focal point does not experience a temperature increase sufficient to cause tissue damage.

4.1.3 Technological Characteristics

The Ablatherm® Integrated Imaging consists of the following primary components:

- An **endorectal probe** composed of two ultrasonic transducers: a high-energy therapy transducer and an imaging transducer.
- A **treatment module** consisting of a subject treatment table, a motorized endorectal probe positioning unit, a high frequency generator to power the transducer, a cooling unit to refrigerate the ultrasound coupling liquid, an ultrasound scanner connected to the endorectal probe to allow visualization of the target tissue on a monitor and built-in safety features.
- A **control module** consisting of a computer to control device operation and a display unit as the user interface
- A **disposable kit** consisting of accessories (balloon, ligature, tubing, coupling liquid) used in combination with the endorectal probe.

During a HIFU procedure, the subject is positioned on the treatment module (table) and the endorectal probe is inserted. Ultrasonic energy is delivered via an endorectal treatment probe. The probe includes both a HIFU treatment transducer and an ultrasound imaging transducer. Ultrasound imaging is used to detect the contours of the prostate and the target treatment volume is defined on the computer screen. Under computer control, the device positions the endorectal probe. During treatment, high-energy ultrasound waves propagate through the rectal wall and are focused on a portion of the prostate, generating intense heat and causing the ablation of tissue within the focal area. The heat distribution within the prostate is concentrated at the focal point of the treatment transducer and the tissue is destroyed when a threshold temperature is reached. If power is maintained at the focal point, the treatment lesion will continue to enlarge at a known and reproducible rate. After each lesion is created, the treatment transducer is repositioned to create the next lesion and the heating process is repeated. The size of the created lesion is dependent on the frequency, power level, and duration of the treatment pulse. The process is then repeated in a stepwise fashion to destroy the targeted tissues and create a treatment lesion within the prostate. The computer successively repositions the probe to deliver HIFU energy according to consecutive treatment blocks defined by the user until all sectors of the prostate have been treated.

4.1.4 Key Safety Features

The endorectal probe has a sharply focused transducer allowing low intensity level at the transducer surface (5 watts/cm²) and high intensity level at the focus point (more than 5000 watts/cm²) thus preserving the intervening tissue. The small focal dimensions (0.5 x 0.8 x 5 mm) result in precise heat disposition.

The probe contains separate transducers for imaging and therapy (7.5 MHz and 3 MHz, respectively). The imaging array is mechanically integrated within the therapy transducer which provides in line ultrasound monitoring with continuous visualization of the ultrasound beam path from the transducer to the focal point, and a safe and precise real time control of the process.

The probe has a disc shape design to ease rectal insertion and is similar in size to other rectal probes. As a result the Ablatherm® probe insertion is well tolerated.

Ablatherm® Imaging treatment is a standardized procedure with three well-differentiated phases:

- Device control and treatment setup
- Treatment planning
- Treatment execution

When the device is powered on, controls of the subassemblies and their communication with the main computer are performed. The treatment process cannot be initiated if any failures are detected. Then the software displays information to guide the operator in the treatment setup (disposable installation and endorectal probe preparation). This first step is terminated by the entry of patient data and operator name.

During treatment planning, software guides the operator in developing a treatment plan to ensure that the entire prostate volume is treated and specific tools are available for reviewing the treatment plan. Real time ultrasound imaging with a 7.5MHz operating frequency allows a high quality image with precise definition of the prostate contours and patient anatomy (rectum, bladder neck, apex sphincter) during both treatment planning and treatment execution.

During treatment planning and execution, the software requires that a step be properly and completely executed before moving to the next step and displays messages to guide the user through the procedure. Multiple safety features are continuously active to ensure that the ultrasound energy is properly delivered to the selected portion of the prostate.

Following are the main safety features of the HIFU Ablatherm® Integrated Imaging device which are divided into three categories:

<u>Control of the position of the transducer focus within the prostate:</u>

- Probe position control: The probe positioning is performed by three stepper motors whose displacements are controlled by encoders. After each displacement, the displacement values given by the encoders are read by the software and compared to the requested value.
- Patient movement control: At all times during the treatment procedure, patient movements are monitored via a single use reflecting sticker that is attached to the patient's hip prior to treatment initiation.

- Prostate movement control: After each probe positioning and prior to each firing sequence, the distance between the transducer and the rectum is measured and compared to the value determined during treatment planning:
    - If the difference is within the range ± 1 mm, the firing sequence starts,
    - If the difference is greater than 1 mm and less than 4 mm, the probe position is automatically adjusted and a new distance measurement is performed. Note that only one automatic adjustment of the probe is allowed.
    - If the difference is greater than 4 mm the treatment is paused.

Control of the energy delivered to the patient:

- Electrical Power control: The electrical power supplied to the transducer is controlled three times during each firing sequence and compared to the requested value.
- Firing duration control: The firing duration is controlled by a timer which is continuously checked to ensure proper functioning. At the end of each firing sequence, a power measurement is performed to verify that the power has been effectively shut down.
- Cooling temperature control: A temperature sensor is embedded into the endorectal probe on the coupling liquid outlet to verify that the coupling liquid temperature remains within the acceptable range.

General safety features:

- Device self-checks when the system is powered on.
- Single use disposable: The singe use disposable allows a safe and standardized procedure by providing all the necessary components including coupling liquid required by the procedure.
- Validated process for endorectal probe cleaning and disinfection. The endorectal probe has been designed to allow effective and reproducible cleaning and disinfection processes.

When any of the above safety features is activated, the treatment is paused and operator information is displayed. The severity level of the alarm determines whether or not treatment continuation is allowed.

4.1.5 Comparison to Cryotherapy Procedure

HIFU and Cryotherapy procedures are both used to ablate prostate tissue. However, there are some important differences between the technologies which make HIFU a more complete and safe ablation procedure. The Ablatherm® focusing technology allows a more precise thermal energy deposition with immediate sharp delineation between treated and untreated tissue whereas cryotherapy requires successive freezing and warming sequences to obtain definitive tissue necrosis surrounded by margins around the prostate that are several millimeters wide where tissue destruction remain uncertain. Also, the preservation of the urethra during cryoablation may result in preservation of periurethral tissue which often contains cancer cells (Leibovich et al 2000[16]).

Table 8 provides a comparison of the HIFU procedure to the cryotherapy procedure.

Table 8: Comparison of HIFU Procedure to Cryotherapy Procedure

HIFU	Cryotherapy
Energy Delivery	
Quick pulse (6 sec) of highly controlled energy deposit	Slow growth of an iceball (over about 20 minutes) which is operator dependent
Single heating sequence resulting in definitive tissue coagulation necrosis	Successive freezing and warming sequences to obtain definitive tissue necrosis
Juxtaposition of small lesion volumes (typically 500) to cover the whole gland and precisely preserve adjacent tissue	Juxtaposition of large lesion volumes to cover the whole gland
Distance from Untreated Tissue to Ablated Tissue	
The distance between ablated tissue and untreated tissue is less than 1 mm.	The distance between ablated tissue (-20 °C) and untreated tissue (-2 °C) ranges from 4-7 mm (Rewcastle et al 2001[17]).
Periurethral Ablation	
HIFU ablates the urethra and all surrounding tissue to ensure complete ablation of cancer.	A urethral warmer is used throughout cryotherapy to maintain the integrity of the urethra. This may also result in preservation of the periurethral tissue which often contains cancer cells.
Real Time Ultrasound Monitoring	
Monitoring of the entire prostate is performed throughout the procedure. This allows for modification of the treatment plan in real time to account for inflammatory changes.	Monitoring is limited to the near (posterior) edge of the iceball due to acoustic reflection which prevents ultrasound penetration.
Computer Assisted Procedure	
Ultrasound image recognition software is used to locate the rectal wall position at every location prior to forming a HIFU lesion above that location.	Temperature monitoring with thermocouples is possible but only provides information on limited discrete locations which may not be representative.
The software assisted procedure offers the operator several tools to assist in: • Treatment planning, • Treatment execution, • Treatment control via safety features covering energy distribution within the prostate.	The software assisted procedure offers the operator several tools to assist in: • Treatment planning, • Treatment execution, • Treatment control via thermocouple monitoring at discrete locations.
Ablation can be stopped by the computer or user instantly.	Cryotherapy iceball growth cannot be initiated or stopped instantly due to thermal inertia. Arresting iceball growth takes tens of seconds or minutes.
Treatment Invasiveness	
HIFU is minimally invasive and as such, surgical risks are not associated with it.	Cryotherapy requires surgical insertion of transperineal probes with associated surgical risks.

5 PRECLINICAL DATA

5.1 Introduction

The nonclinical studies were conducted in compliance with 21 CFR 58 Good Laboratory Practices for non-clinical laboratory studies.

5.2 Summary of Preclinical Studies

5.2.1 Technical and Performance Testing

Technical and performance testing consisted of the treatment transducer testing and calibration. The objectives of the tests were to calculate measurements for the following parameters: electrical impedance, transducer dimension, ultrasonic beam profile, acoustic intensity, radiation force, reference electrical power, and acoustical power stability verification. Software simulations were first performed and prototypes were manufactured and tested on *in vitro* models then on *in viv*o models before clinical investigation.

5.2.2 Software

The Ablatherm® software validation confirms that the device performs as intended for the following functions:

- To control the device functioning via a dedicated hardware,
- To record the operator instructions related to the treatment management,
- To provide the operator with information related to the treatment follow-up.

5.2.3 Biocompatibility

Biocompatibility assessment of the patient contacting components consisted of cytotoxicity, irritation and sensitization testing. These tests were performed on the materials constituting the endorectal probe and the adhesive strip which is used to attach the balloon containing the Ablasonic® coupling liquid. The Ablatherm® Integrated Imaging passed all biocompatibility tests.

5.2.4 Electrical Safety and Electromagnetic Compatibility

Testing to applicable portions of IEC 60601-1 Medical electrical equipment Part 1: General requirements for Safety and EMC testing according to the standard CEI/IEC 60601-1-2 has been completed on the Ablatherm® Integrated Imaging System. The Ablatherm® Integrated Imaging complies with all tests performed.

5.2.5 Animal Studies

Animal studies were conducted on canine and rabbit models, as well as calf liver**.** Table 9 outlines the animal testing performed.

Table 9: Animal Studies

Type of Test	Purpose	Results/ Conclusions
Evaluation of Tissue Destruction (Rat)	To define the treatment pulse constants necessary to produce a localized tissue lesion at the focal point of the transducer.	The study determined that the tissue damage thresholds and the tissue ablation threshold could be accurately defined for the selected transducers.
Evaluation of Lesions in the Canine Kidney	To evaluate the ability to produce internal lesions in an extracorporeal treatment session.	This study showed that it is possible to produce in-depth lesions in the dog kidney using extracorporeal high focused ultrasound.
Evaluation of Prostate Cancer – Adenocarcinomas Implanted in Rats (Mat-Ly-Lu Strain)	To evaluate the effect of a high intensity focused ultrasound treatment on a known, highly aggressive adenocarcinoma tumor strain.	This study showed that the HIFU treatment was capable of destroying the Mat-Ly-Lu prostatic adenocarcinoma subline, without any adjuvant treatments.
Evaluation of Prostate Cancer – Adenocarcinomas Implanted in Rats (AT2 Strain)	To evaluate the effect of high intensity focused ultrasound on a less aggressive adeno-carcinoma tumor strain.	In the study 64% of the treated rats were observed to demonstrate sustained control of the tumor, with no signs of either local or distant metastases. The metastasis factor as observed was 28% among the control animals and 16% among the treated animals.
Transrectal Application/Acoustical Intensity Evaluation Study	To determine the feasibility of using endorectal application of high intensity focused ultrasound to obtain coagulation necrosis lesions in the dog's prostate without affecting the rectum wall.	This study showed that HIFU treatment destroyed the glandular prostate tissue without destroying the fibrous architecture of the gland or creating capsular lesions with excellent preservation of the intra-prostate urethra wall.
Biological Markers Evaluation Study	To evaluate the effect of prostatic coagulation necrosis on the biological markers of 16 dogs.	The abrupt and immediate rise in ASAT transaminases and the rise in the CPK count were indicative of the immediate nature of cellular and tissue necrosis. These changes did not cause any metabolic perturbation (*e.g.*, no coagulation problems).
Temperature measurement at the transducer focal point	To measure the tissue temperature at the transducer focus during a HIFU lesion formation.	The tissue temperature at the focal point of the transducer reached 85 °C during the HIFU lesion formation. The temperature diffusion was limited to a 3-mm distance from the focal

Type of Test	Purpose	Results/ Conclusions
		point.
Treatment Parameter Experiments on Rabbit Livers	To evaluate the effect of different treatment parameters on the rabbit liver.	The treatment parameters were determined to be appropriate for clinical evaluation.
In vitro Calf Liver	To validate necrotic lesions in terms of quality, dimension and position with the probe.	The parameters of the necrotic lesions were validated.
Rabbit Liver	To validate or adjust the treatment parameters in living tissue before performing a clinical study: dimension and position of lesions; efficacy on focus and preservation of surrounding tissue.	In terms of Minimal Shot Depth, the parameters of the lesions induced by the probe were validated.

5.3 Conclusions

The pre-clinical tests confirmed the expected performance of the Ablatherm® HIFU device hardware and software, and the biocompatibility of the patient contacting components. The animal testing confirmed that the product mechanism of action would yield the safe ablation of prostate tissue.

6 OVERVIEW OF CLINICAL STUDIES

EDAP has collected a comprehensive set of both intermediate-term (biochemical survival at 2 years) and long-term (freedom from metastasis and prostate cancer specific survival at 8 and 10 years) effectiveness data on Ablatherm® HIFU. Safety data for the HIFU procedure was collected through 24 months. Due to difficulties in enrolling prospective control cohorts, described in more detail below, this data is presented in comparison with relevant literature data on cryotherapy and radical prostatectomy that provide context and appropriate comparators for the observed HIFU results.

A significant body of data has been collected on patients treated with Ablatherm® HIFU including:

- **HIFU IDE:** Prospective data from the pivotal HIFU IDE study conducted in the U.S. and Canada;
- **HIFU Literature:** A systematic review and meta-analysis of the HIFU literature; *and*
- **HIFU OUS Data:** Data from a registry and three studies of HIFU patients treated outside of the United States (OUS).

The following sections summarize the original IDE study, challenges encountered in its execution, and changes made in light of these challenges, including revisions to the control group to compare Ablatherm® HIFU to cryotherapy literature rather than a prospective cryotherapy arm. In addition, the following sections describe the supporting data (HIFU Registry and Meta-Analysis) that demonstrate the consistency of the results observed in the HIFU IDE study in terms of biochemical survival and safety. Finally, long-term data on clinical outcomes with HIFU is also presented, in comparison to long-term data reported in the literature for radical prostatectomy.

6.1 HIFU IDE Study

6.1.1 Original Study Design

The HIFU IDE study (G050103) was a multicenter, non-randomized, concurrently controlled trial designed to demonstrate non-inferiority of Ablatherm® HIFU in comparison to cryotherapy for the treatment of low-risk localized prostate cancer. The control device was the Endocare CRYOcare system originally cleared by FDA via the 510(k) process in 1995 (K942299). The primary effectiveness endpoint of the HIFU IDE study was achievement of PSA nadir ≤ 0.5 ng/ml and stability of PSA according to ASTRO criteria (3 consecutive PSA increases) through 24 months follow-up without a positive biopsy. Additional effectiveness endpoints included the 2006 ASTRO criteria which is termed the "Phoenix" definition of biochemical survival and defined as PSA ≤ PSA nadir + 2 ng/ml [18] and the composite clinical success criteria using the Phoenix criteria instead of ASTRO (i.e., Nadir/Phoenix/Biopsy Survival). The projected sample size was 184 patients in each study arm. The study enrollment was planned for 205 patients per arm to account for a 10% attrition rate.

6.1.2 Challenges Encountered in Conducting the IDE Study

Significant accrual difficulties were encountered in both arms of this investigation, particularly in the control arm. There were several reasons for this. The inclusion/exclusion criteria of the IDE were often not met by the typical man seeking whole gland cryotherapy today (primarily due to growing lack of interest in this treatment option by younger potent men, who typically have the smaller prostate sizes required for study entry), the rapidly growing use of focal (as opposed to whole gland) cryotherapy for men with low risk, localized disease, and the lack of interest in eligible men seeking cryotherapy to enroll into a clinical trial, primarily due to the requirement for biopsy at 2 years (which is no longer standard clinical practice).

6.1.3 Changes to Analysis Plan

EDAP met with FDA to discuss these accrual difficulties and EDAP implemented a number of changes in an attempt to increase enrollment, including:

- Increased the number of study sites;
- Added the Galil Medical CRYOhit (K980913), an additional cryotherapy control device;
- Added Canadian study sites to both the HIFU and Control arms;
- Decreased the age limit for both arms;
- Increased the maximum anterior posterior prostate size in the control arm eligible for enrollment;
- Conducted investigator and coordinator meetings and calls; and
- Invested in an extensive marketing campaign to support study subject accrual.

Despite these efforts, only 5 subjects were enrolled in the cryotherapy arm of the study, and the HIFU IDE arm was closed below the target enrollment.

EDAP met with FDA and discussed proposed changes to the IDE study design to increase subject accrual by allowing the inclusion of intermediate risk subjects and allowing investigators to "right-size" (reduce) the prostate prior to treatment by means of either short-term hormone therapy, a conditioning HIFU procedure or pre-HIFU transurethral resection of the prostate (TURP). However, these changes were not made as FDA expressed concern that they could confound the study results. EDAP also proposed modifying the concurrent control arm to a

prospectively defined collection of retrospective data from subjects who have already undergone cryoablation.

FDA requested that EDAP provide a re-evaluation of cryotherapy as the control arm for evaluating the safety and effectiveness of HIFU. Following receipt of this re-evaluation, FDA agreed with EDAP that it is "clear that cryotherapy represents the best option for use as a control for evaluating the safety and effectiveness of HIFU"[19] and expressed concern that there was a lack of clarity on how best to proceed. Furthermore, FDA recognized that the issues facing EDAP were relevant to future studies as well. As such, FDA conducted a general issues Panel meeting in December 2009. Unfortunately, consensus was not reached on most discussion topics but it remained clear that proceeding with a prospective cryotherapy control was not a viable path.

Subsequent to this Panel meeting, EDAP met with FDA to discuss changing the control therapy from cryotherapy to brachytherapy. EDAP still believed cryotherapy was the most appropriate control for HIFU but recognized that the company was unable to accrue a sufficient number of subjects in the CRYO IDE arm. FDA expressed concern over the length of time needed for brachytherapy results to become meaningful due to PSA bounce and the interpretability of biopsy outcomes post brachytherapy in the short- and intermediate-term and encouraged EDAP to reconsider a randomized trial regardless of the control.

Following these meetings, EDAP considered the agency's suggestions but believed that a randomized trial would be impossible to conduct, given the significant difficulties with enrolling a concurrently controlled study, and the historical difficulties in conducting randomized trials for prostate cancer. EDAP discussed the design issues with its investigators and clinical and regulatory advisors and decided to close enrollment in the study at the end of June 2010. After 4 years of accrual, 13 HIFU sites had enrolled 136 HIFU subjects and 11 cryotherapy sites had enrolled only 5 cryotherapy subjects. The decision to close the enrollment phase was based solely on the accrual difficulties and with no knowledge of the study results.

6.2 Clinical Data Sources for Evaluation of Safety and Effectiveness

This PMA includes a comprehensive compilation of the data available to EDAP on HIFU treatment for low-risk, localized prostate cancer compared to cryotherapy and radical prostatectomy. These data are divided into intermediate-term (2-5 years) and long-term (8-10 years) HIFU results. Comparisons based on biochemical (surrogate) endpoints are made to cryotherapy in the intermediate term. Long-term clinical (non-surrogate) endpoint comparisons (freedom from metastasis and prostate cancer specific survival) are made between HIFU and radical prostatectomy.

Although the IDE study was originally designed to compare the HIFU arm of the HIFU IDE Study to a concurrently enrolled cryotherapy arm, only 5 subjects were enrolled in the CRYO IDE arm. To replace the CRYO arm, a retrospective study was then conducted to collect data on subjects who had been treated with cryotherapy (CRYO Retro). However, despite the screening of over 1,500 potential subjects, comparison to the CRYO Retro was also underpowered due to low enrollment with only 67 subjects enrolled. Next, a systematic review and meta-analysis of the cryotherapy literature (CRYO MA) was performed, from which a HIFU performance goal (HIFU PG) was derived to serve as the comparator for the HIFU IDE biochemical survival results.

Thus, the principal intermediate-term effectiveness analysis was of a comparison of the two-year biochemical survival data from the HIFU IDE cohort compared against the HIFU performance goal. Given the limitations of this biochemical analysis, the company sought to bolster the

evaluation of Ablatherm® HIFU effectiveness with long-term clinical data. In this regard, long-term Ablatherm® HIFU clinical data (8-10 year freedom from metastasis data) from three European sites was collected (HIFU Long Term cohort) and compared against published long-term data from radical prostatectomy (PIVOT study).

Table 10 summarizes the data sources used to evaluate the safety and effectiveness of Ablatherm® HIFU compared to cryotherapy for the treatment of low-risk localized prostate cancer in the intermediate term. The table also summarizes the long term Ablatherm® HIFU safety and effectiveness cohorts as well as the literature controls used for comparative purposes.

Table 10: Clinical Data Sources in Support of Ablatherm® Integrated Imaging HIFU

Treat-ment	Cohorts	Description	Sample Size	Role	Principal Endpoints	Comparator
Intermediate-Term Results						
HIFU	HIFU IDE	Prospective, multicenter, collected in US IDE G050103	135	Principal Effectiveness, Safety	Phoenix Biochemical Survival Rate and adverse events	CRYO PG
	HIFU MA	Prospectively defined systematic review and meta-analysis of HIFU studies	13 articles 623 subjects	Principal Safety Supporting Effectiveness	Adverse event rates	CRYO MA
	HIFU Registry	Prospectively defined data abstraction, multicenter, collected in Europe from prospectively managed registry	115[1]	Internal Consistency	n/a	n/a
Control	HIFU PG	Based on systematic review and meta-analysis of cryotherapy studies	25 articles 687 subjects	Principal Effectiveness	Biochemical Survival Rate	HIFU IDE
	CRYO MA	Systematic review and meta-analysis of cryotherapy studies	25 articles 687 subjects	Principal Safety Supporting Effectiveness	Adverse event rates	HIFU MA
	CRYO Retro	Prospectively defined retrospective collection of cryotherapy data	67	n/a	n/a	n/a
	CRYO IDE	Prospective,	5	n/a	n/a	n/a

Treat-ment	Cohorts	Description	Sample Size	Role	Principal Endpoints	Comparator
		multicenter, collected in US IDE G050103				
Long-Term Results						
HIFU	HIFU Long Term Refined	Prospective protocol for retrospective data abstraction, multicenter, collected in Europe; Sub-cohort of the HIFU Long-Term Cohort	227	Principal Effectiveness	Freedom from Metastasis Rate	PIVOT RP
	HIFU Prospective Safety	Prospective protocol for retrospective data abstraction, multicenter, collected in Europe; Sub-cohort of the HIFU Long-Term Cohort	62	Safety	Adverse events	PIVOT RP
Control	PIVOT RP	Prospective, multi-center, randomized trial comparing radical prostatectomy to observation	148	Principal Effectiveness Safety	Freedom from Metastasis Rate and adverse events	HIFU IDE
	SPCG-4 RP	Prospective, multi-center, randomized trial comparing radical prostatectomy to observation	166	Supporting effectiveness	-	HIFU IDE
[1] Some of the subjects in this cohort may be included in the HIFU Long-Term Cohort.						

6.2.1 Intermediate-Term Clinical Data Sources

The intermediate-term analyses principally compare HIFU results at 24 months post-treatment to cryotherapy for the treatment of low-risk localized prostate cancer. Like HIFU, cryotherapy immediately ablates the prostate tissue with the goal of ablating the entire prostate gland at the time of treatment. As such, HIFU and cryotherapy are expected to have similar biochemical responses. The cryotherapy procedure was standardized in the late 1990s and the technique,

technology and dosing have not changed from a fundamental prospective since this point. Thus, cryoablation is the best choice of comparison arm for the evaluation of HIFU in the intermediate-term for biochemical survival and safety.

The intermediate-term results include HIFU data from: the IDE study (HIFU IDE); a systemic literature review and meta-analysis (HIFU MA); and a European registry (HIFU Registry).

6.2.1.1 Intermediate-Term Clinical Data Sources for HIFU

HIFU IDE Cohort

The HIFU IDE Cohort is data collected in the HIFU arm of the IDE study (G050103) which was designed to demonstrate non-inferiority of Ablatherm® HIFU in comparison to cryotherapy for the treatment of low-risk localized prostate cancer. For this study, the following standard definition of low risk, localized prostate cancer was used: stage T1-2a and PSA < 10ng/mL and Gleason score <6). Thus, this cohort provides 2-year safety and effectiveness information on 135 patients treated with Ablatherm® HIFU.

Systematic Review and Meta-Analysis of the HIFU Literature (HIFU MA)

To provide supportive evidence to supplement the HIFU IDE results, EDAP systematically reviewed and performed a meta-analysis of the HIFU literature, as there is a body of peer-reviewed evidence from studies of HIFU outside the U.S. The purpose of these analyses was to review the contemporary evidence of biochemical disease-free survival and morbidity following whole gland HIFU for low-risk, localized prostate cancer. An electronic search was performed and relevant reports were identified using the PubMed and EMBASE databases spanning a 15-year period from 1997 to 2012. Criteria for inclusion in the systematic review and meta-analysis included prospective or retrospective cohort studies of patients with low-risk, localized prostate cancer treated with HIFU. Thirteen studies were identified and included in the HIFU meta-analysis. Pooled estimates of adverse events as well as biochemical survival rates at 2 and 5 years were analyzed and reported.

Thus, this meta-analysis provides 2- and 5-year safety and effectiveness information on patients treated with Ablatherm® HIFU.

HIFU Registry Cohort

European HIFU Registry data were analyzed to provide additional supportive evidence of the safety and effectiveness of the Ablatherm® HIFU device. EDAP has sponsored a prospectively designed registry of Ablatherm® cases conducted in Europe and Canada since 1996. EDAP prospectively developed a protocol to standardize subject selection, to pre-specify data abstraction and define data analysis methods for the HIFU registry data collection. Therefore, selection of subject records for this HIFU cohort was performed in an unbiased way.

A consecutive series of whole gland HIFU patients similar to those in the IDE study according to the critical comparability characteristics was identified. This includes patients treated since 2000 with either the Ablatherm® Integrated Imaging or an earlier device, the Ablatherm® Maxis device. The records of approximately 8,500 consecutive patients were reviewed and all who met the inclusion criteria were identified. Three centers met the minimum case criterion and all agreed to participate. All eligible patients at those sites were included in the HIFU Registry cohort. The results of the HIFU Registry support the internal consistency of the HIFU effectiveness results.

6.2.1.2 Intermediate-Term Clinical Data Sources for CRYO

Retrospective Cryotherapy Study (CRYO Retro cohort)

EDAP initiated the multi-center prospectively defined retrospective cryotherapy data collection proposed during its March 2009 meeting with FDA to replace the cryotherapy arm of the IDE study, which failed to enroll subjects. This cohort consisted of evaluation of a consecutive series of contemporary cryotherapy procedures that were conducted to treat low-risk, localized prostate cancer. This cohort was designed with a goal of enrolling 125 subjects at four to seven study sites. The patient selection criteria were as similar as possible to that of the IDE study. The primary effectiveness endpoint was achievement of PSA nadir ≤ 0.5 ng/ml and stability of PSA according to ASTRO criteria through 24 months follow-up without a positive biopsy. Although more than 1,500 potential subjects were screened, only 67 were included in the CRYO Retro cohort. This was largely due to subjects who had undergone previous hormone therapy or off-label focal cryotherapy treatment, which were exclusion criteria for the study. The accrual of only 53% of the target in this study was lower than the number necessary to allow for statistical comparisons of sufficient power.

Performance Goal (HIFU PG) and Meta-Analysis of Cryotherapy (CRYO MA)

In the absence of a sufficiently large clinical data set of cryotherapy subjects to use as a control for the assessment of the clinical performance of HIFU data collected in the IDE Study, EDAP met with FDA to discuss other options for a scientifically valid cryotherapy control, which included a performance goal. Based on the availability of multiple well-controlled cryotherapy studies, EDAP decided on its own accord to establish a performance goal to provide an objective performance measure for comparison to the HIFU IDE cohort. Using a methodology identical to that described above for the HIFU MA, a systematic review and meta-analysis of the cryotherapy literature on the treatment of low risk localized prostate cancer was conducted by an independent statistician. Twenty-five studies were identified and included in the cryotherapy meta-analysis. Pooled estimates of adverse events as well as biochemical survival at 2 and 5 years were established. A performance goal (HIFU PG) for 2-year biochemical survival was derived from those results and was established without knowledge of the HIFU IDE study results. None of the cryotherapy literature reported biochemical survival results based on the composite endpoint defined in the IDE study, as the Phoenix Definition of biochemical failure (PSA nadir plus 2.0 ng/ml) has emerged as the preferred definition of biochemical failure following cryotherapy (Pitman et al 2012[20]). Thus, EDAP established a performance goal based on biochemical survival and that performance goal was defined as the principal comparator for the effectiveness of HIFU IDE. The delta selected for the performance goal was 5% which is half that specified in the original IDE. It is important to note that the Phoenix Definition of biochemical failure was a pre-specified secondary endpoint in the IDE study. Although derived from cryotherapy results, the performance goal is termed the HIFU PG as it is the goal for the HIFU IDE results.

6.2.2 Long-Term Data Sources

6.2.2.1 Long-Term Data Sources for HIFU

HIFU Long Term Refined Cohort and HIFU Prospective Safety Cohort

The HIFU Long Term project was designed in response to a request from FDA to demonstrate the effectiveness of the HIFU device using clinical, non-surrogate endpoints. Additionally, FDA requested evidence of safety and long-term effectiveness from a single data set.

The purpose of this project was to document long-term freedom from metastasis and prostate cancer-specific survival from the European clinical experience with Ablatherm® HIFU for the treatment of low-risk localized prostate cancer. The data used in the HIFU Long Term data collection were derived from databases maintained at three European sites that recently published long-term treatment results of Ablatherm® HIFU for low-risk localized prostate cancer.

Three HIFU cohorts were derived from this dataset. Inclusion and exclusion criteria similar to those used in the HIFU IDE study were applied to select the subjects included in the HIFU Long Term cohort. Based on discussions with FDA, the HIFU Long Term Refined cohort, a subset of the HIFU Long Term cohort, further excludes subjects with previous hormone therapy, previous TURP and incidental prostate cancer (Stages Ta and T1b). The HIFU Long Term Refined cohort was selected for the principal analysis of long-term effectiveness. The HIFU Long Term cohort results were included in the PMA as supportive evidence but are not discussed here since it includes subjects with previous hormone therapy, previous TURP and incidental prostate cancer (Stages Ta and T1b) which are not comparable to the HIFU IDE Cohort or consistent with the proposed product intended use. The third cohort, the HIFU Prospective Safety cohort, is a subset of the subjects in the HIFU Long Term cohort who had also been followed in one of three previously conducted prospective HIFU studies and, as a result, had prospectively collected safety data available.

6.2.2.2 Long-Term Data Sources for Radical Prostatectomy

PIVOT and SPCG-4 Cohorts

Historical radical prostatectomy controls were used to assess the relative safety and effectiveness of the HIFU Long Term Refined cohort. The radical prostatectomy results in low risk cases were taken from publications of two randomized controlled studies:

- Prostate Cancer Intervention Versus Observation Trial (PIVOT)[21]
- Scandinavian Prostate Cancer Research Group-4 Trial (SPCG-4)[22]

These prostate cancer studies were chosen as literature controls due to their prospective controlled randomized trial design. The PIVOT trial was chosen as the primary comparator as it was a study conducted in the USA during the PSA era and additional information beyond the manuscript was available from the New England Journal of Medicine website in the form of a Supplementary Appendix. The Supplementary Appendix provides stratified outcomes by risk group.

6.3 Methodology and Analyses

The principal safety and effectiveness evaluations of the Ablatherm® HIFU based on the data sources described above are summarized below in Table 11 and further described in the sections that follow.

Table 11: Principal Safety and Effectiveness Evaluations

Evaluations	Principal Endpoint	Principal Comparison	Supporting Data
Intermediate-term effectiveness	Phoenix Biochemical Survival rate at 24 months	HIFU IDE Cohort vs. HIFU PG	Comparisons of HIFU IDE cohort with: • HIFU Registry Cohort • HIFU Meta-analysis

			• CRYO Meta-analysis
Long-term effectiveness	Freedom from metastasis at 8 years	HIFU Long Term Refined Cohort vs. PIVOT RP	Comparisons of freedom from metastasis at 10 years in the HIFU Long Term Refined Cohort with SPCG-4 RP arm
Safety	Adverse events	HIFU meta-analysis vs. CRYO meta-analysis	Comparisons of HIFU IDE Cohort and HIFU Prospective Safety Cohort with PIVOT RP arm

6.3.1 Intermediate-Term Analyses

The sponsor regularly discussed with FDA their proposed approaches to evaluate the safety and effectiveness of HIFU in light of the difficulty of subject recruitment in the HIFU IDE study. All of the changes that were implemented had been discussed with FDA and, although, FDA did not agree to all of them, EDAP planned the changes with as much consideration of FDA's comments as possible. The principal effectiveness endpoint of the intermediate-term HIFU results is Phoenix Biochemical Survival at 24 months compared to the HIFU PG. Safety is principally demonstrated by a comparison of the adverse events from the systematic review and meta-analysis of HIFU studies (HIFU MA) and cryotherapy studies (CRYO MA), because these two data sources are the most similar in terms of AE reporting. Also, the HIFU MA and CRYO MA provide supporting evidence of effectiveness that is consistent with the HIFU IDE results. Finally, the results from a cohort of subjects enrolled in a European HIFU registry (HIFU Registry) were analyzed to additionally demonstrate the internal consistency of the HIFU effectiveness results.

Principal Effectiveness Endpoint

Use of a performance goal necessitated a change in the principal endpoint as no publication identified in the systematic review of the literature used the composite endpoint defined in the IDE study, and many do not report biopsy results. Biochemical survival is the most commonly reported surrogate for the evaluation of the efficacy of cryotherapy and HIFU. Specifically, the Phoenix Definition of biochemical failure (PSA nadir + 2.0 ng/ml) is the most common definition utilized in the contemporary peer reviewed literature for both HIFU (Chaussy et al., 2013[23]) and cryotherapy (Pitman et al., 2012[24]). As such, after reviewing the contemporary literature, the Phoenix Biochemical Survival was determined to be the most scientifically valid and clinically relevant effectiveness endpoint for an intermediate-term comparison of HIFU and cryotherapy. Therefore, after discussing the plan with FDA at a pre-submission meeting, the sponsor decided to change the endpoint to the Phoenix Biochemical Survival. This endpoint change was made before any data analysis on biochemical survival was performed and without any knowledge of the study results.

The Phoenix Biochemical Survival does not rely on biopsy results. Biopsy in the absence of other symptoms such as a rising PSA is not standard of care and a positive biopsy does not necessarily indicate disease significance, progression probability or threat to the patient. Likewise, a negative biopsy does not rule out prostate cancer. Certainly a positive biopsy represents the presence of disease but does not evaluate the clinical significance of the disease. It is well recognized that small volume, low-grade disease is not clinically significant and that many men live with such disease without threat to their quality or quantity of life. The Prostate Cancer Prevention Trial (PCPT) found in a screening population that 17.5% of men with PSA <

4.0 ng/ml and normal digital rectal exam had positive biopsy (Thompson et al 2003[Error! Bookmark not defined.]). This is not surprising as the autopsy presence of prostate cancer is 30% for men in their thirties and rises to 80% for men in their eighties (Sakr et al., 1993[Error! Bookmark not defined.]).

The revised analysis plan defined the principal effectiveness endpoint as Phoenix Biochemical Survival at 24 months following study treatment. The Phoenix Biochemical Survival is defined as no PSA obtained between 6 and 24 months following study treatment that is greater than the PSA nadir (obtained within 6 months following study treatment) plus 2 ng/ml. This endpoint was a secondary endpoint in the original IDE analysis plan. All other effectiveness endpoints in the IDE analysis plan were included as secondary endpoints.

6.3.2 Long-Term Analyses

For the principal effectiveness endpoint for the long-term HIFU data, the HIFU Long Term Refined results were compared to the PIVOT radical prostatectomy (PIVOT RP) results for freedom from metastasis at 8 years. As evidence of supporting effectiveness, the HIFU Long Term Refined results for freedom from metastasis at 10 years were compared to the SPCG-4 radical prostatectomy (SPCG-4 RP). Assessment of safety is based on a comparison of the HIFU Prospective Safety Cohort to the low risk subgroup of the radical prostatectomy arm of the PIVOT. Safety comparisons are also made between the HIFU IDE Cohort and the radical prostatectomy arm of PIVOT.

6.4 Clinical Data Sources for the Evaluation of Safety and Effectiveness

This PMA includes a comprehensive compilation of the data available to EDAP on HIFU treatment for low-risk, localized prostate cancer compared to cryotherapy and radical prostatectomy. These data are divided into intermediate-term (2-5 years) and long-term (8-10 years) HIFU results. Comparisons based on biochemical (surrogate) endpoints are made to cryotherapy in the intermediate term. Long-term clinical (non-surrogate) endpoint comparisons (freedom from metastasis and prostate cancer specific survival) are made between HIFU and radical prostatectomy.

Additional information on the clinical data sources in this PMA including summaries of the intermediate and long-term data sources is discussed in Sections 7 and 8.

6.5 Comparability of Cohorts

The relevant baseline factors used to determine low-risk prostate cancer patients are cancer stage Gleason score and PSA levels. The stage and Gleason score of the prostate cancer along with the PSA determine the risk level of the cancer. In order to assess the comparability of patient characteristics of the HIFU IDE and cryotherapy literature from which the HIFU PG was derived, we considered these factors and patient age. The inclusion/exclusion criteria for HIFU IDE allowed enrollment of only low risk subjects, and the cryotherapy articles from which the HIFU PG was derived, reported stratified results for men with low risk, prostate cancer.

Although direct assessment of comparability of these cohorts is not possible due to the lack of reporting of the baseline factors for the low-risk subjects within any of the cryotherapy literature used to establish the HIFU PG, it is possible to provide a level of assurance that the populations are comparable as summarized below.

Age: The standard of care is to only offer definitive local therapy to men diagnosed with low-risk prostate cancer with a life expectancy of at least 10 years. The performance goal is based upon biochemical survival at two years. There is no evidence in the

literature indicating that treatment response is age dependent. Further, it is unlikely that a difference in age would result in bias in the evaluation of efficacy due to low probability of prostate cancer specific death within the two-year period. Until recently, in Europe where much of the HIFU literature was generated, HIFU was often used for non-surgical candidates. These men tend to be older which may result in older subjects included in the HIFU cohorts. As older patients may be more susceptible to develop adverse events, this could have resulted in a bias against HIFU in terms of the safety profile.

Stage of Prostate cancer: The D'Amico definition of low-risk prostate cancer (PSA < 10 ng/ml and Stage $\leqslant$ T2a and Gleason $\leqslant$ 6) has remained constant since introduced in 1998 and all papers used in the meta-analysis of the cryotherapy literature, upon which the HIFU PG is based, were published later. There were only 6 T1a and T1b subjects in the HIFU IDE cohort. It is likely that few if any T1a or T1b subjects would have been included in any cryotherapy studies as pre-treatment TURP is a contraindication for cryotherapy.

Gleason: The vast majority of men who are diagnosed with low risk prostate cancer today have a Gleason of 6. Prior to the 2005 reclassification of the Gleason grading system, men were sometimes diagnosed with a Gleason 3, 4 or 5, but these diagnoses are now classified as Gleason 6. As such, the vast majority of subjects with low risk prostate cancer are Gleason 6, which is consistent with the HIFU IDE population.

PSA: The publications do not report the average PSA of the low risk patients only. However, despite slight variability in definitions of low risk patient, a PSA of 10 ng/ml or less is universally accepted as the PSA threshold for low risk patients.

Although the data is not available to provide a detailed comparison between the two cohorts, if the low-risk subjects included in the cryotherapy literature are significantly different from the subjects in the HIFU IDE cohort, the literature is likely to include men with less severe disease who would be expected to have higher rates of biochemical survival. Inclusion of men with more severe disease would not be possible as higher stage, Gleason or PSA would result in their exclusion from the low risk population. As such, the performance goal developed for biochemical survival based on the cryotherapy literature would likely to be biased towards a higher and more difficult to meet value.

7 INTERMEDIATE-TERM ANALYSES

7.1 HIFU IDE Study

7.1.1 Introduction

The objective of the Ablatherm® HIFU IDE study was to determine the safety and effectiveness of the Ablatherm® Integrated Imaging (HIFU) as compared to cryotherapy indicated for the treatment of low risk, localized prostate cancer. Enrollment in the study was slower than anticipated, particularly in the cryotherapy control arm. In spite of the exhaustive efforts by the sponsor to increase enrollment, enrollment was closed after 4 years with only five subjects enrolled in the cryotherapy arm.

After discussions with FDA regarding options for a suitable alternative control for the HIFU IDE cohort, the sponsor conducted a retrospective study on subjects treated with cryotherapy. This cohort is called the CRYO Retro cohort. Similar to the cryotherapy arm of the HIFU IDE study,

the enrollment was lower than the number necessary to allow statistical comparisons of sufficient power to provide a reasonable assurance of effectiveness of HIFU. After additional discussions with FDA, the sponsor conducted a systematic review and meta-analysis of published cryotherapy studies (CRYO MA) to determine a performance goal, which was used as the principal comparator for the HIFU IDE cohort. The CRYO MA results were also compared to the results of a systematic review and meta-analysis of published HIFU studies (HIFU MA, described below).

The sponsor provided additional supporting intermediate-term evidence by analyzing HIFU data from a European Registry (HIFU Registry cohort) and conducting a systematic review and meta-analysis of the published HIFU studies (HIFU MA) which were analyzed as supporting comparisons.

7.1.2 Study Design

The EDAP Ablatherm® Integrated Imaging High Intensity Focused Ultrasound (HIFU) Indicated for Treatment of Low Risk, Localized Prostate Cancer (G050103) is a multi-center, prospective, non-randomized, concurrently controlled clinical trial that will compare two treatment methods (HIFU and cryotherapy) for treating low risk, localized prostate cancer. The primary hypothesis of this clinical investigation is that HIFU with the Ablatherm® Integrated Imaging is non-inferior to minimally invasive cryotherapy with the Endocare CRYOcare Cryosurgical or Galil Medical CRYO-HIT Systems as an effective treatment method for low risk, localized prostate cancer. The following definition of low risk, localized prostate cancer was used: stage T1a - T2a and PSA < 10ng/mL and Gleason score ≤6).

Inclusion Criteria
The key inclusion criteria were:

- Diagnosis of prostate cancer confirmed by PSA and prostate biopsy;
- Male subject, age ≥ 50 years;
- Organ-confined prostate cancer, clinical stage T1a, T1b, T1c or T2a;
- At least one positive biopsy within the previous 6 months;
- PSA ≤ 10 ng/ml;
- Gleason Score ≤ 6;
- Histological grading of 3+3, 3+2, 2+3, 2+4 or 2+2 based upon the baseline TRUS-guided 10 core biopsy results
- Prostate Volume ≤ 40 cc;
- For HIFU arm only Prostate AP diameter < 25 mm;
- For CRYO arm only Prostate AP diameter ≤ 30 mm
- Normal rectal anatomy and rectal mucosa;
- Maximum rectal wall measurement 6 mm;

Exclusion Criteria
The key exclusion criteria were:

- Evidence of seminal vesicle involvement, lymph node involvement or metastasis;
- Any previous treatment for prostate cancer; including EBRT, hormone therapy and/or previous bilateral orchiectomy;
- Previous surgery or procedure of the prostate (except prostate biopsy) or urethra within the prior one year;
- Calcification inducing a shadow in the prostate which cannot be included in the targeted volume;

- Large median lobe of the prostate which cannot be included in the target volume;
- Use within the previous 2 months of finasteride;
- Previous rectal surgery (other than hemorrhoidectomy) or history of rectal disease;
- Active inflammatory bowel syndrome;
- Current superficial bladder cancer, urethral stricture or bladder neck contracture;
- Active urinary tract infection or acute prostatitis (the subject may be enrolled once the infection has been treated and has resolved);
- Compromised renal function or upper urinary tract disease as a result of urinary obstruction;
- A history of bleeding disorders/coagulopathy or ongoing treatment for this condition;
- Urinary tract or rectal fistula;
- Rectal fibrosis, rectal stenosis or other anomalies making the Ablatherm® Integrated Imaging rectal probe insertion difficult;
- Anatomical anomaly of the rectum or anomaly of the rectal mucous membrane;
- Prostate seroma, prostate abscess or urethral stenosis;
- An intraprostatic implant such as a stent or catheter, or any implant or prosthesis at less than 1 cm from the prostate;
- Interest in future fertility;

Methodology

Subjects in the HIFU IDE cohorts were evaluated prior to the study treatment and then followed routinely at 5 days (phone interview), 1 month, 3 months, 6 months, 9 months, 12 months, 15 months, 18 months, 21 months and 24 months post-treatment. Subjects who have reached the 24-month visit are being followed annually until the study is terminated. Assessments including clinical, laboratory, biopsy and subject self-assessments were conducted to evaluate the subject's status during the course of the study. Subject follow up assessment time points and evaluations were the same for investigational and control treatment groups.

7.1.2.1 Effectiveness Endpoints

The original, pre-specified primary effectiveness endpoint was the Nadir/ASTRO/Biopsy Survival, which is defined as attainment of PSA nadir ≤ 0.5 ng/ml, and stability of PSA according to ASTRO criteria through 24 month follow up, and the absence of a positive biopsy. Additional effectiveness endpoints were Phoenix biochemical success and the composite clinical success criteria using the Phoenix criteria instead of ASTRO: Nadir/Phoenix/Biopsy Survival.

The secondary effectiveness endpoints were:

- Achievement of a nadir PSA within 6 months ≤ 0.5 ng/ml (Nadir Success)
- Phoenix Biochemical Survival (2005 ASTRO criteria)
- Overall survival, defined as the time to death due to any cause
- Disease-specific survival, defined as the time to death due to the underlying disease
- Change from baseline in the UCLA QOL
- Change from baseline in the IPSS score
- PSA levels and additional clinical information beyond 24 months will be used to assess PSA stability and cancer recurrence
- Phoenix Survival rate defined as the time of treatment failure: time to PSA nadir + 2ng/ml, time of first positive biopsy or time of salvage therapy.

7.1.2.2 Safety

All adverse events were collected during the IDE study regardless of their perceived relationship to the study treatment. Adverse event reporting on each patient started from the screening visit and continued with each study contact. Adverse events reported by study patients during phone contacts or extra visits between planned visits were also reported. The investigator classified each event by relationship to the device, relationship to the procedure, severity, and whether or not it was an unanticipated adverse device effect. All adverse effects were reviewed and coded by the study Medical Monitor. For analysis purposes, all adverse events that were classified as "Other" were reviewed and reclassified where appropriate to provide more meaningful descriptions of the adverse events. The Medical Monitor reviewed all of the adverse events that were reclassified. An Unanticipated Adverse Device Effect (UADE) was defined as any serious adverse effect on health or safety or any life threatening problem or death caused by, or associated with, the Ablatherm® Integrated Imaging, if that effect, problem, or death was not identified in nature, severity, or degree of incidence in this investigational plan or any other unanticipated serious problem associated with the Ablatherm® Integrated Imaging related to the rights, safety, or welfare of the subjects participating in this study.

7.1.2.3 Quality of Life

The following quality of life measures are reported: International Prostate Symptom Score (IPSS), and the UCLA Prostate Cancer Index Questionnaire: Urinary, Bowel and Sexual Bother Scores, Urinary Return to Function and Aggregate Mental and Physical Health Component Scores.

7.1.2.4 Statistical Analysis

Study Hypothesis
The primary hypothesis of the Ablatherm® HIFU IDE was that HIFU with the Ablatherm® Integrated Imaging is non-inferior to minimally invasive cryotherapy as an effective treatment method for low risk, localized prostate cancer. The statistical analysis plan for the Ablatherm® HIFU IDE specified the primary effectiveness analysis as a test of non-inferiority of HIFU treatment (Ablatherm® Treatment System) to the cryosurgery control, to within 10 percentage points.

Sample Size Calculations
The calculated sample size was 368 patients enrolled with a 1:1 allocation to the investigational and control groups (184 in the HIFU group and 184 in the cryosurgery group) to provide 80% power to reject the non-inferiority hypothesis at the 5% level of significance. The sample size was increased to a total of 410 patients (205 in the HIFU group and 205 in the cryosurgery group) to account for a 10% attrition rate.

Analysis Populations
The intent to treat cohort includes all treated subjects. The 24 Month Follow-up completer population is defined as all subjects in whom biochemical survival to 24 months can be assessed.

The primary effectiveness endpoint that was defined in the original analysis plan, Nadir/ASTRO/Biopsy Survival, is reported among the intent to treat population as well as the 24 Month Follow-up completers. The *principal* effectiveness endpoint that is defined in the revised analysis plan, Phoenix Biochemical Survival, is analyzed in the ITT population and 24 Month Follow-up completers. The 24 Month Follow-up completers included as failures the subjects who were withdrawn prior to 24 months and met the definition of biochemical failure prior to withdrawal.

The safety analyses are conducted on the safety population, which consists of all subjects who were treated with the Ablatherm® HIFU in the IDE study.

7.1.3 Changes to the Study Design

Changes were made to the study design to increase enrollment, to replace the prospective cryotherapy arm, to update the obsoleted primary effectiveness endpoint with the current standard, and to provide additional, supporting evidence of safety and effectiveness. A list of changes is provided in Table 12.

Table 12: Changes to Study Design by Reason, HIFU IDE Study

Reason	Change to Study Design
Increase Enrollment	Increased the number of study sites
	Added an additional cryotherapy device as a control
	Added Canadian study sites to both the HIFU and Control arms
	Eliminated a separate cohort of 'Ablatherm® Training Patients' reducing the total number of patients needed to complete the trial
	Decreased the age limit for patient enrollment increasing the number of eligible patients
	Increased the maximum Anterior Posterior prostate size in the control arm eligible for enrollment
Replace Prospective Cryotherapy Control	Changed the control to the CRYO Retro cohort
	Changed the control to a performance goal (HIFU PG) based on published cryotherapy studies
Updated Primary Endpoint to Reflect Current Standard	Changed the primary effectiveness endpoint to Phoenix Biochemical Survival (formerly a secondary endpoint) from the outdated ASTRO Biochemical Survival This change was made prior to any data analyses.
Provide Additional Supporting Evidence	Added HIFU Registry, HIFU meta-analysis and cryotherapy meta-analysis cohorts as supporting evidence of safety and effectiveness

The principal effectiveness endpoint for the HIFU IDE cohort was changed to the Phoenix biochemical survival at 24 months and the control was changed to a performance goal (HIFU PG).

7.1.4 Derivation of Performance Goal

A performance goal (HIFU PG) for 2-year biochemical survival was derived from the results of the systematic review and meta-analysis of cryotherapy literature (CRYO MA) which is discussed in Section 7.5. The performance goal was defined as the principal comparator for the effectiveness of HIFU IDE. It is important to note that the Phoenix Definition of biochemical failure was a pre-specified secondary endpoint in the IDE study. Although derived from cryotherapy results, the performance goal is termed the HIFU PG.

The purpose of establishing a performance goal for HIFU treatment is to provide an objective performance goal against which the HIFU IDE cohort can be compared to determine effectiveness of the Ablatherm® HIFU device. The principal effectiveness evaluation is the comparison of the Phoenix Biochemical Survival at 24 months between the HIFU IDE cohort and the HIFU PG.

The estimate of biochemical success for cryotherapy at 24 months from the meta-analysis was used as the basis for establishing the lower bound performance goal (PG) against which the HIFU treatment biochemical survival rates were to be compared. The purpose of the comparison of the HIFU biochemical survival rate against the PG is to demonstrate that the biochemical survival rate following HIFU treatment is similar to biochemical survival rate following cryotherapy reported in the literature. The lower bound performance goal was set at 5% lower than the estimated cryotherapy biochemical survival rate. Note that this non-inferiority margin is half of that specified in the original IDE.

7.1.5 Study Results

7.1.5.1 Subject Enrollment and Accountability

Of the 141 subjects enrolled in the IDE study, 136 subjects were enrolled (with 135 treated) in the HIFU IDE cohort at 12 US and one Canadian sites. Five subjects were enrolled in the CRYO IDE cohort at 2 US sites. The first subject was enrolled on May 4, 2006 and the last subject was enrolled on June 30, 2010 when enrollment was terminated due to extremely slow subject accrual. Due to the small number of subjects in CRYO IDE arm, no analyses were performed nor were any conclusions drawn regarding this cohort. Instead, a retrospective study was conducted to collect data on subjects treated with cryotherapy to provide a control for the HIFU IDE cohort.

All subjects who met the study entrance criteria (presence of inclusion criteria and absence of exclusion criteria) and signed the informed consent form were enrolled in the study. Each site was designated to provide treatment with either the Ablatherm® HIFU investigational device or the cryotherapy control device.

Enrollment by site for the HIFU IDE cohort is summarized in Table 13. Subject 121-006 was enrolled but not treated when calcifications in the prostate, an exclusion criterion, were observed immediately prior to treatment.

Table 13: Enrollment by Site, HIFU IDE Cohort

HIFU Sites			
Site No.	**Site Name**	**Principal Investigator**	**No. of Subjects Enrolled**
104	Vanderbilt University Medical Center, Nashville, TN	Sam Chang, M.D.	3
106	Virginia Urology, Richmond, VA	Anthony Sliwinski, M.D.	20
109	Duke University Medical Center, Durham, NC	Cary Robertson, M.D.	28
111	Florida Foundation for Healthcare Research, Ocala, FL	Russell Locke, M.D.	9
113	Urology Associates of Texas, Arlington, TX	Richard Bevan-Thomas M.D.	6

114	University of Colorado Hospital and Health Science Center, Denver, CO	David Crawford, M.D.	8
115	Hackensack University Medical Center, Hackensack, NJ	Ihor Sawczuk, M.D.	5
116	Sloan Memorial Kettering Institute, New York, NY	James Eastham, M.D	3
117	MD Anderson, Houston, TX	John Ward, M.D.	13
118	Medical College of Wisconsin, Milwaukee, WI	Robert Donnell, M.D.	7
119	Maple Leaf HIFU, Hamilton, ON	William Orovan, M.D.	13
120	University of North Carolina School of Medicine, Chapel Hill, NC	Eric Wallen, M.D.	14
121	Brooklyn Heights Urology Associates, Brooklyn, NY	Ivan Grunberger, M.D.	7*
Total			**136**

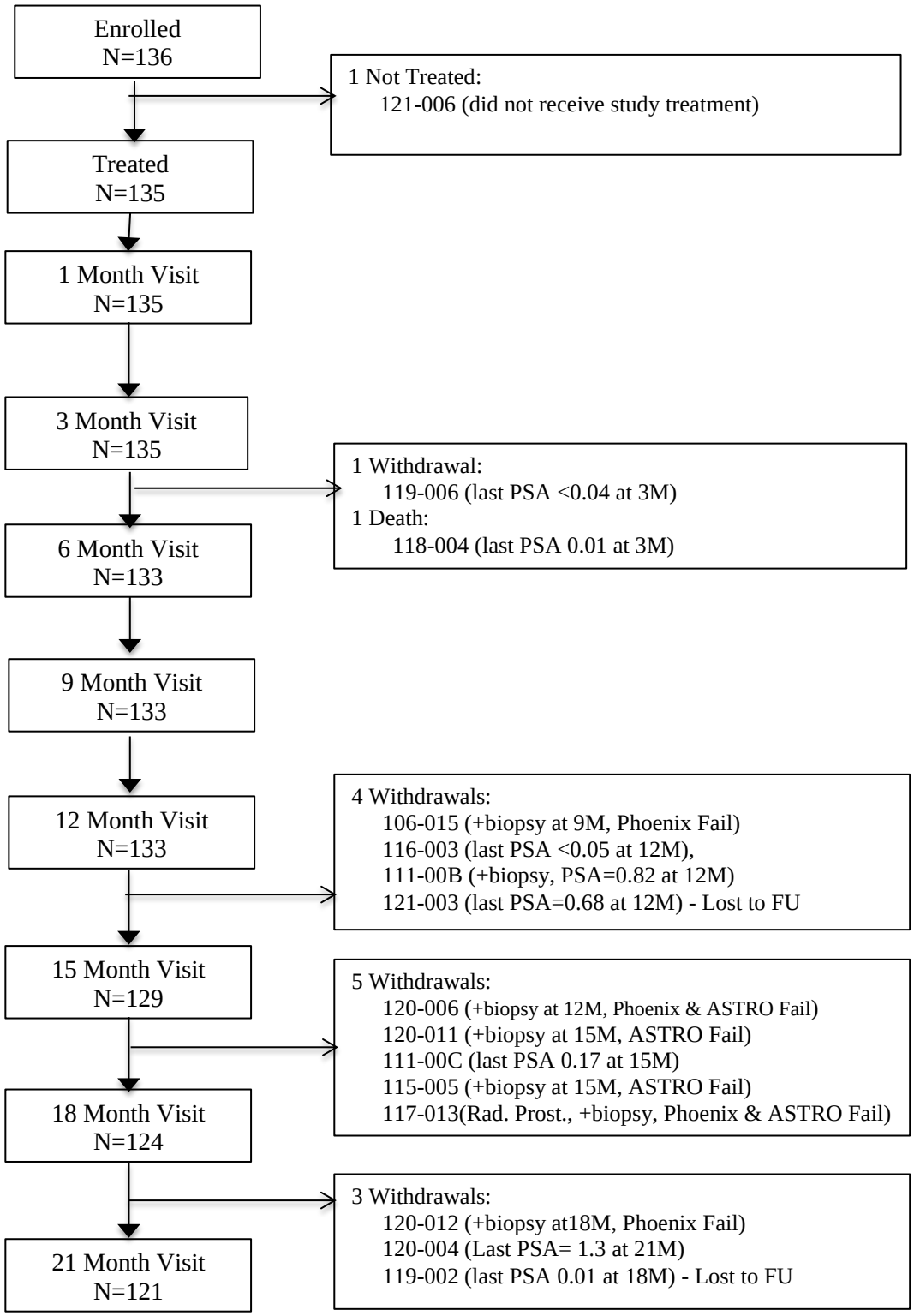
[1]Only six subjects were treated as one subject (121-006) was enrolled but found to have calcifications prior to treatment and was not treated

The Ablatherm® HIFU IDE protocol required follow-up visits at 5 days, 1, 3, 6, 9, 12, 15, 18 and 21 months, and 2 years following the study procedure. The follow-up rate at 24 months is 96.6% and ranges from 90.9 to 100% for the follow-up intervals prior to 24 months. At Month 24, PSA values and biopsy results are available for 79% (107/135) and 77% (104/135) subjects, respectively. Subject accountability for the HIFU IDE cohort is summarized in Table 14 and Figure 1.

Table 14: Subject Accountability by Visit, HIFU IDE Cohort, mITT

	Visit										
	Day 0	**Day 5**	**Mo 1**	**Mo 3**	**Mo 6**	**Mo 9**	**Mo 12**	**Mo 15**	**Mo 18**	**Mo 21**	**Mo 24**
Theoretically Due	135	135	135	135	135	135	135	135	135	135	135
Death	0	0	0	0	1	1	1	1	1	1	2
Withdrawn	0	0	0	0	1	1	1	5	10	13	16
Expected[1]	135	135	135	135	133	133	133	129	124	121	117
Actual Visits[2]	135	135	135	134	133	132	131	123	116	110	113
PSA obtained	135		133	134	132	131	131	120	114	107	107
Biopsy obtained	134										104
Follow-up (%)	100.0	100.0	100.0	99.3	100.0	99.2	98.5	95.3	93.5	90.9	96.6

Flowchart of Eligible Subjects, Withdrawals and Deaths by Visit



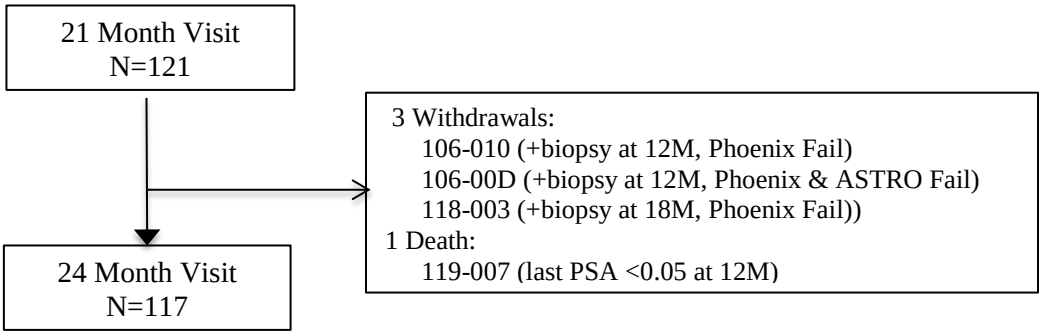


Figure 1: Eligible Subjects, Withdrawals and Deaths by Visit

7.1.5.2 Demographics and Baseline Characteristics

The demographic and baseline characteristics for the HIFU IDE are presented in Table 15. In the HIFU IDE cohort, the age of the subjects ranged from 51.3 to 80 years with a mean of 64.1 years. The pre-treatment PSA ranged from 0.3 to 9.9 ng/ml with a mean of 4.6 ng/ml. The majority (97.0%) of subjects had a Gleason score of 6 with a histology grade of 3+3, 1.5% (n=2) had a Gleason score of 7 with a histology grade of 3+4, and the Gleason score was not specified in 1.5%. More than three quarters (80.7%) of the subjects had a cancer stage of T1c, 2.2% were classified as T1a, 2.2% as T1b, 14.2% as T2a and the stage was not specified in 0.7%.

Table 15: Demographics and Baseline Characteristics, HIFU IDE

Characteristic		HIFU IDE N=135
Age (yrs)	Mean±SD (N)	64.1±6.7 (135)
	Median (Range)	63.2 (32.8, 80.0)
Weight (lbs)	Mean±SD (N)	190.0±34.2 (135)
	Median (Range)	185.0 (120.0, 342.0)
Race	Caucasian	82.2% (111)
	African American	13.3% (18)
	Hispanic	3.0% (4)
	Other/ Not specified	1.5% (2)
PSA	Mean±SD (N)	4.6±2.4 (135)
	Median (Range)	4.5 (0.3, 9.9)
Prostate Vol. (cc)	Mean±SD (N) Median (Range)	22.7±12.5 (135) 21.6 (9.7, 152.0)
Time from Cancer Diagnosis (mos)	Mean±SD (N)	6.7±18.5 (135)
	Median (Range)	3.8 (0.4, 213.0[1])
Gleason Score	6	97.0% (131)
	7	1.5% (2)
	Not specified	1.5% (2)
Histology Grade	3+3	97.0% (131)
	3+4	1.5% (2)
	Not specified	1.5% (2)

Characteristic		HIFU IDE N=135
Cancer Stage	T1a	2.2% (3)
	T1b	2.2% (3)
	T1c	80.7% (109)
	T2a	14.1% (19)
	Not specified	0.7% (1)

7.1.5.3 HIFU Treatment

The HIFU procedure time in the HIFU IDE study ranged from 61 to 257 minutes with a mean of 138.5 minutes. Most (85.2%) of the subjects were administered general anesthesia during the procedure with 14.8% receiving spinal anesthesia and 7.4% other anesthesia which included sedation, IV sedation and Versed. The power delivered ranged from 37.5 to 53.6 watts with an average of 47.5 watts. The mean number of treated lesions was 515.8 and the mean total duration of treatment was 134.7 minutes. The mean volume of prostate treated was 28.3 cc. See Table 16 for further details.

Table 16: HIFU Treatment, HIFU IDE Cohort

Characteristic		N=135[1]
Procedure Time (min)	Mean±SD	138.5±33.0
	Median (Range)	136.0 (61.0, 257.0)
Anesthesia Type	Spinal	14.8% (20/135)
	General	85.2% (115/135)
	Other: Sedation, IV Sedation, Versed	7.4% (10/135)
Average power delivered (watts)	Mean±SD	47.5±3.0
	Median (Range)	47.6 (37.5, 53.6)
Total treated lesions	Mean±SD	515.8±95.4
	Median (Range)	517.0 (69.0, 739.0)
Total duration of treatment (min)	Mean±SD	134.7±24.8
	Median (Range)	129.0 (91.0, 227.0)
Volume treated (cc)	Mean±SD	28.3±8.3
	Median (Range)	26.9 (10.5, 48.4)

7.1.5.4 Effectiveness Endpoints

Principal Effectiveness Endpoint, Phoenix Biochemical Survival

The principal effectiveness endpoint is the Phoenix Biochemical Survival rate at 24 months following study treatment. For the Phoenix Biochemical Survival endpoint, a subject was considered a success if he did not have PSA obtained between 6 and 24 months post study treatment that was greater than or equal to the nadir PSA (obtained within 6 months following study treatment) plus 2:

No PSA between 6 and 24 months post treatment ≥ PSA Nadir + 2

At least one PSA obtained at or after 24 months is required to determine this endpoint. The 24 Month Follow-up completers group includes all subjects with a PSA obtained on or after 24 months. Additionally, subjects not assessed at or after 24 months who met the definition of biochemical failure prior to 24 months are included in the 24 Month Follow-up completers

analysis as failures. In the HIFU IDE cohort, 77.8% of subjects in the ITT and 90.5% in the 24 Month Follow-up completers met the definition of the Phoenix Biochemical Survival endpoint, as summarized in Table 17.

Table 17: Phoenix Biochemical Survival, HIFU IDE Cohort

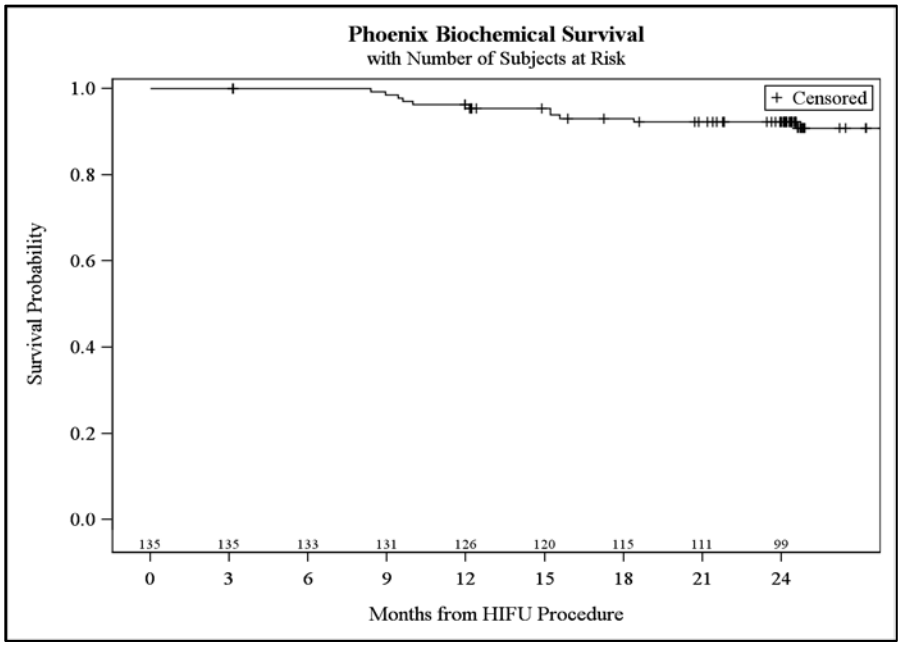
Phoenix Biochemical Survival	Cohort	% (n/N)	95% CL
Biochemical survival by Phoenix criteria[1]	ITT	77.8% (105/135)	70.8, 84.8%
	24 Month Follow-up[2]	90.5% (105/116)	85.2, 95.8%

[1]Requires at least one PSA obtained at or after 24 months.

[2]Includes subjects not assessed at or after 24 months who met the definition of biochemical failure

The ITT result of Phoenix biochemical survival presented in Table 21 represents the worst-case scenario. An alternative ITT analysis, the Phoenix biochemical survival time to 24 months among the ITT population is shown as Kaplan-Meier (KM) curve in Figure 2. Subjects without evidence of Phoenix biochemical failure are censored at the last available follow-up PSA.

Figure 2: Phoenix Biochemical Survival Time – ITT Population, HIFU IDE



The survival estimates by follow up time are given below in Table 18. The KM biochemical survival estimate at 24 months is 90.9% (95% confidence interval: 83.9, 94.9%).

Table 18: Phoenix Biochemical Survival Estimates by Time, HIFU IDE Cohort

Time Point	Number of Subjects at Risk	Biochemical Survival Estimate	95% CLs
Month 12	126	95.5%	90.2, 97.9%
Month 18	120	92.3%	86.1, 95.8%
Month 24	99	90.9%	83.9, 94.9%

HIFU PG Results

The estimated biochemical survival rate for cryotherapy from the meta-analysis described in Section 7.5 is 87% with a range of 69% to 96% at 24 months post-treatment. The lower bound performance goal was set at 5% lower than the estimated cryotherapy biochemical survival rate. Note that this non-inferiority margin is half of that specified in the original IDE. Therefore, the 24-month PG was 82%.

Comparison of HIFU IDE to HIFU PG

The most appropriate HIFU IDE population to compare to the HIFU PG is the 24 Month Follow-up completers as the studies included in the meta-analysis of cryotherapy biochemical success report biochemical success among subjects assessed at 24 months post treatment. The derivation of the performance goal is discussed in Section 7.5. As shown in Table 19, the Phoenix biochemical survival in the HIFU IDE cohort met the HIFU performance goal (HIFU PG) of 82%.

Table 19: Principal Effectiveness, HIFU IDE vs. HIFU PG

Cohort	Biochemical Survival Rate	95% CL or Range[1]	p-value
HIFU IDE	90.5%	85.2, 95.8%	0.009
HIFU PG	82%	n/a	

Secondary Effectiveness

- Nadir/ASTRO/Biopsy Survival

In the HIFU IDE cohort, 45.2% of subjects in the ITT population met the requirements of the Nadir/ASTRO/Biopsy Survival endpoint, 74.1% met the definition of the PSA Nadir Survival endpoint, 63.7% met the definition of the ASTRO Biochemical Survival endpoint, and 71.9% met the definition of the Biopsy Survival endpoint. In the 24 Month Follow-up completers, 50.0% of subjects met the requirements of the Nadir/ASTRO/Biopsy Survival endpoint, 74.1% met the definition of the PSA Nadir Survival endpoint, 77.5% met the definition of the ASTRO Biochemical Survival endpoint, and 67.8% met the definition of the Biopsy Survival endpoint.

Table 20: Nadir/ASTRO/Biopsy Survival – ITT and 24 Month Completers, HIFU IDE Cohort

Endpoint	% (n/N)	95% CL
ITT		
Nadir/ASTRO/Biopsy Survival[1]	45.2% (61/135)	36.8, 53.6%
Nadir Success	74.1% (100/135)	66.7, 81.5%
ASTRO Biochemical Survival	63.7% (86/135)	55.6, 71.8%
Biopsy Survival	71.9% (97/135)	64.3, 79.4%
24 Month Completers		
Nadir/ASTRO/Biopsy Survival[1]	50.0% (61/122)	41.1, 58.9%
Nadir Success	74.1% (100/135)	66.7, 81.5%
ASTRO Biochemical Survival	77.5% (86/111)	69.7, 85.2%
Biopsy Survival	67.8% (80/118)	59.4, 76.2%

[1]Does not have 3 consecutive PSA measurements with increasing PSA value. Requires minimum of 3 PSA measurements between 6 and 24 months with at least one obtained at or after 24 months. Success determined on absence of positive biopsy, negative biopsy not required.

- Nadir/Phoenix/Biopsy Survival

The Nadir/Phoenix/Biopsy Survival requires a subject to meet the requirements of Nadir Survival and Phoenix Biochemical Survival and Biopsy Survival. In the HIFU IDE cohort, 55.7% of subjects in the 24 month completer population met the requirements of the Nadir/Phoenix/Biopsy Survival endpoint. The Biopsy component of this endpoint contributed heavily to the results. In fact, when the endpoint was calculated with only the Nadir/Phoenix/Survival requirements, the survival rate increased to 69.4% in the 24 month completer population. A summary of results is provided in Table 21.

Table 21: Nadir/Phoenix/Biopsy Survival - 24 Month Follow-up Completers, HIFU IDE Cohort

Endpoint	% (n/N)	95% CL
Nadir/Phoenix/Biopsy Survival[1]	55.7% (68/122)	46.9, 64.6%
Nadir Survival	74.1% (100/135)	66.7, 81.5%
Phoenix Biochemical Survival	90.5% (105/116)	85.2, 95.8%
Biopsy Survival	67.8% (80/118)	59.4, 76.2%

[1]Does not have a PSA measurement between 6 and 24 months ≥ Nadir+2. Success determined on absence of positive biopsy, negative biopsy not required.
[2]Among subjects with either composite endpoint failure or evaluated at 24 months follow-up

- Overall and Disease Specific Survival

There were 5 deaths in the HIFU IDE study cohort. The causes of death were reported as lung cancer, myocardial infarction, sepsis, cardiovascular disease and cardiovascular attack. None were related to prostate cancer. One was within 24 months of the HIFU procedure, two were between 24 and 36 months post procedure and two were between 36 and 60 months post procedure. Details of the deaths are provided in Section 7.1.6. The disease specific survival is 100% as there were no deaths reported in the IDE study due to prostate cancer.

7.1.5.5 Safety

A total of 1012 adverse events were reported in 131 subjects (97.0%) in the HIFU IDE Cohort. At the time of database closure, the vast majority (811) of the adverse events were resolved, 192 were ongoing, 3 had resulted in permanent disability and 5 had resulted in death. Additionally, 755 were reported as possibly, probably or definitely related to the Ablatherm® HIFU device and/or the procedure, and 257 as not or unlikely to be related to the device or procedure. Further, more than half (531) of the adverse events were reported with a severity of mild, 352 of moderate and 129 as severe. Five deaths were reported in the Ablatherm® HIFU IDE study. None of the deaths were related to the study device or procedure. The causes of death were: lung cancer, myocardial infarction, sepsis, cardiovascular disease and cardiovascular attack.

Three subjects were reported to have permanent impairment from adverse events: erectile dysfunction that was reported as probably related to the device and definitely related to the procedure; urinary stricture that was reported as unlikely related to the device and definitely related to the procedure; and a partial finger amputation – accidental that was reported as not related to the device or the procedure.

Of the 192 adverse events that were ongoing at the time of database closure, 99 were reported as mild in severity, 72 as moderate and 21 as severe. Also, 67 of the ongoing adverse events were reported by subjects who withdrew from the study or died. An overview of all adverse events is provided in Table 22.

Table 22: Overview of All Adverse Events, HIFU IDE Cohort – All Treated Subjects (N=135)

	All Adverse Events		Adverse Events at Least Possibly Related to Device and/or Procedure	
Adverse Event Category	No. Events	% Subj.	No. Events	% Subj.
Overall	1012	97.0% (131)	755	95.6% (129)
Severity				
Mild	531	87.4% (118)	386	80.7% (109)
Moderate	352	76.3% (103)	273	72.6% (98)
Severe	129	41.5% (56)	96	34.1% (46)
Resolution				
Resolved	811	95.6% (129)	616	93.3% (126)
Ongoing	192	67.4% (91)	137	59.3% (80)
Permanent disability	3	2.2% (3)	2	1.5% (2)
Death	5	3.7% (5)	0	0

The events reported with the highest frequency are: erectile dysfunction with 95 events in 67.4% of subjects; incontinence with 68 events in 38.5% of subjects, urinary tract infection with 60

events in 34.1% of subjects; urinary retention with 53 events in 27.4% of subjects; hematuria with 51 events in 32.6% of subjects; and perineal/ penile/rectal/prostate pain with 51 events in 27.4% of subjects.

A summary of all adverse events occurring in greater than 3% of subjects in the HIFU IDE by severity and status is provided in Table 23.

Table 23: Adverse Events in > 3% of Subjects by Severity and Status, HIFU IDE Cohort

	Overall (N=135)		Severity						Status					
			Mild		Moderate		Severe		Resolved		Ongoing		Perm. Imp./ Death	
Adverse Event[1]	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.
Erectile Dysfunction	95	67.4% (91)	22	15.6% (21)	48	35.6% (48)	25	17.8% (24)	34	24.4% (33)	60	44.4% (60)	1	0.7% (1)
Incontinence	68	38.5% (52)	49	29.6% (40)	16	11.9% (16)	3	2.2% (3)	47	31.1% (42)	21	15.6% (21)	0	0
Urinary Tract Infection	60	34.1% (46)	30	18.5% (25)	30	16.3% (22)	0	0	60	34.1% (46)	0	0	0	0
Urinary Retention	53	27.4% (37)	5	3.7% (5)	21	14.1% (19)	27	13.3% (18)	50	25.9% (35)	3	2.2% (3)	0	0
Hematuria	51	32.6% (44)	38	26.7% (36)	13	8.1% (11)	0	0	50	31.9% (43)	1	0.7% (1)	0	0
Perineal/Penile/Rectal/Prostate Pain	51	27.4% (37)	31	20.0% (27)	18	11.1% (15)	2	1.5% (2)	48	25.9% (35)	3	2.2% (3)	0	0
Bladder Urgency	45	28.9% (39)	26	17.8% (24)	17	11.9% (16)	2	1.5% (2)	33	21.5% (29)	12	8.9% (12)	0	0
Slow Stream	39	24.4% (33)	34	21.5% (29)	5	3.7% (5)	0	0	32	20.7% (28)	7	5.2% (7)	0	0
Urinary Stricture	38	19.3% (26)	5	3.7% (5)	25	14.1% (19)	8	5.2% (7)	35	18.5% (25)	2	0.7% (1)	1	0.7% (1)
Dysuria	36	23.0% (31)	24	15.6% (21)	11	7.4% (10)	1	0.7% (1)	34	22.2% (30)	2	1.5% (2)	0	0
Bladder Neck Contracture	35	17.8% (24)	10	4.4% (6)	13	8.1% (11)	12	7.4% (10)	33	17.0% (23)	2	1.5% (2)	0	0
Bladder Spasms	35	23.0% (31)	22	15.6% (21)	11	8.1% (11)	2	0.7% (1)	34	22.2% (30)	1	0.7% (1)	0	0
Urinary Frequency	29	18.5% (25)	19	12.6% (17)	9	6.7% (9)	1	0.7% (1)	19	13.3% (18)	10	7.4% (10)	0	0
Obstruction (2-17 days Post Op)	25	17.0% (23)	7	4.4% (6)	11	8.1% (11)	7	5.2% (7)	25	17.0% (23)	0	0	0	0
Unrelated Other	24	14.8% (20)	17	10.4% (14)	5	3.7% (5)	2	1.5% (2)	10	7.4% (10)	14	9.6% (13)	0	0
Unrelated Aches / Pains / Pressure (non orthopedic)[1]	22	14.1% (19)	13	8.1% (11)	9	5.9% (8)	0	0	15	10.4% (14)	6	4.4% (6)	0	0
Unrelated Respiratory / Pulmonary	22	12.6% (17)	10	6.7% (9)	8	3.7% (5)	4	3.0% (4)	21	12.6% (17)	1	0.7% (1)	0	0
Nocturia	20	13.3% (18)	13	9.6% (13)	6	4.4% (6)	1	0.7% (1)	10	7.4% (10)	10	7.4% (10)	0	0
Urethral Sloughing	17	12.6% (17)	13	9.6% (13)	2	1.5% (2)	2	1.5% (2)	13	9.6% (13)	4	3.0% (4)	0	0
Unrelated Cardiac	14	9.6% (13)	3	1.5% (2)	5	3.7% (5)	6	4.4% (6)	11	8.1% (11)	2	1.5% (2)	1	0.7% (1)
Unrelated Urological	13	8.9% (12)	10	7.4% (10)	3	2.2% (3)	0	0	8	5.2% (7)	5	3.7% (5)	0	0
Scrotal Swelling	12	8.1% (11)	9	6.7% (9)	3	2.2% (3)	0	0	12	8.1% (11)	0	0	0	0
Perineal/Penile/Rectal/Prostate Discomfort	11	8.1% (11)	9	6.7% (9)	2	1.5% (2)	0	0	10	7.4% (10)	1	0.7% (1)	0	0

	Overall (N=135)		Severity						Status					
			Mild		Moderate		Severe		Resolved		Ongoing		Perm. Imp./ Death	
Adverse Event[1]	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.
Bladder Outlet Obstruction	10	7.4% (10)	1	0.7% (1)	6	4.4% (6)	3	2.2% (3)	9	6.7% (9)	1	0.7% (1)	0	0
Unrelated GI	10	5.9% (8)	5	3.7% (5)	2	1.5% (2)	3	1.5% (2)	8	4.4% (6)	2	1.5% (2)	0	0
Blood at tip of penis / urethral bleeding	8	5.9% (8)	8	5.9% (8)	0	0	0	0	8	5.9% (8)	0	0	0	0
Constipation	8	5.9% (8)	2	1.5% (2)	6	4.4% (6)	0	0	7	5.2% (7)	1	0.7% (1)	0	0
Skin Cancer	8	3.7% (5)	6	3.0% (4)	2	0.7% (1)	0	0	8	3.7% (5)	0	0	0	0
Incomplete Bladder Emptying	7	5.2% (7)	6	4.4% (6)	1	0.7% (1)	0	0	6	4.4% (6)	1	0.7% (1)	0	0
Unrelated Accidents and Injuries	7	5.2% (7)	4	3.0% (4)	3	2.2% (3)	0	0	5	3.7% (5)	1	0.7% (1)	1	0.7% (1)
Diarrhea	6	4.4% (6)	5	3.7% (5)	1	0.7% (1)	0	0	6	4.4% (6)	0	0	0	0
Unrelated Orthopedic	6	3.7% (5)	3	1.5% (2)	3	2.2% (3)	0	0	1	0.7% (1)	5	3.0% (4)	0	0
Fatigue	5	3.7% (5)	3	2.2% (3)	1	0.7% (1)	1	0.7% (1)	5	3.7% (5)	0	0	0	0
Hernia	5	3.7% (5)	2	1.5% (2)	1	0.7% (1)	2	1.5% (2)	5	3.7% (5)	0	0	0	0

[1] Adverse event of Unrelated Aches / Pains / Pressure (non orthopedic) has an unspecified status

A device/procedure related adverse event is any adverse event that was reported by the investigator as possibly, probably or definitely related to the Ablatherm® HIFU device or the procedure or both the device and procedure. An Unrelated Adverse Event is any adverse event that was reported as unlikely or not related to both the device and the procedure. There were no device/procedure related deaths. Of the 755 device/procedure related adverse events, approximately half (386) were rated as mild in severity, 273 as moderate and 96 as severe. The majority (616) of the device/procedure related adverse events were resolved, 137 were ongoing and 2 (1 erectile dysfunction and 1 urinary stricture) had resulted in permanent disability or impairment at the time of database closure. Of the 137 adverse events that were ongoing at the time of database closure, 61 were reported as mild in severity, 59 as moderate and 17 as severe. Additionally, subjects who withdrew from the study or died and therefore could not have had a resolved status reported 45 of the ongoing adverse events. The device/procedure related events reported with the highest frequency are: erectile dysfunction in 66.7% of subjects; incontinence in 35.6% of subjects; hematuria in 28.9% of subjects; urinary retention in 25.9% of subjects; perineal/penile/rectal/prostate pain in 25.2% of subjects; urinary tract infection in 25.2% of subjects; and bladder urgency in 24.4% of subjects. All of these adverse events were anticipated adverse events identified in the IDE protocol.

Of the 755 device/procedure related adverse events reported, all but 137 resolved. Of these, 58 were erectile dysfunction and 15 were incontinence. Lower Urinary Tract Symptoms (reported as urgency, slow stream, dysuria, incomplete bladder emptying, nocturia, or LUTS) account for 38 ongoing adverse events.

A summary of all device/procedure related adverse events reported in greater than 3% of subjects in the HIFU IDE cohort is presented in Table 24. A listing of all device/procedure related adverse events reported in the HIFU IDE cohort is presented in Appendix 1.

Table 24: Device/Procedure Related Adverse Events: Any Occurrence in > 3% of Subjects and Unresolved at 24 Months

Adverse Event	Any Occurrence[1]	Unresolved at 24 Months[1]
Erectile Dysfunction	66.7%	43.7%
Incontinence	35.6%	11.1%
Hematuria	28.9%	0%
Urinary Retention	25.9%	2.2%
Perineal/Penile/Rectal/Prostate Pain	25.2%	2.2%
Urinary Tract Infection	25.2%	0%
Bladder Urgency	24.4%	7.4%
Other	23.7%	6.7%
Urinary Stricture	18.5%	1.4%
Slow Stream	23.0%	4.4%
Bladder Neck Contracture	17.8%	0.7%
Dysuria	17.8%	0.7%
Bladder Spasms	17.8%	0%
Obstruction (2-17 days Post Op)	17.0%	0%
Urinary Frequency	15.6%	6.7%
Nocturia	11.1%	5.9%
Urethral Sloughing	12.6%	3.0%
Scrotal Swelling	8.1%	0%
Perineal/Penile/Rectal/Prostate Discomfort	8.1%	0.7%
Bladder Outlet Obstruction	6.7%	0.7%
Blood at tip of penis / urethral bleeding	5.2%	0%
Constipation	5.2%	0.7%
Incomplete Bladder Emptying	5.2%	0.7%

The adverse events recorded during the HIFU IDE study must be considered in an appropriate clinical context. Many of the adverse events reported in the HIFU IDE cohort are transient, easily managed and related to recovery from the procedure. Such adverse events fall under the umbrella of 'Treatment Recovery.' Additionally, there are several 'Treatment Effects' specific to HIFU which are also transient in nature and easily managed. 'Side Effects' are those adverse events which are not transient in nature and do not resolve. The 24-month study endpoint is a reasonable time to evaluate whether or not an adverse event is a treatment effect or side effect. The adverse event rates referred to in the following discussion are those related to the device and/or the procedure as it is often difficult to definitively know if an adverse event is caused by the device or the procedure.

Treatment Recovery Adverse Events
All prostate cancer treatments result in several transient and manageable adverse events that occur during the perioperative period. Most are related to anatomical structures adjacent to the prostate including the urethra and bladder. Below are comments on clinical significance, management and resolution of treatment recovery adverse events.

- Urinary retention, acute urinary retention, intermittent urinary retention are expected adverse events that often occur within 1 month of treatment and result from the prostate expanding during and after the HIFU procedure. It is a usually a transient treatment effect that can be managed with catheterization or self-catheterization.
- Obstruction (including obstructions: 2 – 17 days post op, bladder outlet obstructions and urinary obstructions) is an expected adverse event that often occurs within 1 month of treatment and results from the prostate expanding during and after the HIFU procedure. It is a usually a transient treatment effect that can be managed with catheterization or self-catheterization.
- Bladder spasms can occur during the first postoperative day or following catheter removal. They dissipate quickly and resolve without intervention within a couple of days. Urinary frequency and irritating urinary voiding symptoms are transient perioperative treatment effects which typically resolve quickly without intervention.
- Perineal/penile/rectal/prostate/abdominal pain and perineal/penile/rectal/prostate/ abdominal discomfort tend to be transient in nature and usually resolve quickly with medication. Urinary tract infections are an expected side effect that occurs after any intervention involving the urethra and increases with indwelling catheter duration. These are manageable and resolved with antibiotics.
- Penile tip irritation or redness and catheter discomfort / incision pain are associated with the use of Foley or suprapubic catheters.
- Catheter clog or malfunctions are events related to the use of a catheter and are resolved by checking, cleaning or replacing the catheter.
- Hematuria is an expected adverse event and usually resolves soon after HIFU.
- Dysuria is an expected adverse event which often occurs after catheter removal or with a urinary tract infection. When associated with the former it usually resolves quickly without intervention and with the latter it usually resolves upon resolution of the infection.
- Scrotal swelling most often occurs as a result of edema following treatment and occurs in the scrotum preferentially due to the fact that the scrotal tissue is expansile. This adverse event resolves without intervention.
- Anal tears resolve without intervention. This occurs with the insertion of the treatment probe while the patient is under anesthesia. This is not a painful event at occurrence or subsequently and patients are usually unaware of it unless informed.
- Blood at tip of penis /urethral bleeding /rectal bleed typically occur in the perioperative period and usually resolve quickly without intervention.
- Constipation / nausea / diarrhea typically occur in the peri-operative period, are usually associated with anesthesia pharmaceuticals and are transient.

<u>Treatment Effects Adverse Events</u>
Below are comments on clinical significance, management and resolution of treatment effects adverse events.

- Urethral sloughing is associated with thermally ablative procedures and sometimes results in diminished urine flow or retention. This adverse event is often easily managed and once resolved, does not usually reoccur. The initial management is urethral catheterization. Afterwards, self-catheterization can be prescribed. Additionally,

cystoscopic removal of necrotic tissue may be performed and provides immediate relief but is not warranted unless catheterization or self-catheterization is not tolerated by the patient.

- Bladder neck contracture, bladder neck stricture and bladder outlet obstruction are expected adverse events that are usually late onset (> 30 day) after HIFU. In most cases, these adverse events are easily managed and resolved with a single bladder neck incision or dilation. It is worthwhile noting that this complication is often associated with a transurethral resection of the prostate (TURP) procedure.
- Lower urinary tract symptoms (LUTS), bladder urgency, urinary urgency, nocturia and urinary hesitancy are relatively prevalent in men of an age to be at risk for prostate cancer and are sometimes symptoms of underlying bladder neck contracture or urethral stricture after HIFU. Urinary stricture results from prostate and urethra scarring after HIFU. This is often simply managed with dilation or cold blade incision.
- Slow stream / incomplete bladder emptying are usually symptoms of adverse events rather than adverse events themselves: namely slow stream symptoms that resolve are usually associated with stricture or sloughing. Non-resolving slow stream may be associated with a poor quality/trabeculated bladder.

Side Effects:

- Erectile dysfunction is a common side effect of all prostate cancer treatments and can represent a major quality of life impact especially in younger men with active sex lives. In most cases, it is possible to return a man to intercourse following HIFU treatment. There are a total of 93 events (66.7% subjects) related to the device or procedure, of which 24 are severe, 48 moderate and 21 mild, 34 resolved and 1 resulted in permanent impairment. Of those unresolved, 8 are mild, 36 moderate and 14 severe. Treatments included medication (60), vacuum erection device therapy (15), therapeutic/diagnostic procedure (2), constriction ring (1), penile rehab (1) and no treatment (14).
- Incontinence is a common side effect of all prostate cancer treatments and can represent a major quality of life impact. There are a total of 57 incontinence events related to the device or procedure, of which 43 are mild, 11 are moderate, 2 are severe; 42 resolved and 15 are ongoing. Of those unresolved, 11 are mild, 2 moderate and 2 severe. Post HIFU incontinence is initially managed with absorbent pads and Kegel exercises. If the condition persists, and the patient is motivated, an artificial sphincter or sling can often be used to treat the condition.

Unanticipated Adverse Device Effects

One UADE of bladder stricture was reported during the study. Approximately 2 years and 9 months following HIFU treatment, adverse events of bladder neck contracture and bladder stone that were severe were reported for a subject. Although the IDE Investigational Plan identifies bladder neck stricture as an expected adverse event, with a 9% rate of incidence based on previously reported Ablatherm® clinical experience outside of the US, the site investigator considered this an unexpected adverse device effect given the finding of a bladder stone and the severity of the stricture. He also considered this adverse event to be possibly related to both the investigational device and procedure. The Sponsor believes that the use of Spanner Stents, which are not cleared for use with the investigational device, may have contributed to this adverse event. However, due to the subject hospitalization (for 23 hours) and after review of the adverse event with FDA, EDAP reported this event to FDA as an UADE.

7.1.5.6 Quality of Life

Quality of life was assessed with the International Prostate Symptom Score (IPSS) and the UCLA Prostate Cancer Index score. The results for IPSS and UCLA Prostate Cancer Index

scores at baseline and at 1 month and 24 months post-procedure are summarized in Table 25. The IPSS ranges from 1 (no symptoms) to 35 (most severe) and scores ranging from 0-7 indicate mild symptoms, scores from 7-15 indicate moderate symptoms, and scores > 15 indicate severe symptoms.[25] An increase in the IPSS scores indicates worsening of the symptoms. The UCLA scores range from 0 (worst) to 100 (best). A decrease in the UCLA scores indicates worsening of the symptoms.

The mean IPSS score in the HIFU IDE cohort was 6.8 at baseline and 8.8 at 24 months. This 24-month score is at the low end of the moderate range, and within 2 points of the baseline score, which is at the high end of the mild range.

The mean UCLA Urinary Score was 87.7 at baseline and 76.8 at 24 months post-procedure. The mean UCLA Sexual Score was 68.3 at baseline and 37.7 at 24 months post-procedure. The study treatment had little effect on the UCLA Bowel Score Mental Health Component Score or the Physical Heath Component Score with subjects almost returning to baseline by 6 months post study treatment.

Table 25: IPSS and UCLA Prostate Cancer Index Scores, HIFU IDE Cohort

Visit	Parameter	N	Mean±SD	Min, Max	95% CL for Mean
IPSS Score					
Baseline	At visit	133	6.8±5.2	0.0, 23.0	6.0, 7.7
Month 1	At visit	114	17.3±8.9	0.0, 35.0	15.6, 18.9
	Change from baseline	112	10.1±8.3	-8.0, 32.0	8.6, 11.7
Year 2	At visit	108	8.8±7.1	0.0, 31.0	7.4, 10.1
	Change from baseline	106	1.6±6.4	-12.0, 26.0	0.4, 2.8
UCLA Urinary Score (normalized to 100)					
Baseline	At visit	134	87.7±12.3	8.3, 93.8	85.6, 89.8
Month 1	At visit	122	63.8±25.3	0.0, 93.8	59.3, 68.4
	Change from baseline	120	-22.8±24.2	-82.8, 33.3	-27.2, -18.5
Year 2	At visit	108	76.8±23.0	0.0, 93.8	72.4, 81.1
	Change from baseline	106	-10.1±21.4	-85.5, 25.0	-14.2, -6.0
UCLA Bowel Score (normalized to 100)					
Baseline	At visit	134	87.5±11.5	22.3, 93.3	85.5, 89.5
Month 1	At visit	132	72.5±23.3	0.0, 93.3	68.5, 76.5
	Change from baseline	131	-14.5±21.7	-93.3, 26.0	-18.2, -10.7
Year 2	At visit	108	84.6±18.1	0.0, 93.3	81.1, 88.0
	Change from baseline	107	-2.3±16.1	-93.3, 26.3	-5.3, 0.8

Visit	Parameter	N	Mean±SD	Min, Max	95% CL for Mean
UCLA Sexual Score (normalized to 100)					
Baseline	At visit	132	68.3±30.9	0.0, 100.0	63.0, 73.6
Month 1	At visit	126	8.9±15.5	0.0, 80.0	6.0, 11.7
	Change from baseline	123	-58.9±31.3	-100.0, 5.0	-64.7, -53.1
Year 2	At visit	98	37.7±35.0	0.0, 100.0	31.0, 44.3
	Change from baseline	96	-28.3±31.2	-100.0, 66.8	-34.3, -22.3
UCLA SF12 Aggregate Mental Component Score					
Baseline	At visit	132	54.6±7.1	33.1, 67.9	53.4, 55.8
Month 1	At visit	126	49.5±10.1	22.0, 65.8	47.7, 51.3
	Change from baseline	123	-4.6±8.8	-35.3, 18.8	-6.2, -3.1
Month 24	At visit	98	53.4±8.7	27.2, 66.0	51.7, 55.2
	Change from baseline	96	-1.4±8.5	-31.8, 21.0	-3.2, 0.3
UCLA SF12 Aggregate Physical Component Score					
Baseline	At visit	132	52.7±8.0	20.1, 64.8	51.3, 54.0
Month 1	At visit	126	45.7±10.1	14.9, 61.8	43.9, 47.5
	Change from baseline	123	-7.0±10.0	-35.7, 24.2	-8.8, -5.3
Month 24	At visit	98	51.2±8.1	26.1, 62.6	49.6, 52.8
	Change from baseline	96	-1.6±7.5	-26.8, 21.8	-3.1, -0.1

7.2 Systematic Review and Meta-Analysis of HIFU Literature

7.2.1 Introduction

The purpose of the literature review was to systematically review the contemporary evidence of biochemical disease free survival and morbidity following HIFU whole gland treatments for low-risk, localized prostate cancer to provide supportive evidence of the longer-term effectiveness and safety of the HIFU investigational treatment. The following standard definition of low risk, localized prostate cancer was used: stage T1 - T2a and PSA ≤ 10 ng/mL and Gleason score ≤ 6. Pooled estimates of adverse events as well as biochemical survival at 2 and 5 years were established. The meta-analyses were performed according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al 2009).

7.2.2 Methodology

The search strategy for the HIFU MA is summarized in Table 26. Searches were performed in PUBMED and EMBASE (accessed through ScienceDirect).

Table 26: Summary of Search Strategy, HIFU MA

Search Engine	Search Strategy
PUBMED	Search terms: high-intensity focused ultrasound ablation OR hifu OR ultrasonography OR ultrasound OR ultrasonics OR Sonablate OR Ablatherm AND prostate OR prostatic OR neoplasms OR cancer OR malignancy OR adenocarcinoma
	Limit search to year ≥ 1997, humans, English language
	Refine search: --add: comparative study, controlled clinical trial, evaluation studies, multicenter study, and randomized controlled trial --eliminate: meta-analysis, practice guideline, review, systematic review
	Settings: Filters activated for: Publication date from 1997/01/01 to 2012/12/31, Humans, English
EMBASE Search, Accessed Through ScienceDirect	Settings: Journals, Advanced Search, Medicine and Dentistry, Articles, Keywords, 1997-present
	Search terms: prostate OR prostatic OR adenocarcinoma AND HIFU OR ultrasound OR high-intensity focused ultrasound OR ablation therapy

The assessments and the time intervals when the assessments were performed were not standardized in the publications. However, the publications typically report a minimum of 2-year follow-up with endpoints that are accepted as clinically relevant by the medical and scientific community. Duplicate publications were excluded and, wherever publications that evaluated the same population group were encountered, the report with the most relevant and comprehensive data was selected.

Criteria for Study Selection

Studies were required to meet the following criteria for inclusion in the meta-analysis:

1. Prospective or retrospective cohort study design (i.e., no case studies or reviews
2. Must include biochemical survival data or safety data on patients with low-risk, localized prostate cancer (stage T1-T2a and PSA ≤ 10 ng/mL and Gleason score ≤ 6)
3. Patients must have been treated with cryotherapy or high intensity focused ultrasound (HIFU)
4. The treatment strategy must have been a whole gland treatment
5. Must include reporting on biochemical survival (using any definition) at a minimum of two years and/or morbidity data

Data Extraction

Articles that met all the inclusion criteria based on their abstracts were retrieved as full text articles. A standard data collection form was used to extract all relevant data from the full text articles. In the case where biochemical survival rates were not reported as stratified rates in the

text of the paper or a table, estimates were extracted from stratified Kaplan-Meier survival curves. Since few studies presented stratified morbidity rates, all that presented the aggregate morbidity rates for entire study samples were abstracted.

Statistical Analysis

Heterogeneity between study outcomes was anticipated due to the inclusion of studies of different designs over a large time period. Therefore, random-effects linear regression models were used to estimate pooled biochemical survival rates at 2 and 5 years. Specific definitions of biochemical failure were disparately reported by treatment, so all rates are aggregated over all definitions.

Since the variances of survival estimates could not be extracted from survival curves, the meta-analysis was conducted assuming survival estimates were proportions (using the total low risk sample size at baseline as the denominator of the proportion). This method underestimates the true variance of the survival estimates due to censoring, so we do not present 95% confidence intervals for the meta-analyzed pooled proportions, but do present the range of all reported statistics.

Further, since many biochemical survival rates were relatively high with some studies reporting 100% survival for treatments at certain time points, we employed an arcsine square-root transformation to ensure convergence of the random-effects models. The meta-analyzed estimates are reported back-transformed to a standard proportion.

Morbidity rates varied considerably in the literature, likely due to differing ranges of follow-up, unreported withdrawal from studies, and inconsistent definitions of adverse events, so these rates are summarized as the median sample statistic with the interquartile range (IQR; 25th and 75th percentiles) and the range of reporting studies.

7.2.3 Study Results

Article Selection

A total of 928 citations were identified for the HIFU MA. Duplicates were removed, abstracts screened, and full text articles were reviewed for those not eliminated based on the abstract. At the end of the selection process, 13 (representing 1,193 pooled subjects) were included in the HIFU MA. All of the articles in the HIFU MA reported studies on the Ablatherm® device. Details of the article selection process for the HIFU MA are provided in Figure 3.

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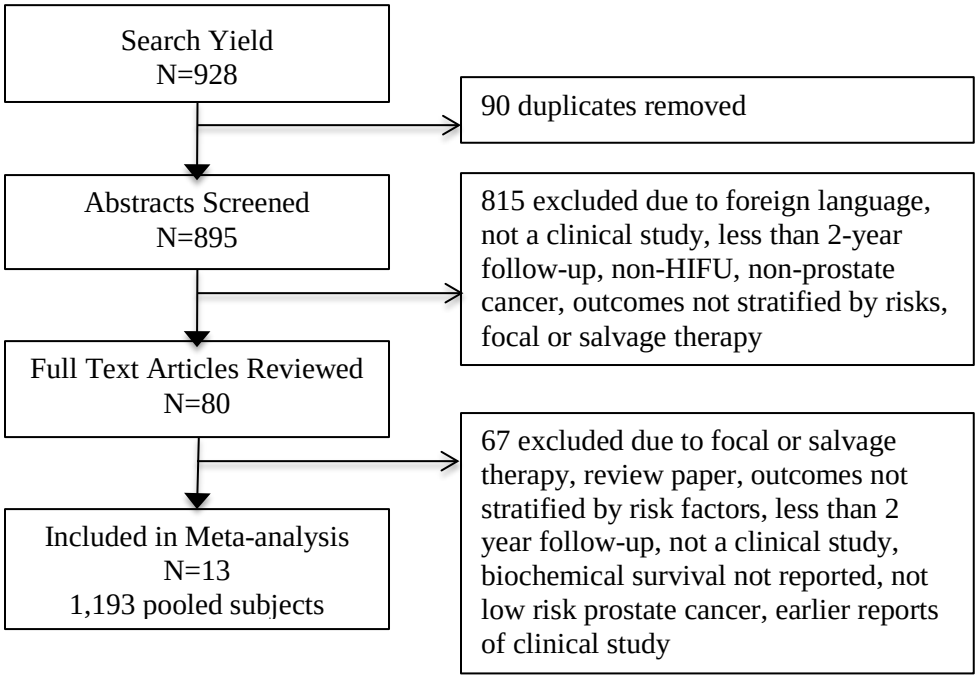

Effectiveness

Pooled biochemical survival rates for HIFU at 2 and 5 years are listed in Table 27. At two years, 7 cohorts reported on HIFU. The pooled survival rate aggregating all biochemical failure definitions was 92% for HIFU.

At five years, 6 cohorts reported biochemical survival rates for HIFU. The pooled survival rate aggregating all biochemical failure definitions was 83% for HIFU.

Table 27: Biochemical Survival – All Definitions, HIFU MA

Time Point	HIFU MA		
	Pooled %	N Cohorts/Subjects	Range
2 Years	92%	6/623	74% - 98%
5 Years	83%	6/730	66% - 88%

Safety

Not all of the selected articles included reports of adverse events. However, when available, the median, interquartile range, and range of adverse event rates were analyzed. The adverse events reported in publications are typically limited to those that are routinely collected by clinicians and that the author deems relevant to the condition and treatment being studied. Consequently, it is not surprising that the adverse events reported in the articles included in this meta-analysis are limited to those closely associated with cryotherapy and HIFU treatment.

The median, interquartile range and range of adverse event rates reported among HIFU in the meta-analyses are listed in Table 28. The most frequently reported adverse event for the HIFU

MA is erectile dysfunction. The median rate in the HIFU MA is 43.2. The median rate for obstruction is 17.3 and the median rate of incontinence is 8.5. The median rates of retention and stricture were 13.9 and 10.8. The median rate of fistulas was 0.

Table 28: Adverse Event Rates, HIFU MA

Adverse Events	HIFU MA		
	Median [IQR] Rate (%)	Range	N Cohorts
Incontinence	8.5 [6.2, 15.6]	0.0 – 20.0	12
Retention	13.9 [7.4 – 19.3]	3.6 – 20.0	4
Obstruction	17.3 [12.9, 20.2]	4.0 – 24.5	4
Stricture	10.8 [7.3, 14.7]	3.2 – 21.7	6
Erectile Dysfunction	43.2 [36.3, 50.0]	13.0 – 77.1	9
Fistula	0.0 [0.0, 0.6]	0.0 – 1.2	3

7.3 HIFU Registry Cohort

7.3.1 Introduction

The HIFU Registry cohort is intended to provide supportive evidence of the effectiveness of the HIFU device in the treatment of low risk, localized prostate cancer. The Phoenix Biochemical Survival and PSA Nadir Survival of the HIFU Registry cohort at 2 and 5 years post-treatment were collected and compared to the CRYO MA results.

EDAP has sponsored a prospectively designed registry of Ablatherm® cases conducted in Europe since 1996. To compile a cohort of HIFU subjects from the registry (HIFU Registry cohort) to support the HIFU IDE cohort, EDAP developed a prospectively defined protocol that standardized subject selection, data abstraction and data analysis for the HIFU Registry cohort. Therefore, selection of subject records for this patient cohort was performed in an unbiased way. Clinical centers with the highest number of low-risk, localized prostate cancer cases were selected for participation in this study. The records of 8,508 consecutive patients were reviewed and all who met the inclusion criteria were enrolled in the study

In Europe, physicians administer repeat treatments of HIFU as needed to slow or halt the progression of low-risk, localized prostate cancer. As is common in the US, physicians monitor patients post-treatment for signs that their prostate cancer is active. Typical signs are an increasing PSA and/or a positive prostate biopsy. When the physician determines that additional treatment is necessary, the physician may choose to administer another HIFU treatment. Being able to offer repeat treatment is considered an advantage of the HIFU treatment. Most of the studies presented in the literature report efficacy and morbidity after one or more HIFU treatments. Blana et al.[26] investigated the morbidity of repeat HIFU treatment and concluded that although there is an increase in morbidity with repeat treatment, the risk of side effects related to additional HIFU sessions is still low.

Additionally, when a European physician encounters a prostate that exceeds the maximum dimensions that can be treated by the Ablatherm® device, the physician often performs a

transurethral resection of prostate to surgically reduce the size of the prostate to one that can be effectively treated with HIFU. This reduction of the prostate for the specific purpose of HIFU treatment is known as "rightsizing."

7.3.2 Data Collection Design

Data for the HIFU Registry cohort were collected from a multi-center, prospectively defined registry of consecutive European patients with low-risk, localized prostate cancer treated with Ablatherm® HIFU, An irreversibly anonymized data set was created from the site's database of patient records.

Data collected included baseline information, a procedure summary, and follow-up information available from the site databases. In addition, access to other patient files (such as clinic charts) was required to gather information on intra-treatment and post-treatment adverse events, if not available in the site databases. Post-treatment follow-up evaluations were collected, to the extent available in the databases, and summarized within the following post- Ablatherm® HIFU procedure intervals: 10 days, and 3, 6, 9, 12, 18, and 24 months, and any subsequent evaluations available. All patient data meeting the selection criteria was included regardless of the availability of biopsy data.

No adverse event data were available in the registry.

Key Inclusion Criteria
The data collection included all consecutively treated subjects who met the following inclusion criteria:

- Subject has undergone whole gland Ablatherm® HIFU for the treatment of prostate cancer confirmed by PSA and prostate biopsy;
- Male subject, age $\geq$ 50 years at time of HIFU procedure;
- Organ-confined prostate cancer, clinical stage T1a, b, or c or T2a;
- At least one positive biopsy prior to the Ablatherm® HIFU procedure;
- PSA $\leq$ 10 ng/ml;
- Gleason Score $\leq$ 6; (Note: a subject with a histological grading of primary 4 is not eligible for study enrollment);
- Pre-treatment Prostate Volume $\leq$ 40 cc at the time of HIFU;
- Pre-treatment Prostate AP diameter ≤ 25 mm at the time of HIFU.

Key Exclusion Criteria
The data collection did not include any treated subjects who met the following exclusion criteria as recorded in the registry or site database:

- Any other prostate procedure prior to the index Ablatherm® HIFU procedure with the exception of Transurethral Resection of the Prostate (TURP);
- Evidence of seminal vesicle involvement prior to the procedure;
- Evidence of lymph node involvement or metastasis prior to the Ablatherm® HIFU procedure;
- Any previous treatment for prostate cancer; including EBRT, hormone therapy and/or previous bilateral orchiectomy prior to the Ablatherm® HIFU procedure;
- Previous surgery or procedure of the prostate (except prostate biopsy) or urethra within one year prior to the Ablatherm® HIFU procedure;
- Use within two month prior to HIFU of finasteride;
- Rectal surgery (other than hemorrhoidectomy) prior to the Ablatherm® HIFU procedure or history of rectal disease;

- Active inflammatory bowel syndrome at the time of the Ablatherm® HIFU procedure;
- Superficial bladder cancer, urethral stricture or bladder neck contracture at the time of the Ablatherm® HIFU procedure;
- Active urinary tract infection or acute prostatitis at the time of the Ablatherm® HIFU procedure;
- Prostate seroma, prostate abscess or urethral stenosis at the time of the Ablatherm® HIFU procedure.

7.3.3 Study Results

7.3.3.1 Enrollment and Accountability

Three centers with a minimum of 25 patients were identified and asked to participate in this project. All three centers agreed and enrolled all of their patients who met the eligibility requirements. A total of 199 subjects were enrolled in the HIFU Registry Cohort and 115 were included in the analysis. Subjects without the PSA values necessary to determine effectiveness endpoints were excluded from analysis. Enrollment by site is provided in Table 29.

Table 29: Enrollment by Site, HIFU Registry Cohort

Site	Number Enrolled	Number Included in Analysis
105 – Lyon	78 (39.2%)	61 (53.0%)
107 – Regensburg	60 (30.2%)	35 (30.4%)
906 – Munich	61 (30.7%)	19 (16.5%)

The difference in the percentage of patients enrolled by site is largely attributable to the fact that the Lyon site treats mostly local men while the Regensburg and Munich sites treat many non-locals who do not typically return for follow-up care.

Of the 199 subjects enrolled, 115 subjects had at least one PSA within 6 months of HIFU to determine the nadir and had additional PSA measurements at or after 24 months post-treatment to determine biochemical survival or had retreatment or salvage treatment prior to 24 months. The flowchart in Figure 4 illustrates the derivation of the HIFU Registry analysis population.

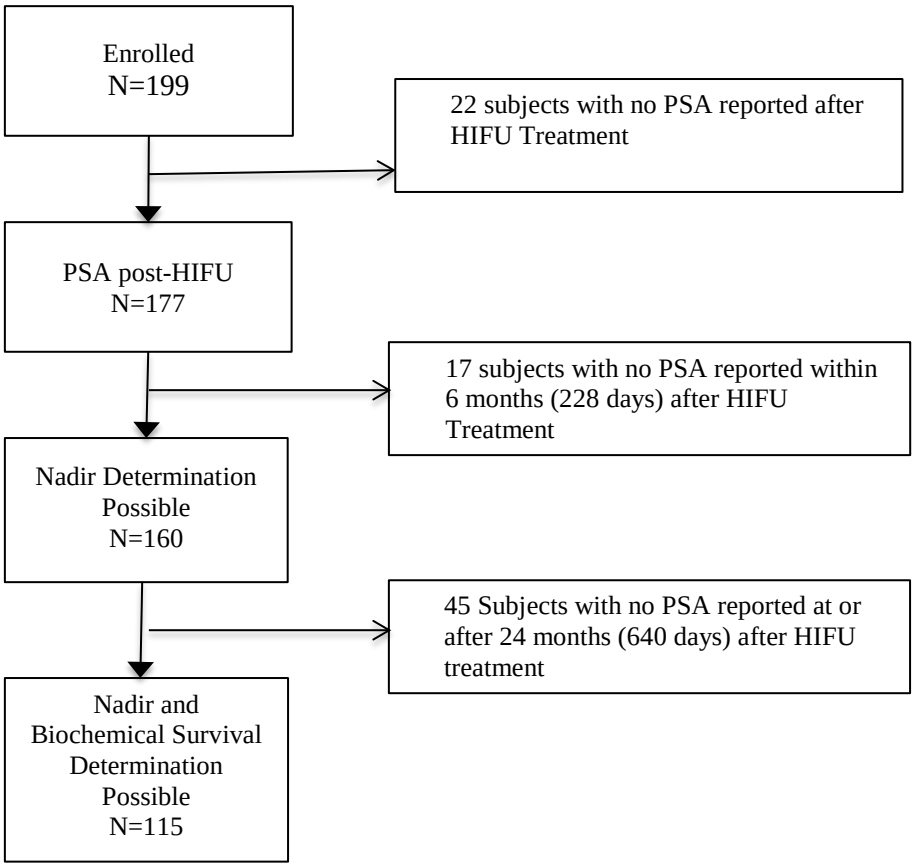

Figure 4: Derivation of Analysis Population

A total of 76 subjects among the 115 have sufficient post-treatment PSA follow-up to determine biochemical survival at 5 years. The analysis population represents a small fraction of the total database population and is reflective of the narrow inclusion and exclusion criteria which closely follow those of the IDE study as well as the study requirement of multiple PSA measurements at fairly specific time points following HIFU treatment. In the real world experience captured by the HIFU Registry, physicians collect PSA measurements as needed and not necessarily within a 24-month window as required for the study (Table 30).
Standard practice with HIFU treatment in the EU allows for additional HIFU treatments. Subjects in the HIFU registry cohorts were stratified into four groups where salvage treatment is defined as an additional treatment other than HIFU:

- Subjects without HIFU retreatment or salvage treatment: 76 subjects
- Subjects with HIFU retreatment only: 24 subjects
- Subjects with salvage treatment only: 7 subjects
- Subjects with both HIFU retreatment and salvage: 8 subjects

Biochemical success was determined according to the Phoenix criteria. All subjects were included in this analysis whether or not the subject had a second HIFU treatment; however, PSA obtained after salvage treatment was not considered for biochemical survival. Continued biochemical success following HIFU retreatment was determined using a recalculated nadir value and PSA values following the retreatment.

Table 30: Subject Accountability, HIFU Registry Cohort

Characteristic	Analysis Cohort N=115
Number enrolled	115
Post-HIFU follow-up (years from initial HIFU to last PSA)	
Mean±SD	5.7±2.8
Median (Min, Max)	5.7 (0.2, 11.8)
Number with retreatment	39
Type of retreatment[1]	
HIFU[2]	32
Radiotherapy	10
Hormonotherapy	6
Cryotherapy	1
Radical surgery	1
Time of first HIFU retreatment	
Within 228 days of initial HIFU	9
Prior to 820 days of initial HIFU	15
>820 days from initial HIFU	8

Characteristic	Analysis Cohort N=115
Time of first salvage retreatment	
Within 228 days of initial HIFU	1
Prior to 820 days of initial HIFU	2
>820 days from initial HIFU	10
Number with biopsy	92
Number with positive biopsy	38
Time of first positive biopsy	
Within 228 days of initial HIFU	16
Prior to 820 days of initial HIFU	8
>820 days from initial HIFU	14
[1]Not mutually exclusive [2]One subject had two HIFU retreatments	

7.3.3.2 Baseline Characteristics and Demographics

Demographic and baseline characteristics for the HIFU Registry cohort are provided in Table 31. The age of the subjects in the HIFU Registry cohort ranged from 49.0 to 79.0 years with a mean of 68.0 years. The pre-treatment PSA ranged from 0.1 to 9.9 ng/ml with a mean of 5.5 ng/ml. The prostate volume ranged from 7.0 to 31.0 cc and the mean was 18.1 cc. About half (49.6%) of the subjects had a Gleason score of 6, 19.1% had a score of 5, 20.0% with a score of 4, 7.0 with a score of 3 and 4.3% with a score 2. Nearly half (47.8%) of the subjects had a cancer stage of T1c, 35.7% were classified as T2a, 9.6% as T1b and 7.0% as T1a.

Table 31: Demographics and Baseline Characteristics, HIFU Registry

Characteristic		HIFU Registry n=115
Age (yrs)	Mean±SD (N) Median (Range)	68.0±6.8 (115) 69.0 (49.0, 79.0)
Weight (lbs)	Mean±SD (N) Median (Range)	Not Reported
Race	Caucasian African American Other/ Not specified	Not Reported
PSA	Mean±SD (N) Median (Range)	5.5±2.4 (115) 5.7 (0.1, 9.9)

Characteristic		HIFU Registry n=115
Prostate Vol. (cc)	Mean±SD (N)	18.1±5.3 (115)
	Median (Range)	18.0 (7.0, 31.0)
Time from Cancer Diagnosis (mos)	Mean±SD (N)	Not Reported
	Median (Range)	
Gleason Score	2	4.3% (5)
	3	7.0% (8)
	4	20.0% (23)
	5	19.1% (22)
	6	49.6% (57)
Cancer Stage	T1a	7.0% (8)
	T1b	9.6% (11)
	T1c	47.8% (55)
	T2a	35.7% (41)

Baseline Gleason scores were compared between subjects treated prior to 2005 and those treated in 2005 or later in the HIFU Registry cohort are shown in Table 32. Baseline Gleason scores are higher for subjects treated after 2005. This is to be expected due to the Gleason grading system being updated at a 2005 consensus conference of international experts in urological pathology, under the auspices of the International Society of Urological Pathology[27]. Consistent with this update, Gleason scores 2–4 were rarely diagnosed after 2005. This is not a result of a change in the disease presented at diagnosis but rather a change in the grading system. A depiction of this change is found in the 2010 Epstein review of the impact of the 2005 Gleason score update, which shows the original Gleason grading system side by side with the updated system[28].

It should also be noted that some of the patients diagnosed with Gleason 6 prior to the year 2005 may have had more aggressive disease according to the updated system. This is because certain patterns (i.e. poorly formed glands) that were originally considered Gleason pattern 3 are now considered Gleason pattern 4 and all cribriform cancer is now graded pattern 4. Therefore, by current Gleason grading standards, it is possible that one or more of the 41 subjects graded as Gleason 6 prior to 2005 would be graded as Gleason 7 today. If this is the case, the HIFU Registry cohort would include subjects with cancer that is more severe than low risk and who would be more likely to become biochemical failures. Therefore, the HIFU Registry results are a more conservative estimate of the effectiveness of the Ablatherm® device.

Table 32: Gleason Score at Diagnosis, HIFU Registry Cohort

Gleason Score at Diagnosis	Pre 2005 N=91	2005 or later N=24
2	5.5% (5/91)	0.0% (0/24)
3	7.7% (7/91)	4.2% (1/24)
4	22.0% (20/91)	12.5% (3/24)
5	19.8% (8/91)	16.7% (6/24)
6	41.5% (41/91)	66.7% (15/24)
P-value from Wilcoxon test comparing baseline Gleason scores between pre 2005 and post 2005 is 0.002		

7.3.3.3 Effectiveness Endpoints

Phoenix Biochemical Survival

For the Phoenix Biochemical Survival endpoint, a subject was considered a success if he had no PSA obtained between 6 and 24 months post study treatment that was greater than or equal to the nadir PSA (obtained within 6 months following study treatment) plus 2 ng/ml. A subject is evaluable if at least one PSA at or after the window open date is available and < Nadir+2 and all prior PSA are < Nadir+2. There are 107 subjects evaluable for Phoenix biochemical survival at 24 months and 76 at 5 years. In the HIFU Registry cohort, 94.4% of subjects met the definition of the Phoenix Biochemical Survival endpoint at 24 months. Results are summarized in Table 33.

Table 33: Phoenix Biochemical Survival - HIFU Registry Cohort

Phoenix Biochemical Survival[1]	% (n/N)	95% CL
Phoenix Biochemical Survival - 24 Months	94.4% (101/107)	90.0, 98.8%
Phoenix Biochemical Survival – 5 Years	82.9% (63/76)	74.4 91.4%
Without positive biopsy or salvage retreatment – 24 Months	72.3% (81/112)	64.0, 80.6%
Without positive biopsy or salvage retreatment – 5 Years	51.1% (46/90)	40.8, 61.4%
[1]Does not have PSA obtained after 228 days post treatment ≥ nadir PSA + 2. Requires at least one PSA obtained on or after 640 days post treatment. Subjects without a six-month nadir determination are included as success if all available follow-up PSA measurement are < 2.		

In the HIFU Registry cohort, 82.9% of subjects met the definition of the Phoenix Biochemical Survival endpoint at 5 years. For the endpoint of biochemical survival without positive biopsy or salvage treatment, subjects must meet the requirements of biochemical survival and not have undergone salvage treatment or had a positive biopsy. 72.3% of subjects at 24 months and 51.1% of subjects at 5 years met the definition of Phoenix biochemical survival without positive biopsy or salvage treatment.

Nadir Success

For the PSA Nadir endpoint, a subject was considered a success if his lowest PSA obtained within six months post HIFU treatment was less than or equal to 0.5 ng/ml. In the HIFU Registry cohort, 84.4% of subjects met the definition of the PSA Nadir endpoint after first or repeat HIFU treatment, as summarized in Table 34.

Table 34: PSA Nadir, HIFU Registry Cohort

Endpoint	Analysis[1]	% (n/N)	95% CL
PSA nadir≤0.5 ng/mL	After 1st HIFU only	75.7% (87/115)	67.8, 83.5%
	After 1st or repeat HIFU	84.4% (97/115)	77.7, 91.0%
[1]Nadir determined by lowest PSA obtained within 228 days of HIFU treatment (either following initial only or after any HIFU treatment)			

7.3.4 Conclusions

The analysis population includes 115 subjects who have sufficient follow-up data for a determination of 24-month biochemical success (at least one PSA on which to determine the 6-month nadir and sufficient follow-up PSA at or later than 24 months post treatment to determine stability) or underwent retreatment or salvage treatment prior to 24 months. A total of 76 subjects among the 115 have sufficient post-treatment PSA follow-up to determine biochemical survival at 5 years.

The percentage of patient meeting biochemical survival, based on the Phoenix definition, for this patient cohort is 94.4% (CI 90.0% - 98.8%) and 82.9% (CI 74.9% - 91.4%) at 2 and 5 years, respectively. The percentage of patients meeting biochemical survival, based on the Phoenix definition, without positive biopsy or salvage treatment is 72.3% (CI 64.0% – 80.6%) and 51.1% (CI 40.8% – 61.4%) at 2 and 5 years, respectively. The analysis of baseline parameters showed no effect of those parameters on biochemical survival, based on the Phoenix definition.

The HIFU Registry provides additional supportive information regarding the durability of HIFU as a therapy for low risk localized prostate cancer.

7.4 Cryotherapy Retrospective Study

7.4.1 Introduction

EDAP initiated the multi-center prospectively defined retrospective cryotherapy data collection it had proposed during its March 2009 meeting with FDA. This comprised of IRB approved evaluation of a consecutive series of contemporary cryotherapy procedures that were conducted to treat low-risk, localized prostate cancer. This study was designed with a goal of enrolling 125 subjects at four to seven study sites. The patient selection criteria were as similar as possible to that of the IDE study, and the primary effectiveness endpoint was achievement of PSA nadir ≤ 0.5 ng/ml and stability of PSA according to ASTRO criteria through 24 months follow up without a positive biopsy. Although 1883 potential subjects were screened, only 67 were enrolled in the CRYO Retro cohort. This was largely due to subjects who had undergone previous hormone therapy or off-label focal cryotherapy treatment. The accrual of only 53% of the target in this study was lower than the number necessary to allow for statistical comparisons of sufficient power to provide a reasonable assurance of effectiveness of HIFU.

7.4.2 Study Design

The inclusion and exclusion criteria were very similar to the IDE study. Data collected included baseline information (demographics, urology history, and baseline laboratory evaluations), a procedure summary (information on the cryosurgery procedure performed and any adverse events), and follow-up information (PSA results, rectal exam results, biopsy results, and any

adverse events reported) available from the subjects' clinic charts. Subjects who were at 2 or more years post-cryotherapy and had not already had a 2-year post-cryotherapy biopsy, were asked to undergo TRUS-guided biopsy. Subjects who had not yet achieved 2 years of follow up were also asked to undergo a TRUS-guided biopsy at 2 years. The enrollment goal of the study was 125 subjects.

The primary effectiveness endpoint was attainment of PSA nadir ≤ 0.5 ng/ml and stability of PSA according to ASTRO criteria through 24 month follow up without a positive biopsy (Nadir/ASTRO/Biopsy Survival). Phoenix Biochemical Survival was included a secondary effectiveness endpoint. Adverse events and device-related adverse events experienced in this study protocol's cryotherapy treatment group were tabulated and summarized.

7.4.3 Study Results

7.4.3.1 Enrollment and Accountability

The goal was to enroll one hundred twenty five (125) subjects at four to seven study sites. Although 1883 potential subjects were screened, subject accrual was low due to near universal pre-treatment hormone therapy at several centers, the increasing use of off label focal (rather than whole gland) cryotherapy for low risk patients, and the request for a prostate biopsy for research purposes only. Even though the biopsy was not required, discussing it as an option was a deterrent for patients to agree to participate. Subject accrual problems for this cohort were similar to those encountered in the cryotherapy arm of the Ablatherm® HIFU IDE study. Only 67 subjects were enrolled in this cohort. Enrollment by site is summarized in Table 35.

Table 35: Enrollment by Site, CRYO Retro Cohort

Site	Number Enrolled	Number with at Least 24 Months Follow-up
305 Urology Associates of North Texas	35	33
303 Adult and Pediatric Urology	14	14
301 Carolina Urological Research Center	8	8
304 Eastern VA Medical Center	6	6
302 Chinn and Chinn	3	3
300 Triangle Urology	1	0
Total	67	64

A summary of subjection selection is provided in Figure 5.

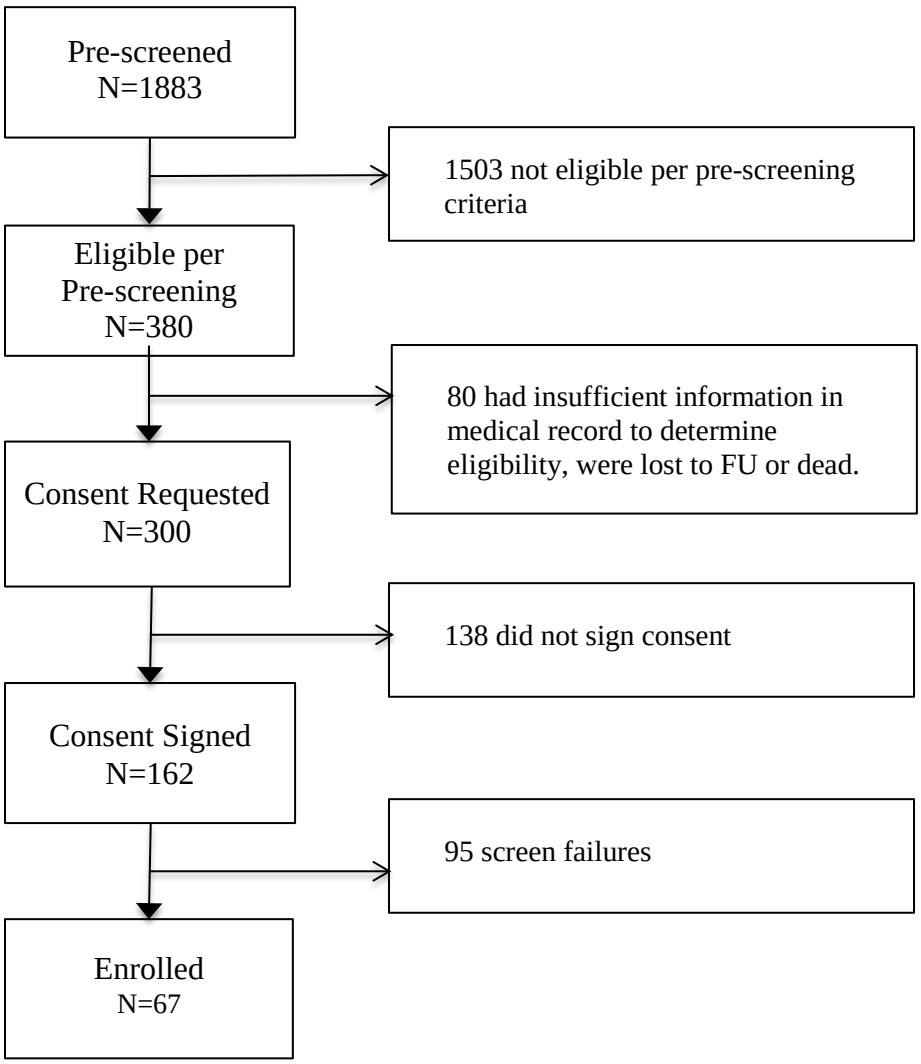

Figure 5: Subject Selection for CRYO Retro Cohort

A total of 67 cryotherapy treated subjects who met the study inclusion and exclusion criteria were identified from the retrospective review. Biochemical success endpoints are evaluated based on subjects with sufficient follow-up PSA (completers) data only. The number of subjects included in effectiveness endpoint determinations is summarized in Table 36.

Table 36: Subjects by PSA Evaluations, CRYO Retro Cohort

Characteristic	N=67
Number enrolled	67
Number with post CRYO PSA	67
Number with PSA evaluation within 228 days of CRYO (nadir determination)	65
Number with PSA evaluation on or after 640 days post CRYO treatment (stability)	64
Number with both nadir and stability determination	62

7.4.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics for the CRYO Retro cohort are presented in Table 37. The age of the subjects ranged from 55.3 to 79.5 years with a mean of 70.0 years. The pre-treatment PSA ranged from 1.0 to 9.7 ng/ml with a mean of 5.3 ng/ml. The majority (95.5%) of subjects had a Gleason score of 6, 1.5% had a Gleason score of 4, 1.5% had a Gleason score of 5 and the score was not specified in 1.5%. More than three quarters of the subjects (83.6%) had a cancer stage of T1c, 13.4% were classified as T2a, and the stage was not specified in 3.0%. Most (92.5%) subjects had a histology grade of 3+3, 1.5% had a histology grade of 3+4 and the histology grade was not specified in 6.0%.

Table 37: Demographics and Baseline Characteristics, CRYO Retro

Characteristic		CRYO Retro N=67
Age (yrs)	Mean±SD (N)	70.0±6.1 (68)
	Median (Range)	71.0 (55.3, 79.5)
Weight (lbs)	Mean±SD (N)	202.7±44.6 (34)
	Median (Range)	201.5 (142.0, 342.0)
Race	Caucasian	86.6% (58)
	African American	7.5% (5)
	Other/ Not specified	6.0% (4)
PSA	Mean±SD (N)	5.3±1.7 (65)
	Median (Range)	5.2 (1.0, 9.7)
Prostate Vol. (cc)	Mean±SD (N)	30.7±6.2 (64)
	Median (Range)	32.1 (17.4, 40.0)
Time from Cancer Diagnosis (mos)	Mean±SD (N)	4.0±5.0 (65)
	Median (Range)	2.8 (0.7, 37.5)
Gleason Score	4	1.5% (1)
	5	1.5% (1)
	6	95.5% (64)
	Not specified	1.5% (1)
Histology Grade	3+2	1.5% (1)
	3+3	92.5% (62)
	Not specified	6.0% (4)
Cancer Stage	T1c	83.6% (56)
	T2a	13.4% (9)
	Not specified	3.0% (2)

Baseline characteristics of age, pre-treatment PSA, prostate size, Gleason score and cancer stage of the HIFU IDE and CRYO Retro cohorts were compared to determine if comparisons of effectiveness would be valid. No evidence of a statistical difference between groups in cancer stage was found while a statistical difference is found for Gleason score. Both groups show very little variation in these two parameters. Over 95% of subjects in both cohorts had a Gleason score of 6. Additionally, 81% and 84% of subjects in the HIFU IDE and CRYO Retro cohorts respectively had prostate cancer stage of T1c with 14% and 13% respectively with stage T2a. These two cohorts show strong statistical evidence of differences in age, pre-treatment PSA and prostate size. Furthermore, based on the results of propensity score analysis, we conclude the HIFU IDE and Cryotherapy retrospective cohorts are not comparable and statistical inferences would be not valid between groups.

7.5 Systematic Review and Meta-Analysis of Cryotherapy Literature

7.5.1 Introduction

In the absence of a sufficiently large clinical data set of cryotherapy subjects to use as a control for the assessment of the clinical performance of HIFU collected in the IDE Study, EDAP met with FDA to discuss other options for a scientifically valid cryotherapy control including a performance goal. Based on the availability of multiple well-controlled cryotherapy studies, EDAP decided to establish an objective performance goal for comparison to the HIFU IDE cohort.

A systematic review and meta-analysis of the cryotherapy literature on the treatment of low risk localized prostate cancer was conducted by a statistician independent of EDAP, and pooled estimates of adverse events as well as biochemical survival at 2 and 5 years were established.

7.5.2 Methodology of CRYO MA

Twenty-five studies were identified and included in the cryotherapy meta-analysis. The details of systematic review and meta-analyses of the cryotherapy literature are the same as those for HIFU which are discussed in Section 7.2.2.

The search strategy for the CRYO MA is summarized in Table 38. Searches were performed in PUBMED and EMBASE (accessed through ScienceDirect).

Table 38: Summary of Search Strategy, CRYO MA

Search Engine	Search Strategy
PUBMED	Search terms: prostate OR prostatic OR adenocarcinoma AND cryosurgery OR cryosurgical OR cryotherapy OR cryoablation
	Limit search to year ≥ 1997, humans, English language
	Refine search: --add: comparative study, controlled clinical trial, evaluation studies, multicenter study, and randomized controlled trial --eliminate: meta-analysis, practice guideline, review, systematic review
	Settings: Filters activated for: Publication date from 1997/01/01 to 2012/12/31, Humans, Clinical Trial, Comparative Study, Controlled Clinical Trial, Evaluation Studies, Multicenter Study, Randomized Controlled Trial, Journal Article, English Search term entered into general search: prostate[Title] AND (cryoablation[Title] OR cryosurgery[Title] OR cryotherapy[Title] OR cryosurgical[Title])
EMBASE Search, Accessed Through ScienceDirect	Settings: Journals, Advanced Search, Medicine and Dentistry, Articles, Title-Abstract-Keywords, 1997-present
	Search terms: prostate OR prostatic OR adenocarcinoma AND cryosurgery OR cryosurgical OR cryotherapy OR cryoablation
Review Article Search	Review papers were searched for citations that had not been discovered during execution of the searches described above.

7.5.3 Results of CRYO MA

Article Selection

A total of 1327 citations were identified for the CRYO MA. Duplicates were removed, abstracts screened, and full text articles were reviewed for those not eliminated based on the abstract. At the end of the selection process, 25 articles (representing 1,864 pooled subjects) were included in the CRYO MA. Details of the article selection process for the CRYO MA is provided in Figure 6.

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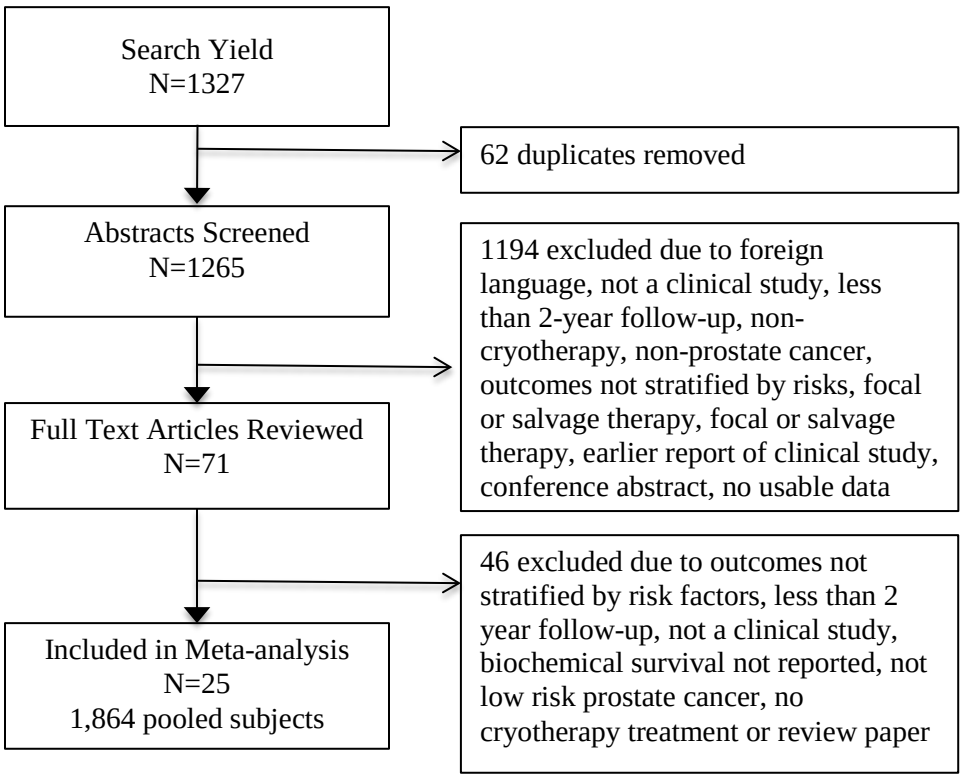

Figure 6: Article Selection for CRYO MA

Effectiveness

The pooled biochemical survival for the CRYO MA is presented in Table 39. At two years, 10 cohorts reported biochemical survival rates for cryotherapy and the pooled survival rate aggregating all biochemical failure definitions was 87%. At five years, 7 cohorts reported biochemical survival rates for cryotherapy and the pooled survival rate aggregating all biochemical failure definitions was 81%.

Table 39: Biochemical Survival: CRYO MA

Time Point	CRYO MA		
	Pooled %	N Cohorts/Subjects	Range
2 Years	87%	10/687	69% - 96%
5 Years	81%	7/429	49% - 93%

Safety

The median, interquartile range and range of adverse event rates reported among cryotherapy in the meta-analysis are presented in Table 40. The most frequently reported adverse events for the CRYO MA were erectile dysfunction (70.0), obstruction (14.8) and incontinence (7.5). The median rate of retention was 4.2, stricture was 0, and fistula was 0.1.

Table 40: Adverse Event Rates, CRYO MA

Adverse Events	CRYO MA		
	Median [IQR] Rate (%)	Range	N Cohorts
Incontinence	7.5 [3.9, 17.2]	0.9 – 32.0	23
Retention	4.2 [2.2, 9.5]	0.0 – 22.0	12
Obstruction	14.8 [11.9, 21.8]	9.0 – 28.7	3
Stricture	0.0 [0.0, 5.2]	0.0 – 17.0	5
Erectile Dysfunction	70.0 [53.0, 89.8]	25.2 – 100	17
Fistula	0.1 [0.0, 0.5]	0.0 – 1.9	15

7.5.4 Conclusions of Systematic Reviews and Meta-analyses

The meta-analysis estimate of biochemical survival between cryotherapy and HIFU indicates a slight advantage of HIFU over cryotherapy. In addition, the reported adverse events also indicate a slight increase in incontinence, retention, obstruction and stricture in HIFU over cryotherapy but a substantially lower rate of erectile dysfunctions in HIFU. Incontinence, retention, obstruction and strictures, although inconvenient and in some cases painful events, are expected and transient events. In contrast, a high frequency of erectile dysfunction has significant effect on quality of life, especially for younger patients. Thus, the meta-analysis supports the conclusion that the effectiveness of the Ablatherm® HIFU is similar to cryotherapy, while the Ablatherm® HIFU rate of erectile dysfunction is significantly lower.

8 LONG-TERM ANALYSES

8.1 HIFU Long Term Refined Cohort

The HIFU Long Term Cohort was created to document long-term freedom from metastasis and prostate cancer specific survival from the European clinical experience with Ablatherm HIFU for the treatment of low-risk localized prostate cancer. The HIFU Long Term Cohort was derived from patient databases maintained at three European sites that recently published long-term treatment results of Ablatherm HIFU for low-risk, localized prostate cancer. The sites are Klinikum Harlaching, Munich, Germany (Thuroff and Chaussy, 2013[29]), Edouard Herriot Hospital, Lyon, France (Crouzet et al., 2013[30]), and the University of Regensburg, Regensburg, Germany (Ganzer et al., 2013[31]). These are the same three centers that enrolled subjects in the HIFU Registry Cohort discussed in Section 7.3; however, the data collected in the site databases include more recent follow-up information. The combination of the patient level data from the three databases into a single dataset allows for a more detailed analysis than the summary statistics provided within the publications and allows analyses within the low-risk cohort of interest. The principal safety and long-term effectiveness of HIFU treatment were evaluated against a historical (literature) control, the radical prostatectomy arm of the Prostate Cancer Intervention Versus Observation Trial (PIVOT).[32]

Three cohorts were derived from this dataset. Inclusion and exclusion criteria similar to those used in the HIFU IDE study were applied to select the subjects included in the HIFU Long Term cohort. The second, the Long Term Refined cohort, a subset of the HIFU Long Term cohort, further excludes subjects with previous hormone therapy, previous TURP and incidental prostate

cancer (Ta, T1b). As the Long Term Refined cohort selection criteria were defined in discussions with FDA, it was selected for the principal evidence of effectiveness. The Long Term cohort results were included in the PMA as supportive evidence but are not discussed here. The third cohort, the HIFU Prospective Safety cohort, is a subset of the subjects in the HIFU Long Term cohort who had also been followed in one of three previously conducted prospective studies and, as a result, have prospectively collected safety data available.

8.1.1 Study Endpoints

Primary Effectiveness Endpoint
The primary effectiveness endpoint is freedom from metastasis at 8 years following Ablatherm® HIFU. The principal evidence of effectiveness is the freedom from metastasis rate at 8 years post-treatment of the HIFU Long Term Refined cohort compared to the radical prostatectomy arm of the PIVOT.

Secondary Effectiveness Endpoints

The secondary endpoints include:

- Cancer specific survival following Ablatherm® HIFU
- The incidence of prostate cancer recurrence within 24 months following the Ablatherm® HIFU procedure: Absence of prostate cancer will be defined as achievement of PSA nadir ≤ 0.5 ng/ml and stability of PSA according to Phoenix (PSA nadir + 2 ng/ml) criteria through 24 months follow-up without a positive biopsy. If biopsy data is not available, the absence of prostate cancer will be established by achievement of PSA nadir ≤ 0.5 ng/ml and stability of PSA according to Phoenix criteria only.
- Biochemical failure at two, five and ten years as defined by the Phoenix criteria of biochemical failure (PSA nadir + 2 ng/ml).

Secondary evidence is provided by comparisons of the HIFU Long Term Refined cohort to other endpoints from the radical prostatectomy arms of PIVOT and the SPCG-4 Trial including overall survival, cancer specific survival, and freedom from salvage treatment following Ablatherm HIFU treatment.

Safety
Safety was assessed by evaluating adverse events and device/procedure-related adverse events.

8.1.2 Data Collection

Data extracted from the site databases included baseline information, a procedure summary, and available follow-up information. In addition, access to other patient files (such as clinic charts) was required to gather information on intra-treatment and post-treatment adverse events, if not already available in the site databases. Post-treatment follow-up evaluations were collected, to the extent available in the databases.

Key Inclusion Criteria for HIFU Long Term Cohort

The data collection included all consecutively treated subjects who met the following inclusion criteria:

- Subject has undergone whole gland Ablatherm® HIFU for the treatment of prostate cancer confirmed by PSA and prostate biopsy;
- Male subject, age ≥ 50 years at time of HIFU procedure;
- Organ-confined prostate cancer, clinical stage T1a, b, or c or T2a;
- At least one positive biopsy prior to the Ablatherm® HIFU procedure;
- PSA ≤ 10 ng/ml;
- Gleason Score ≤ 6; (Note: a subject with a histological grading of primary 4 is not eligible for study enrollment);
- Pre-treatment Prostate Volume ≤ 40 cc at the time of HIFU;
- Pre-treatment Prostate AP diameter ≤ 25 mm at the time of HIFU.

Key Exclusion Criteria for HIFU Long Term Cohort

The data collection did not include any treated subjects who met the following exclusion criteria as recorded in the registry or site database:

- Any other prostate procedure prior to the index Ablatherm® HIFU procedure with the exception of Transurethral Resection of the Prostate (TURP);
- Evidence of seminal vesicle involvement prior to the procedure;
- Evidence of lymph node involvement or metastasis prior to the Ablatherm® HIFU procedure;
- Any previous treatment for prostate cancer; including EBRT, hormone therapy and/or previous bilateral orchiectomy prior to the Ablatherm® HIFU procedure;
- Previous surgery or procedure of the prostate (except prostate biopsy) or urethra within one year prior to the Ablatherm® HIFU procedure;
- Use within two month prior to HIFU of finasteride;
- Rectal surgery (other than hemorrhoidectomy) prior to the Ablatherm® HIFU procedure or history of rectal disease;
- Active inflammatory bowel syndrome at the time of the Ablatherm® HIFU procedure;
- Superficial bladder cancer, urethral stricture or bladder neck contracture at the time of the Ablatherm® HIFU procedure;
- Active urinary tract infection or acute prostatitis at the time of the Ablatherm® HIFU procedure;
- Prostate seroma, prostate abscess or urethral stenosis at the time of the Ablatherm® HIFU procedure.

8.2 Controls

Radical prostatectomy, the urological gold standard therapy for the treatment of localized prostate cancer, was selected as the control for this study for several reasons. Radical prostatectomy is considered a stable procedure as the physical foundation (surgical removal of the prostate) does not change unlike radiation therapy which continuously evolves in terms of technology, dosing strategy and adjuvant (hormone therapy) usage. Although technological advances have led radical prostatectomy to evolve from open surgery to a laparoscopic and now robotic laparoscopic approach, the fundamentals and outcomes remain similar. Importantly, the

availability of the Prostate Cancer Intervention Versus Observation Trial (PIVOT)'s high quality data on radical prostatectomy made it an ideal choice for the control.

8.2.1 PIVOT Study

In 1994, the Prostate Cancer Intervention Versus Observation Trial (PIVOT),[33] a multicenter randomized controlled trial comparing radical prostatectomy with observation in men with clinically localized prostate cancer was initiated. A total of 731 men were enrolled at 52 US medical centers. The primary and secondary endpoints were all-cause mortality and prostate cancer mortality, respectively. Bone metastases were documented on the basis of positive results of bone scanning or skeletal radiography and were reported at 8 years. Thirty-day perioperative harms and the prevalence of urinary incontinence and erectile and bowel dysfunction at 2 years were evaluated.

With a median follow-up of 10 years, the mean age of enrollees was 67 years and nearly one-third of these men were African American. Approximately 85% reported that they were fully active. The median PSA was 7.8 ng/mL (mean 10.2 ng/mL). In three-fourths of men, the primary reason for biopsy leading to a diagnosis of prostate cancer was a PSA elevation. Using previously developed tumor risk categorizations incorporating PSA levels, Gleason histologic grade, and tumor stage, it was found that approximately 40% had low-risk, 34% had medium-risk, and 21% had high-risk prostate cancer based on local histopathology.

During follow-up, 171 of 364 men (47.0%) assigned to radical prostatectomy died, as compared with 183 of 367 (49.9%) assigned to observation (hazard ratio, 0.88; 95% confidence interval [CI], 0.71 to 1.08; P=0.22; absolute risk reduction, 2.9 percentage points). Among men assigned to radical prostatectomy, 21 (5.8%) died from prostate cancer or treatment, as compared with 31 men (8.4%) assigned to observation (hazard ratio, 0.63; 95% CI, 0.36 to 1.09; P=0.09; absolute risk reduction, 2.6 percentage points). The effect of treatment on all-cause and prostate-cancer mortality did not differ according to age, race, coexisting conditions, self-reported performance status, or histologic features of the tumor. Radical prostatectomy was associated with reduced all-cause mortality among men with a PSA value greater than 10 ng/mL (P=0.04 for interaction) and possibly among those with intermediate-risk or high-risk tumors (P=0.07 for interaction). Adverse events within 30 days after surgery occurred in 21.4% of men, including one death. The study concluded that among men with localized prostate cancer detected during the early era of PSA testing, radical prostatectomy did not significantly reduce all-cause or prostate-cancer mortality, as compared with observation, through at least 12 years of follow-up. The absolute differences were less than 3 percentage points.

8.2.2 SPCG-4 Study

The Scandinavian Prostate Cancer Research Group-4 Trial (SPCG-4),[34] also studied radical prostatectomy and reported results of 10-year follow-up. The radical prostatectomy arm of the SPCG-4 was selected for the supporting effectiveness comparisons.

In SPCG-4, 695 men with early prostate cancer were randomly assigned to watchful waiting or radical prostatectomy.[35] To be eligible, men had to be less than 75 years old, have a general medical condition that would permit radical prostatectomy and follow-up of at least 10 years, have a tumor in stage T2 (confined to the prostate) or lower that was well or moderately well differentiated, have no metastases or urinary tract obstruction and have a PSA level of less than 50 ng/mL. The end points were disease-specific mortality, rate of distant metastases and overall mortality. Analysis was done according to the intention-to-treat principle and was based on complete follow-up of all eligible participants. During a median of 12.8 years follow-up, 166 of

the 347 men in the radical-prostatectomy group and 201 of the 348 in the watchful-waiting group died (P=0.007). In the case of 55 men assigned to surgery and 81 men assigned to watchful waiting, death was due to prostate cancer. This yielded a cumulative incidence of death from prostate cancer at 15 years of 14.6% and 20.7%, respectively (a difference of 6.1 percentage points; 95% confidence interval [CI], 0.2 to 12.0), and a relative risk with surgery of 0.62 (95% CI, 0.44 to 0.87; P=0.01). The survival benefit was similar before and after 9 years of follow-up, was observed also among men with low-risk prostate cancer, and was confined to men younger than 65 years of age. The number needed to treat to avert one death was 15 overall and 7 for men younger than 65 years of age. Among men who underwent radical prostatectomy, those with extracapsular tumor growth had a risk of death from prostate cancer that was 7 times that of men without extracapsular tumor growth (relative risk, 6.9; 95% CI, 2.6 to 18.4).

The authors concluded that radical prostatectomy was associated with a reduction in the rate of death from prostate cancer. Men with extracapsular tumor growth may benefit from adjuvant local or systemic therapy.

8.2.3 Comparability of European Population to US Population

The incidence and aggressiveness of prostate cancer varies in different ethnic groups. However, the aggressiveness and prognosis of the disease are dependent on the characteristics of the disease (i.e., PSA, Gleason, stage, risk group), not the ethnicity of the patient. For example, a multivariate analysis of 4342 prostatectomy patients from the Cancer of the Prostate Strategic Urologic Research Endeavor (CaPSURE) registry published in 2008 did not find race to be a predictor of treatment failure.[36] Therefore, a European population with low risk prostate cancer has similar disease characteristics, aggressiveness, and prognosis as a US population with low-risk disease. Further, the population in HIFU Long Term Refined Cohort is comparable to the HIFU IDE population and is relevant to the intended use population in the US. Finally, the standard of care for patients with low risk prostate cancer is very similar in the United States and Europe and is based only on disease characteristics, not on ethnicity.[37,38]

8.2.4 HIFU Long Term Results

8.2.4.1 Enrollment and Accountability

A total of 4,632 potential subjects were screened at the three centers and 925 subjects were included in HIFU Long Term cohort and 227 in the HIFU Long Term Refined cohort. A summary of the reasons for exclusion and the number excluded is shown in Table 41.

Table 41: Summary of Exclusions for HIFU Long Term and HIFU Long Term Refined Cohorts

Description of Exclusion or Not Inclusion	# Excluded Patients	# Remaining Patients
Whole gland HIFU subjects at Lyon, Regensburg and Munich	-	4632
Any previous definitive local radiation treatment for prostate cancer including EBRT or brachytherapy;	625	4007
Previous surgery or procedure of the prostate (except prostate biopsy or HIFU) or urethra within one year prior to the Ablatherm HIFU procedure;	66	3941

Description of Exclusion or Not Inclusion	# Excluded Patients	# Remaining Patients
Any other prostate procedure prior to the index Ablatherm HIFU procedure with the exception of Trans Rectal Resection of the Prostate (TURP);	0	3941
Previous bilateral orchiectomy prior to the Ablatherm HIFU procedure;	56	3885
Any hormone therapy lasting more than 6 months prior to HIFU or hormone therapy not discontinued at the time of HIFU;	421	3464
Evidence of lymph node involvement or metastasis prior to the Ablatherm HIFU procedure;	143	3321
Evidence of seminal vesicle involvement prior to the procedure;[1]	284	3037
Rectal surgery (other than hemorrhoidectomy) within one year prior to the Ablatherm HIFU procedure or history of rectal disease;	0	3037
Male subject, age $\geq$ 50 years at time of HIFU procedure;	16	3021
Organ-confined prostate cancer with a known stage, known Gleason, known PSA prior to the index Ablatherm HIFU procedure;[2]	137	2884
Low risk disease (defined as Gleason ≤ 6, PSA ≤ 10, Stage ≤ T2a;	1959	925[1]
No previous hormone therapy	208	717
No previous TURP	467	250
No incidental prostate cancer (T1a, T1b)	23	227[2]

[1] HIFU Long Term Cohort
[2] HIFU Long Term Refined Cohort

The number and percent of subjects in the HIFU Long Term Refined cohort by site is summarized in Table 42.

Table 42: Number of Subjects by Site

Site	HIFU Long Term Refined Cohort
Lyon	70.9% (161)
Munich	17.6% (40)
Regensburg	11.5% (26)
Total	227

8.2.4.2 Demographics and Baseline Characteristics

The baseline characteristics for subjects in the HIFU Long Term Refined and the HIFU Prospective Safety cohorts are summarized and presented in Table 43 along with those of the HIFU IDE cohort for ease of comparison. For the HIFU Long Term Refined cohort, the median age was 69 years (range 50 to 81). The cancer stage of subjects was either stage T1c (64.3%)

or T2a (35.7%) and most subjects were Gleason score 6 (66.5%). The median PSA was 5.8 ng/mL.

For the HIFU Prospective Safety Cohort, the median age is 71 years (range 53 to 78) and the median PSA was 6 ng/mL, while for the Long Term Refined Cohort, it is 69 years (range 50 to 81) and 5.8 ng/mL. Like the Long Term Refined Cohort, subjects in the HIFU Prospective Safety Cohort were mostly stage T1c (61%) or T2a (34%) and Gleason 6 (82%). Most subjects were treated between 2000 and 2004 (60%) and 11% received an adjuvant HIFU treatment within 365 days of the index procedure. The median available follow-up was 5.0 years.

The overall similarities of the baseline characteristics demonstrate the generalizability of the safety results of the HIFU Prospective Safety Cohort to the HIFU Long Term Refined Cohort.

Table 43: Demographic and Baseline Characteristics, HIFU IDE, HIFU Long Term Refined and HIFU Prospective Safety Cohorts

Characteristic		HIFU IDE N=135	HIFU Long Term Refined N=227	HIFU Prospective Safety N=62
Age (yrs)	Mean±SD (N) Median (Range)	64.1±6.7 (135) 63.2 (32.8, 80.0)	68.0+/-6.5 (227) 69.0 [50.0, 81.0]	70.3+/-5.6 (62) 71.0 [53.0, 78.0]
PSA	Mean±SD(N) Median (Range)	4.6±2.4 (135) 4.5 (0.3, 9.9)	5.7+/-2.4 (227) 5.8 [0.0, 10.0]	5.9+/-2.3 (62) 6.0 [0.3, 10.0]
Prostate Vol. (cc)	Mean±SD(N) Median (Range)	22.7±12.5 (134) 21.6 (9.7, 152.0)	26.7+/-11.3 (212) 24.9 [5.8, 79.0]	26.1+/-7.0 (57) 25.5 [11.7, 43.8]
Gleason Score	2	-	3.1% (7)	-
	3	-	4.4% (10)	-
	4	0.0% (0)	8.4% (19)	3.2% (2)
	5	0.0% (0)	17.6% (40)	14.5% (9)
	6	97.0% (131	66.5% (151)	82.3% (51)
	7[2]	1.5% (2)	-	-
	Not specified	1.5% (2)	-	-
Cancer Stage				
Cancer Stage	T1a	2.2% (3)	-	1.6% (1)
	T1b	2.2% (3)	-	3.2% (2)
	T1c	80.7% (109)	64.3% (146)	61.3% (38)
	T2a	14.1% (19)	35.7% (81)	33.9% (21)
	Not specified	0.7% (1)	-	-

The treatment information and follow-up time for the HIFU Long Term Refined and HIFU Prospective Safety cohorts are summarized in Table 44 below. For the HIFU Long Term Refined cohort, the earliest treatment date is 1993 and the latest is 2013. A total of 35 subjects

(15.4%) received an adjuvant HIFU treatment within one year (365 days) of the index HIFU treatment. The median follow-up time (years from initial HIFU to date of last contact or death) is 6.6 years. The year of treatment indicates the generation of device utilized. Prior to 2000, subjects were treated with the prototype, between 2000 and 2004 subjects were treated with the Ablatherm® Maxis and from 2005 forward, subjects were treated with the Ablatherm® Integrated Imaging.

Table 44: HIFU Treatment Summary HIFU Long Term Refined Cohort

Parameter		HIFU Long Term Refined Cohort N=-227	HIFU Prospective Safety Cohort N=62
HIFU Treatment Year (%) (N)	<2000	18.9% (43)	0% (0)
	2000-2004	41.0% (93)	29.0% (18)
	2005-2009	18.1% (41)	59.7% (37)
	2010-2013	22.0% (50)	11.3% (7)
Adjuvant HIFU (%) (N)		15.4% (35)	11.3% (7)
Follow-up time (years) (N)		6.4+/-4.3 (227) 6.6 [0.0, 17.1]	5.2+/-2.8 (62) 5.0 [0.3, 10.0]
Years Follow-up (N)	2 or more	179	52
	5 or more	134	31
	8 or more	94	15
	10 or more	56	0

Table 45 summarizes the differences between the three device generations. The most significant changes between the Ablatherm® Prototype and the Ablatherm® Maxis is the establishment of standard parameters for the treatment of primary prostate cancer, the introduction of treatment parameters for the treatment of salvage and repeat HIFU and the introduction of the Ablapak disposable cooling kit. The Ablatherm® Maxis and prototype have the same principles of operation and similar energy levels as the Ablatherm® Integrated Imaging device. The main difference between the devices is that the Ablatherm® Integrated Imaging device has a single imaging and treatment probe that allows for real time monitoring of the procedure and comparison of the planned treatment to the treatment being implemented. Therefore, anatomical changes (such as prostate swelling during the procedure) and internal prostate movement can be detected and accommodated with the Ablatherm® Integrated Imaging device. The two previous models had separate imaging and treatment probes embedded in the same endorectal system, which required the imaging probe to be retracted following treatment planning to allow the positioning of the treatment probe.

Table 45: Comparison of Ablatherm® Prototype, Maxis and Integrated Imaging Devices

	Ablatherm® Prototype	Ablatherm® Maxis	Ablatherm® Integrated Imaging
Treating Frequency for primary	2.25 – 3MHz	3.0 MHz	3.0 MHz
Shot Duration	4.5 to 5 seconds	5 seconds	6 seconds
Single imaging and treatment probe	No	No	Yes
Rectal wall cooling	Yes	Yes	Yes
Disposable Ablapak for improved consistency	No	Yes	Yes
Non primary treatment protocols	No	Yes	Yes

Many of the device improvements were safety related and have resulted in an improvement of the Ablatherm® safety profile with time. Thuroff et al investigated the impact of device generation safety. In their series, 170 subjects were treated with a prototype device, 358 with the Ablatherm® Maxis and 176 with the Ablatherm® Integrated Imaging. Statistical significance was not reported but a reduction in incontinence (grade 2 or 3), fistula and perineal discomfort. Rates of UTI, and obstruction requiring a second intervention remained relatively constant through device generations.

Crouzet et al (2013) examined the rates of morbidity with the different iterations of technology in a series of over 1000 patients. They observed statistically significant reductions in the rates of grade 2/3 incontinence, urinary tract infections, bladder outlet obstruction and post treatment stenosis. No statistically significant increases in morbidity were observed.

Thuroff et al (2013) also investigated the efficacy of the different device iterations. They used post treatment PSA Nadir and PSA velocity as measures of efficacy. Although neither measure represents a validated surrogate of metastasis development or prostate cancer specific survival, it can be generally stated that a lower PSA nadir and/or PSA velocity indicate a more complete ablation. They observed the Integrated® Imaging to have the lowest mean and median PSA nadir as well as the lowest median PSA velocity. This indicates the effectiveness of the device has increased with subsequent generations.

The long term report of Ganzer et al (2013) included 43 (8%), 355 (66%), and140 (26%) subjects treated with a prototype, Maxis and Integrated Ablatherms, respectively, found a statistically significant difference in post treatment bladder outlet obstruction according to HIFU device: 39.5%, 30.1% and 20.0% in patients treated with the prototype, Maxis and Integrated Imaging, respectively ($p<0.03$).

Taken as a whole, these three studies show that the changes in the device over time have resulted in a safer and more effective device. The outcomes of the HIFU Long Term Cohort and the HIFU Long Term Revised Cohort can therefore be considered to negatively biased in comparison to a series in which all patients were treated with the Ablatherm® Integrated Imaging, the subject of the PMA application. The safety and effectiveness of the Ablatherm® Integrated Imaging can be considered to be at least as effective as that of the HIFU Long Term Cohorts.

8.2.4.3 Effectiveness Results

Principal Effectiveness Endpoint: Freedom from Metastasis

Freedom from metastasis was summarized using Kaplan-Meier analyses and is shown in Figure 7 and Table 46. The date of metastasis was imputed as the midpoint between the interval of the last subject evaluation and the date of diagnosis or death due to prostate cancer. Subjects were censored at the date of death or the date of last contact. A total of 3 subjects experienced metastasis within 10 years of HIFU treatment. Overall, freedom from metastasis is 99.5% (96.3%, 99.9%), 98.2% (94.5%, 99.4%), 98.2% (94.5%, 99.4%) and 98.2% (94.5%, 99.4%) at 2, 5, 8 and 10 years post-HIFU, respectively. These freedom from metastasis rates are excellent and with their proximity to 100% are likely to compare favorably to any other treatment for low risk prostate cancer.

A limitation of the HIFU Long Term Refined Cohort is that within it bone scans were performed at the discretion of the physician. In comparison, within PIVOT bone scans were obtained at 5, 10, and 15 years or at the last visit for persons with less than 15 years of follow-up, with additional scans obtained at the clinician's discretion. This difference in approach may result in under reporting of metastasis in the Long Term HIFU Cohort. The AUA provides guidelines for bone scan prior to radiation therapy, which are "radiographic staging (CT and bone scan) is recommended for patients with a Gleason score $\geqslant$ 8 or a PSA level > 20 ng/mL prior to treatment".[39] There are no guidelines provided by either the AUA or the European Association of Urology for post treatment bone scan. However, potential metastasis after treatment is hallmarked similarly as it is prior to treatment: with a highly elevated PSA (> 20 ng/ml). All participating centers performed a bone scan on any subject with a PSA > 20 ng/ml.

Figure 7: Freedom from Metastasis HIFU Long Term Refined Cohort

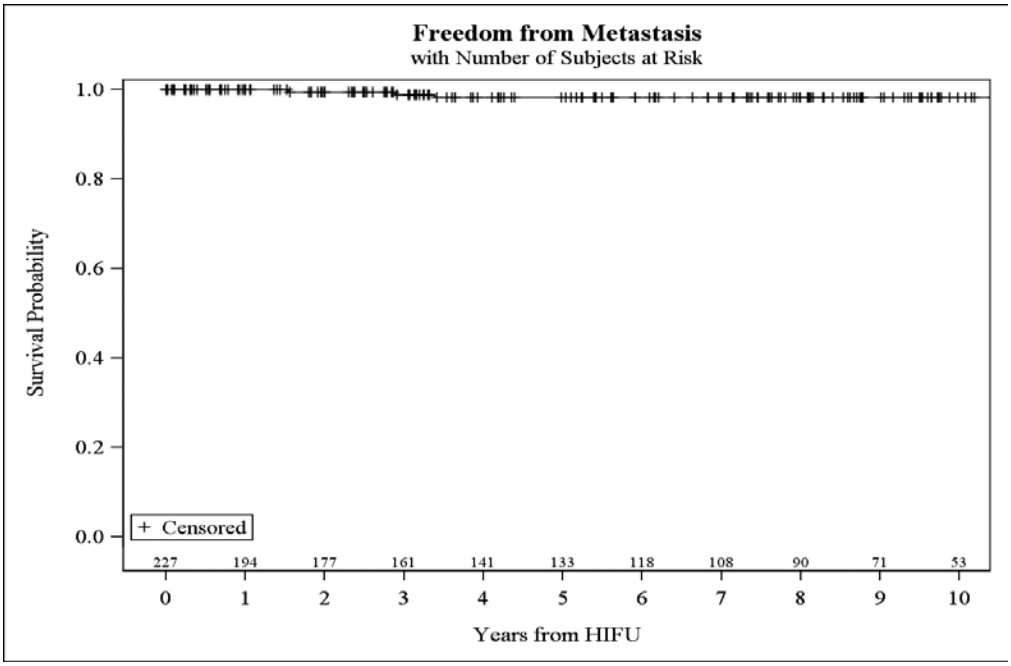

Table 46: Survival Estimates for Freedom from Metastasis HIFU Long Term Refined Cohort

Time (Years)	Number at Risk	Number Failed	Survival	Lower 95% Confidence Limit	Upper 95% Confidence Limit
1	194	0	1.0000	N/A	N/A
2	177	1	0.9947	0.9627	0.9992
5	133	3	0.9820	0.9449	0.9942
8	90	3	0.9820	0.9449	0.9942
10	53	3	0.9820	0.9449	0.9942

In addition to the survival analyses presented above, a competing risks analysis was conducted to obtain risk estimates for metastasis with the presence of the competing risk of death. The 8-year cumulative risk estimates for the primary endpoint of cancer metastasis are given in Table 47 for the HIFU Long Term Refined Cohort and the PIVOT RP Cohort. The estimates show similar rates of metastasis between the HIFU treated subjects and those with radical prostatectomy with overlapping confidence limits (1.1% with 95% CI: 0.1% to 2.0% vs. 1.4% with 95% CI: 0.4%, 4.8%). Therefore, the results of HIFU treatment are similar to those of radical prostatectomy.

Table 47: Cumulative risk estimates of metastasis at 8 years: HIFU Long Term Refined Cohort versus PIVOT RP

Cohort	Cumulative Incidence (%)	95% CI
HIFU Long Term Refined Cohort	1.1	(0.1, 2.0)
PIVOT RP Cohort	1.4	(0.4, 4.8)

Supporting Analyses

This finding is strengthened by the supporting analyses of the rates of metastasis and death from prostate cancer in the HIFU Long Term and Long Term Refined Cohorts compared to the PIVOT and SPCG-4 RP Cohorts. A summary of the supporting endpoints by cohorts is also shown in Table 48. The 10 year freedom from metastasis incidence of the HIFU Long Term Refined Cohort compared the SPCG-4 is 1.5% with 95% CI: 0.3% to 2.7% vs. 4.9% with 95% CI: 2%, 11.6%. The 8 year death from prostate cancer incidence of the HIFU Long Term Refined Cohort compared to the PIVOT is 0.4% with 95% CI: 0.0% to 1.0% vs. 1.4% with 95% CI: 0.4%, 4.8%. The 10 year death from prostate cancer incidence of the HIFU Long Term Refined Cohort compared to the SPCG-4 is 0.4% with 95% CI: 0.0% to 1.0% vs. 4.1% with 95% CI: 1.5%, 11.0%.

Table 48: Competing Risk Estimates for Metastasis and Death due to Prostate Cancer from HIFU Long-Term FDA, HIFU Long Term, PIVOT RP and SPCG-4 RP Cohorts

Effectiveness Endpoints	Cohort	Metastasis		Death from Prostate Cancer	
		Cumulative Incidence (%)	95% CI	Cumulative Incidence (%)	95% CI
8 Years	HIFU Long Term Refined	Principal		0.4	(0.0, 1.0)
	PIVOT RP			1.4	(0.4, 4.8)
10 Years	HIFU Long Term Refined	1.5	(0.3, 2.7)	0.4	(0.0, 1.0)
	SPCG-4 RP	4.9	(2.0, 11.6)	4.1	(1.5, 11.0)

Additional Supporting Analyses

Additional secondary effectiveness outcome measurements are: overall survival following Ablatherm® HIFU; cancer specific survival following Ablatherm® HIFU; and freedom from salvage treatment following Ablatherm® HIFU.

- Overall Survival

Overall survival was estimated using Kaplan-Meier analyses and is shown in Table 49. Subjects were censored at the date of last contact. A total of 18 subjects died within 10 years of HIFU treatment. Overall survival is 100%, 97.9%, 89.4% and 83.0% at 2, 5, 8 and 10 years post-HIFU, respectively.

Table 49: Survival Estimates for Overall Survival in HIFU Long Term Refined Cohort

Time (Years)	Number at Risk	Number Failed	Survival	Lower 95.00% Confidence Limit	Upper 95.00% Confidence Limit
1	194	0	1.0000	N/A	N/A
2	178	0	1.0000	N/A	N/A
5	134	3	0.9793	0.9372	0.9933
8	90	13	0.8936	0.8228	0.9371
10	53	18	0.8298	0.7393	0.8911

- Cancer Specific Survival

Cancer specific survival was estimated using Kaplan-Meier analyses and is shown in Table 50. Subjects were censored at the date of death due to causes other than prostate cancer or the date of last contact. One subject died due to prostate cancer within 10 years of HIFU treatment. Overall, cancer specific survival is 100%, 100%, 99.2% and 99.2% at 2, 5, 8 and 10 years post-HIFU, respectively.

Table 50: Survival Estimates for Cancer Specific Survival in HIFU Long Term Refined Cohort

Time (Years)	Number at Risk	Number Failed	Survival	Lower 95.00% Confidence Limit	Upper 95.00% Confidence Limit
1	194	0	1.0000	N/A	N/A
2	178	0	1.0000	N/A	N/A
5	134	0	1.0000	N/A	N/A
8	90	1	0.9916	0.9419	0.9988
10	53	1	0.9916	0.9419	0.9988

- Competing Risks Analysis

A competing risks analysis was also conducted with the outcomes of metastasis, cancer specific survival and overall survival. Table 51 presents the cumulative incidence at 1, 2, 5, 8 and 10 years for: (a) death from any cause; (b) death from prostate cancer (with death from other causes treated as competing risk); and (c) presence of metastases (with death from any cause other than prostate cancer treated as competing risk). The 10-year cumulative incidence of prostate cancer specific death is 0.4% (95% CI 0.0%, 1.0%) and metastasis is 1.5% (95% CI 0.3%, 2.7%).

Table 51: Competing Risks Analysis HIFU Long Term Refined Cohort

Risk (%)	Time (years)				
	1	2	5	8	10
Death from Any Cause	0.6 (0.1 to 1.1)	1.1 (0.4 to 1.8)	3.8 (2.3 to 5.3)	9 (6.2 to 11.6)	13.5 (9.5 to 17.3)
Death from Prostate Cancer	0 (0 to 0)	0 (0 to 0)	0.2 (0 to 0.5)	0.4 (0 to 1)	0.4 (0 to 1)
Metastases	0 (0 to 0)	0.1 (0 to 0.4)	0.7 (0.1 to 1.4)	1.1 (0.1 to 2)	1.5 (0.3 to 2.7)

- Freedom from Salvage Treatment

Freedom from salvage treatment is a clinically relevant endpoint but it difficult to contextualize. Following the standard treatments of prostatectomy and radiation therapy the initiation of salvage therapy following failure of primary prostate cancer therapy can be a complex decision process, for multiple reasons. For instance, many definitions of what constitutes a biochemical failure following both radiation and surgery have been proposed. Furthermore, many variables must be considered, such as pathologic findings at RP (seminal vesicle or margin positivity), PSA doubling time, PSA value at beginning of salvage radiation or prostatectomy, and Gleason grade. Despite this information, the decision to offer local versus systemic salvage therapy can remain challenging. No specific guidelines address indications for salvage therapy following established therapies and variation in practice are expected.[40] The decision to treat following HIFU is even more complicated.

In the Long Term Refined Cohort, salvage treatments following HIFU treatment included hormone therapy, radiotherapy and radical surgery. In addition, any HIFU treatment more than 1

year following the index HIFU treatment is considered salvage treatment. As summarized in Table 52, seventy-seven (77) subjects (33.9%) had at least one salvage treatment; 54 with one, 19 with two, 3 with 3 and 1 with 4. A summary of the number and percent of subjects with post-HIFU salvage treatment is given in Table 52 and the Kaplan-Meier survival for freedom from salvage treatment is shown in Table 53. Overall, freedom from salvage treatment was 83.0%, 65.9%, 59.8% and 51.9% at 2, 5, 8 and 10 years post-HIFU, respectively.

Table 52: Salvage Treatment Summary HIFU Long Term Refined Cohort

Salvage Treatment	Overall
Any salvage treatment	33.9% (77/227)
Repeat HIFU	18.5% (42/227)
Radiotherapy	13.2% (30/227)
Hormone therapy	10.1% (23/227)
Radical surgery	2.2% (5/227)

Table 53: Survival Estimates for Freedom from Salvage Treatment HIFU Long Term Refined Cohort

Time (Years)	Number at risk	Number Failed	Survival	Lower 95% Confidence Limit	Upper 95% Confidence Limit
1	194	7	0.9667	0.9315	0.9840
2	178	33	0.8299	0.7689	0.8760
5	134	61	0.6592	0.5833	0.7247
8	90	68	0.5984	0.5164	0.6711
10	53	73	0.5189	0.4200	0.6089

Freedom from salvage treatment is presented without comparison to PIVOT or SPCG-4 outcomes as neither trial reported rates of salvage treatment. A majority of the subjects with salvage procedures (42 of 77 or 54%) received an additional HIFU procedure, which occurred more than 12 months after the index HIFU treatment.

8.2.4.4 Safety

A total of 62 subjects in the HIFU Long Term Cohort were treated with HIFU and followed under prospective studies at the Lyon site. For this subset of subjects known as the Prospective Safety Cohort, adverse event data were collected prospectively, including assessments of intensity, the relationship to HIFU, any intervention required and the resolution of the event. This analysis of adverse events in the Prospective Safety Cohort was performed to address a request from FDA that safety and effectiveness of HIFU be assessed in the same population to facilitate the risk-benefit analysis.

The number of adverse events and the number and percent of subjects reporting the event are given by the follow-up interval and by type of event in Table 53. There are no metastasis events among the 62 subjects. The most common events were erectile dysfunction (29%), urinary tract

infection (19%) and Grade 1 urinary incontinence (24%). Most (79%) of the adverse events were reported within the first 3 months following the HIFU treatment.

Table 54: Adverse Events by Follow-up Intervals in HIFU Prospective Safety Cohort

			Number of Events and Percent of Total Events by Follow-up Interval					
Adverse Event	**# AE**	**# Subj. (% of 62)**	**≤ 1 Mo**	**3 Mo**	**6 Mo**	**12 Mo**	**24 Mo**	**>24 Mo**
Total	75	39 (63%)	33 (44%)	26 (35%)	7 (9%)	4 (6%)	4 (6%)	1 (1%)
Erectile Dysfunction	19	18 (29%)	6 (31%)	7 (37%)	3 (16%)	1 (5%)	1 (5%)	1 (5%)
Urinary Tract Infection	16	12 (19%)	5 (31%)	9 (56%)	1 (6%)	0 (0%)	1 (6%)	0 (0%)
Urinary incontinence (Grade 1)	15	15 (24%)	9 (60%)	5 (33%)	0 (0%)	0 (0%)	1 (7%)	0 (0%)
Retention	7	7 (11%)	3 (43%)	0 (0%)	2 (29%)	2 (28%)	0 (0%)	0 (0%)
Dysuria	4	4 (6%)	2 (50%)	1 (25%)	0 (0%)	0 (0%)	1 (25%)	0 (0%)
Hematuria	2	2 (3%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Urinary incontinence (Grade 2)	2	2 (3%)	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Glans infection	1	1 (2%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypertermia	1	1 (2%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Increase of rectal wall thickness	1	1 (2%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Ischemic stroke	1	1 (2%)	0 (0%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)
Polakiuria	1	1 (2%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rectal lesion seen at MRI	1	1 (2%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Rectal wall injury	1	1 (2%)	0 (0%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Retention+Hematuria	1	1 (2%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Sloughing	1	1 (2%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Urethral stenosis	1	1 (2%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Of the 75 events reported, 43 were resolved, 24 were ongoing, 1 was resolved with sequelae, and the resolution was unknown for 7 at the time of data collection. Most erectile dysfunction events were ongoing while most urinary tract infection events resolved. Six Grade 1 incontinence events were ongoing. All events of retention, dysuria and hematuria resolved.

The number of events and the number and percent of subjects reporting the event are given by the assessed relationship to HIFU overall and by type of event in Table 54. Of the 75 events reported, 46 were assessed as possibly related to HIFU while a relationship was ruled out for 2

and 27 were either not evaluable or had an unknown relationship to HIFU treatment. There were 12 events of erectile dysfunction in 11 subjects (18%), 13 events of urinary tract infection in 12 (19%) of subjects and 10 events of Grade 1 urinary incontinence in 10 subjects (16%) assessed as possibly related to HIFU treatment.

Table 55: Adverse Event Relationship to HIFU in HIFU Prospective Safety Cohort

	Relationship to HIFU							
	Possible		Not Related		Not evaluable		Unknown	
Adverse Event	# AE	# Subj (%)	# AE	# Subj (%)	# AE	# Subj (%)	# AE	# Subj (%)
Total	46	32 (52%)	2	2 (3%)	18	11 (18%)	9	6 (10%)
Erectile Dysfunction	12	11 (18%)	0	0 (0%)	5	5 (8%)	2	2 (3%)
Urinary Tract Infection	13	12 (19%)	1	1 (2%)	2	1 (2%)	0	0 (0%)
Urinary incontinence (Grade 1)	10	10 (16%)	0	0 (0%)	4	4 (6%)	1	1 (2%)
Retention	3	3 (5%)	0	0 (0%)	2	2 (3%)	2	2 (3%)
Dysuria	3	3 (5%)	0	0 (0%)	1	1 (2%)	0	0 (0%)
Hematuria	0	0 (0%)	0	0 (0%)	2	2 (3%)	0	0 (0%)
Urinary incontinence (Grade 2)	1	1 (2%)	0	0 (0%)	1	1 (2%)	0	0 (0%)
Glans infection	1	1 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Hyperthermia	0	0 (0%)	0	0 (0%)	1	1 (2%)	0	0 (0%)
Increase of rectal wall thickness	0	0 (0%)	0	0 (0%)	0	0 (0%)	1	1 (2%)
Ischemic stroke	0	0 (0%)	1	1 (2%)	0	0 (0%)	0	0 (0%)
Polakiuria	0	0 (0%)	0	0 (0%)	0	0 (0%)	1	1 (2%)
Rectal lesion seen at MRI	1	1 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Rectal wall injury	1	1 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)
Retention+Hematuria	0	0 (0%)	0	0 (0%)	0	0 (0%)	1	1 (2%)
Sloughing	0	0 (0%)	0	0 (0%)	0	0 (0%)	1	1 (2%)
Urethral stenosis	1	1 (2%)	0	0 (0%)	0	0 (0%)	0	0 (0%)

Safety Comparisons

The HIFU Prospective Safety and HIFU IDE Cohorts are compared to the PIVOT RP Cohort to establish a relative safety profile of the HIFU device. The adverse events in the large HIFU IDE Cohort were rigorously documented per the IDE protocol.

As shown in Table 56, a total of 43 procedure-related perioperative adverse events including wound infection, sepsis, transfusion, myocardial infarction, bowel injury requiring surgical repair

and 1 death, were reported only in the radical prostatectomy cohort. The rates of the perioperative adverse events such as urinary tract infection, urinary catheter, urinary retention, dysuria and hematuria were higher in the HIFU Prospective Safety Cohort than the PIVOT RP. In fact, there were no reports of urinary retention, dysuria and hematuria in the in the PIVOT RP Cohort even though these are commonly occurring events following prostate cancer treatment.

Table 56: Important Adverse Events Regardless of Relationship by Cohort

Adverse Events	HIFU IDE (n=135)	HIFU Prospective Safety (n=62)	PIVOT RP (n=280)[1] From Wilt et al 2012
Any	131 (97.0%)	39 (62.9%)	60 (21.4%)[2]
Erectile Dysfunction	91 (67.4%)	18 (29.0%)	Not Reported
Erectile Dysfunction unresolved at 2 years	60 (44.4%)	Not reported	231 (81.1%)[3]
Urinary Incontinence	52 (38.5%)	17 (27.4%)	Not Reported
Urinary Incontinence unresolved at 2 years	21 (15.6%)	Not reported	49 (17.1%)[4]
Urinary Obstruction, Stricture, Bladder Neck Contracture, Urinary Retention	81 (60.0%)	7 (11.3%)	6 (2.1%)5
Urinary Obstruction	33 (24.4%)	0	Not Reported
Urinary Stricture	26 (19.3%)	0	Not Reported
Bladder Neck Contracture	24 (17.8%)	0	Not Reported
Urinary Retention resolved by day 30	12 (8.9%)	6 (9.7%)	Not Reported
Urinary Retention not resolved by day 30 or onset ≥ 30 days	28 (20.7%)	1 (1.6%)	6 (2.1%)[5]
Perioperative Death	0	0	1 (0.4%)[2]
Perioperative Wound Infection	0	0	12 (4.3%)[2]
Perioperative Sepsis	2 (1.5%)[6]	0	3 (1.1%)[2]
Perioperative Deep Vein Thrombosis	0	0	2 (0.7%)[2]
Perioperative Stroke	0	0	1 (0.4%)[2]
Perioperative Pulmonary Embolism	0	0	2 (0.7%)[2]
Perioperative Myocardial Infarction	0	0	3 (1.1%)[2]

Adverse Events	HIFU IDE (n=135)	HIFU Prospective Safety (n=62)	PIVOT RP (n=280)[1] From Wilt et al 2012
Perioperative Renal Failure or Dialysis	0	0	1 (0.4%)[2]
Perioperative Anal Tear/Rectal Wall Injury	4 (3.0%)	1 (1.6%)	Not Reported
Perioperative Bowel injury requiring surgical repair	0	0	3 (1.1%)[2]
Perioperative additional surgical repair	0	0	7 (2.5%)[2]
Perioperative Bleeding Requiring Transfusion	0	0	6 (2.1%)[2]
Perioperative Pneumonia	0	0	2 (0.7%)[2]
Urinary Tract Infection	46 (34.1%)	12 (19.4%)	7 (2.5%)[2]

[1]Any adverse events occurring within 30 days after surgery for the 280 subjects who completed RP.

[2]Within the perioperative period of 30 days.

[3]Erectile dysfunction was defined as the patient reported inability to have an erection or an erection sufficient for vaginal penetration two years following the procedure; n=285.

[4]Urinary incontinence was defined by patient reports ("have a lot of problems with urinary dribbling," "lose larger amounts of urine than dribbling but not all day," "have no control over urine," or "have an indwelling catheter") two years following the procedure; n=287.

[5]Catheterization ≥ 30 days

[6]Both cases of Sepsis were not related to ether the device or procedure (Table 30 of the PMA Application Clinical Study Report)

Table 56 presents a combined urinary adverse event classification which includes urinary obstruction, stricture, bladder neck contracture, and urinary retention. Figure 8 presents the combined urinary adverse events by time showing the percentage of subjects with mild, moderate or severe urinary adverse events at 1, 3, 6, 9, 12, 15, 18, 21 and 24 months. The percent of subjects with a mild, moderate or severe urinary adverse event (as defined above) at 1 month was 8.25, 21.5%, and 14.1%, respectively. By 12 months this was reduced to 4.4%, 8.4% and 1.5%, respectively, for mild, moderate and severe. At 24 months, 1.5%, 5.2% and 0.7% of subjects had urinary adverse events reported as mild, moderate or severe, respectively.

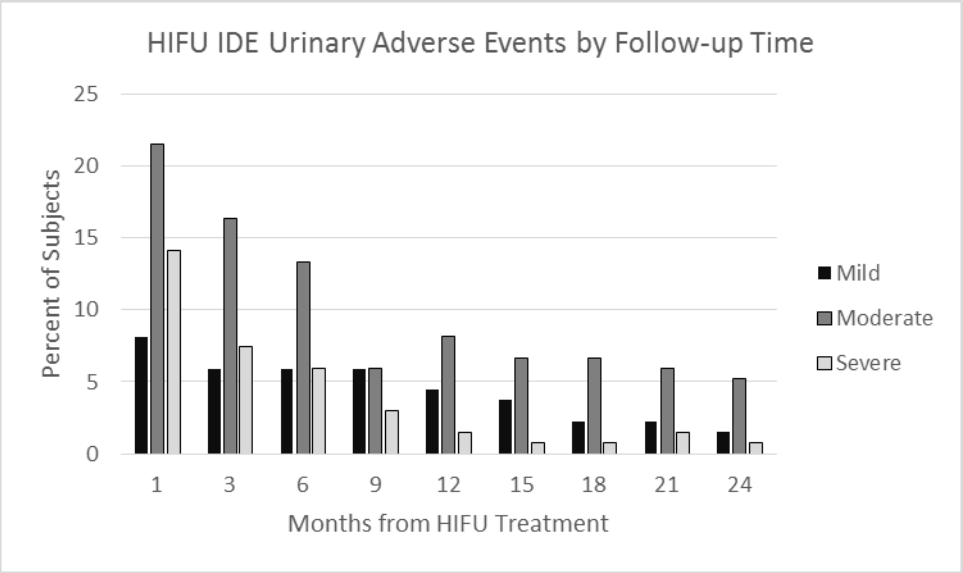

Figure 8: Urinary adverse event evolution with time including all adverse events regardless of relationship to device or procedure.

Patient reported incontinence, erectile dysfunction and bowel dysfunction following radical prostatectomy and HIFU are compared in Table 57.

Table 57: Comparison of patient reported incontinence, erectile dysfunction and bowel dysfunction, HIFU IDE and PIVOT RP Cohorts

	Visit	HIFU IDE	PIVOT RP
Incontinence	Baseline	3/134 (2.2%)	28/315 (8.9%)
	2 Years	9/109 (8.3%)	49/287 (17.1%)
Erectile Dysfunction	Baseline	37/132 (28.0%)	107/ 329 (32.5%)
	2 Years	78/107 (72.8%)	231/285 (81.1%)
Bowel Dysfunction	Baseline	3/131 (2.3%)	18/ 286 (6.3%)
	2 Years	6/107 (5.6%)	35/286 (12.2%)

The rates of incontinence (17.1%) and erectile dysfunction (81.1%) reported in the PIVOT RP Cohort at 2 years following Prostatectomy are higher than those observed in the HIFU IDE Cohort (8.3%. and 72.8%, respectively). This difference is more noteworthy in that 38% of the cases of radical prostatectomy were nerve sparing whereas none of the HIFU cases were nerve sparing. The bowel dysfunction rate (12.2%) at 2-years following radical prostatectomy in PIVOT is higher than the 5.6% observed in the HIFU IDE Cohort.

8.3 Conclusions

The HIFU Long Term Refined Cohort provided estimates of 0.4% (95% CI 0.0% to 1.0%) and 0.4% (95% CI 0.0% to 1.0%) for death due to prostate cancer at 8 and 10 years, respectively. The confidence intervals for the estimated cumulative incidence overlap with those from the PIVOT RP Cohort at 8 years and are lower than those from the SPCG-4 RP Cohort. The HIFU Long Term Refined Cohort provided estimates of 1.1% (95% CI 0.1% to 2.0%) and 1.5% (95% CI 0.3% to 2.7%) for metastasis at 8 and 10 years, respectively. The confidence intervals for the estimated cumulative incidence overlap with those from the PIVOT RP Cohort at 8 years and for the SPCG-4 RP group at 10 years. This supports the finding that HIFU treatment is similar to radical prostatectomy.

The clinical data on the Ablatherm HIFU device indicate a potential risk of retention and stricture, which are clinically manageable and usually transient. However, due to the non-invasive nature of the Ablatherm HIFU procedure, the risk of surgical adverse events is lower than with a standard of care surgical procedure (radical prostatectomy). In addition, the risk of more permanent and longer-term risks, such as erectile dysfunction and incontinence, was reduced with the use of Ablatherm HIFU device when compared to radical prostatectomy.

9 INTEGRATED EFFECTIVENESS CONCLUSIONS

9.1 Introduction

For the assessment of the intermediate-term results, EDAP compared the Ablatherm® HIFU clinical data to a performance goal (HIFU PG) derived from a literature-based meta-analysis for cryotherapy (CRYO MA). The CRYO MA cohort consisted of a systematic review of contemporary literature evidence to estimate the biochemical survival rates at 2 and 5 years and the morbidity following whole gland cryotherapy for low-risk, localized prostate cancer. Twenty-five published studies were included. In addition, the HIFU MA cohort resulting from a systematic literature review and meta-analysis of HIFU literature using the same methodology as the CRYO MA and the HIFU Registry cohort that included 115 subjects collected from a European HIFU registry using prospectively defined inclusion criteria chosen for comparability with the HIFU IDE cohort, were analyzed.

The long-term effectiveness analyses were designed to address the Agency's concern that Phoenix Biochemical Failure rate is not validated as a surrogate endpoint to assess treatments for low risk prostate cancer. Additionally, FDA requested evidence of both safety and effectiveness from the same data set. The HIFU Long Term Refined Cohort includes subjects with up to 17 years of follow-up. The freedom from metastasis rate is a critical endpoint when evaluating the effectiveness of treatment for low risk prostate cancer. Long-term data permitting analysis of this endpoint eliminates the need for surrogate endpoints. Non-surrogate based outcomes are presented at 8 and 10 years following treatment with the HIFU Ablatherm.

9.2 Intermediate Term Effectiveness: HIFU IDE vs. Performance Goal

The principal effectiveness determination is based on a comparison of the Phoenix Biochemical Survival in the HIFU IDE to the HIFU PG. The most appropriate HIFU IDE population to compare to the HIFU PG is the 24 Month Follow-up completers as the studies included in the meta-analysis of cryotherapy biochemical success report biochemical success among subjects assessed at 24 months post treatment. Therefore this HIFU IDE population of completers is equivalent to the population included in published studies from which the HIFU PG was derived.

The principal effectiveness endpoint for the intermediate-term clinical assessment was the Phoenix definition of biochemical survival (PSA nadir + 2.0 ng/ml) at 24 months of the HIFU IDE cohort compared to the HIFU PG, which is shown in Table 58. The observed 24-month Phoenix biochemical survival rate is compared to the HIFU PG of 82% using a one-sided, asymptotic binomial test of proportion. The Phoenix Biochemical Survival rate in the HIFU IDE cohort is 90.5% with a lower bound confidence limit of 85.2%, demonstrating that a biochemical survival rate of 82% or less can be ruled out (p=0.009).

Similarly, the 24-Month Phoenix Biochemical Survival rate of the HIFU MA (92%) was higher than the CRYO MA (87%). Additionally, the 24-Month Phoenix Biochemical Survival rates of the HIFU IDE cohort (90.5%), the HIFU Registry cohort (94.4%) and the HIFU MA (92%) are all similar, and the confidence limit range of the HIFU IDE falls within the ranges of both the HIFU Registry Cohort and the HIFU MA, which further demonstrates the internal consistency of the analyses. Thus, this evaluation is indicative of the effectiveness of the Ablatherm® HIFU for the treatment of low-risk, localized prostate cancer.

Table 58: Principal Effectiveness Comparison of Phoenix Biochemical Survival at 24 Months, HIFU IDE vs. HIFU PG and Supporting Effectiveness

Effectiveness Endpoints	Cohort	Biochemical Survival Rate	95% CL or Range[1]	p-value
Principal	HIFU IDE	90.5%	85.2, 95.8%	0.009
	HIFU PG	82%	n/a	
Supporting	HIFU Registry	94.4%	90.0, 98.8%	N/A
	HIFU MA	92%	74 – 98%	
	CRYO MA	87%	69 - 96%	
[1] Range of biochemical success estimates given for the HIFU MA and CRYO MA results.				

The pooled biochemical survival rates for the CRYO MA at 2 and 5 years are presented and compared to the HIFU MA results in Table 59. At two years, 10 cohorts reported biochemical survival rates for cryotherapy and 7 cohorts reported on HIFU. The pooled survival rates aggregating all biochemical failure definitions were 87% for cryotherapy and 92% for HIFU. At five years, 7 cohorts reported biochemical survival rates for cryotherapy and 6 cohorts reported on HIFU. The pooled survival rates aggregating all biochemical failure definitions were 81% for cryotherapy and 83% for HIFU.

Table 59: Biochemical Survival – All Definitions, CRYO MA and HIFU MA

Time Point	HIFU MA			CRYO MA		
	Pooled %	N Cohorts/Subjects	Range	Pooled %	N Cohorts/Subjects	Range
2 Years	92%	6/623	74% - 98%	87%	10/687	69% - 96%
5 Years	83%	6/730	66% - 88%	81%	7/429	49% - 93%

The meta-analysis estimate of biochemical survival between cryotherapy and HIFU indicates a slight advantage of HIFU over cryotherapy.

9.3 Long Term Effectiveness: HIFU Long Term Refined vs. PIVOT Radical Prostatectomy

The principal effectiveness endpoint for the long-term clinical assessment was the freedom from metastasis rate at 8 years post-treatment of the HIFU Long Term Refined cohort compared to the PIVOT RP cohort. The 8-year cumulative risk estimates for the principal endpoint of cancer metastasis are shown in Table 60 for the HIFU Long Term Refined Cohort and the PIVOT RP Cohort. The estimates show similar rates of metastasis between the HIFU treated subjects and those with radical prostatectomy with overlapping confidence limits (1.1% with 95% CI: 0.1% to 2.0% vs. 1.4% with 95% CI: 0.4%, 4.8%). Therefore, the results of HIFU treatment are similar to those of radical prostatectomy.

This finding is strengthened by the supporting analyses of the rates of metastasis and death from prostate cancer in the HIFU Long Term and Long Term Refined Cohorts compared to the PIVOT and SPCG-4 RP Cohorts. A summary of the supporting endpoints by cohorts is also shown in Table 60.

Table 60: Competing Risk Estimates for Metastasis and Death due to Prostate Cancer from HIFU Long-Term FDA, HIFU Long Term, PIVOT RP and SPCG-4 RP Cohorts

<table>
<tr><th rowspan="2">Effectiveness Endpoints</th><th rowspan="2">Cohort</th><th colspan="2">Metastasis</th><th colspan="2">Death from Prostate Cancer</th></tr>
<tr><th>Cumulative Incidence (%)</th><th>95% CI</th><th>Cumulative Incidence (%)</th><th>95% CI</th></tr>
<tr><td colspan="6">Principal</td></tr>
<tr><td rowspan="2">8 Years</td><td>HIFU Long Term Refined</td><td>1.1</td><td>(0.1, 2.0)</td><td colspan="2" rowspan="2">Supporting</td></tr>
<tr><td>PIVOT RP</td><td>1.4</td><td>(0.4, 4.8)</td></tr>
<tr><td colspan="6">Supporting</td></tr>
<tr><td rowspan="2">8 Years</td><td>HIFU Long Term Refined</td><td colspan="2" rowspan="2">Principal</td><td>0.4</td><td>(0.0, 1.0)</td></tr>
<tr><td>PIVOT RP</td><td>1.4</td><td>(0.4, 4.8)</td></tr>
<tr><td rowspan="2">10 Years</td><td>HIFU Long Term Refined</td><td>1.5</td><td>(0.3, 2.7)</td><td>0.4</td><td>(0.0, 1.0)</td></tr>
<tr><td>SPCG-4 RP</td><td>4.9</td><td>(2.0, 11.6)</td><td>4.1</td><td>(1.5, 11.0)</td></tr>
</table>

The comparison of the freedom of metastasis rate of the HIFU Long Term and Long Term Refined Cohorts to the PIVOT RP and SPCG-4 RP Cohorts provides reasonable assurance of the effectiveness of HIFU treatment of low-risk, localized prostate cancer.

9.4 Conclusions

The effectiveness of the Ablatherm® device has been demonstrated by a thorough analysis of all available scientific evidence. Although a prospective, randomized, concurrently controlled trial (RCT) is considered the gold standard for clinical evidence of safety and effectiveness, FDA may

rely on additional sources of valid scientific evidence in determining that there is a reasonable assurance that a device is safe and effective. Valid scientific evidence is defined in the Code of Federal Regulations as: "evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use" [21 CFR 860.7 (c) (2)]. The HIFU PG, HIFU Registry cohort, HIFU MA and CRYO MA meet the definition of valid, scientific evidence and were designed specifically as a control for the HIFU IDE cohort or to provide additional HIFU evidence.

The IDE study provides the largest cohort of subjects treated with HIFU and prospectively collected within a study conducted in accordance with the IDE standards in the US. The HIFU IDE cohort met the performance goal of 82% Phoenix biochemical survival at 24 months, which was derived from a meta-analysis of relevant cryotherapy literature. These results are supported by the similarity of the HIFU Registry and HIFU MA results with the HIFU IDE results. Furthermore, the results of the HIFU Registry cohort and the HIFU meta-analysis provide real world evidence of the effectiveness of the device at 2 and 5 years post-treatment. This real world evidence is often not available prior to premarket approval of a device.

Principal and supportive effectiveness endpoints were calculated in order to provide a comprehensive review of the study results and to present the originally defined effectiveness success and other clinically relevant definitions of success. Biochemical success is widely used as an effectiveness endpoint for prostate cancer treatment in the literature and is the basis of the AUA Prostate Cancer Treatment Guidelines. The definition of biochemical survival selected prior to data analysis as the principal effectiveness endpoint for this report was Phoenix Biochemical Survival, which was included as a secondary endpoint in the original HIFU IDE study.

Long-term clinical evaluation of the European experience with the EDAP Ablatherm® Integrated Imaging HIFU device showed a 99.5% freedom from metastasis rate (non-surrogate endpoint) at 2 years and 98.2% at 5, 8 and 10 years post-HIFU, respectively. These freedom from metastasis rates are excellent, and their proximity to 100% compares favorably to any other treatment for low risk prostate cancer. The 8-year cumulative risk estimates for the primary endpoint of cancer metastasis show similar rates of metastasis between the HIFU treated subjects and those with radical prostatectomy from the PIVOT study with overlapping confidence limits (1.1% with 95% CI: 0.1% to 2.0% vs. 1.4% with 95% CI: 0.4%, 4.8%). Therefore, the results of HIFU treatment are similar to those of radical prostatectomy.

In total, EDAP has presented the results of treatment with the Ablatherm® HIFU from prospective clinical trials, retrospective data collected from real world experience and a meta-analysis of published data. The principal endpoint for intermediate effectiveness, the Phoenix Biochemical Survival rate, demonstrated that the HIFU IDE, and HIFU MA Cohorts were similar. Additionally, the principal endpoint for longer-term success, the rate of freedom from metastasis at 8 years, demonstrated that the HIFU Long Term Refined Cohort was similar to that of the PIVOT RP Cohort. Secondary effectiveness endpoints were consistent with and supported the findings of the principal effectiveness endpoints.

All subjects analyzed in the prospective and retrospective cohorts were selected according to predefined inclusion and exclusion criteria without consideration of results. The analyses were conducted in accordance with predefined statistical analysis plans by independent statisticians following best statistical practices.

The data presented in this PMA represent a thorough analysis of all available data to evaluate a novel prostate cancer therapy. The long-term analyses eliminate the need for surrogate endpoints. Furthermore, this unique body of evidence offers additional assurance of safety and effectiveness not typically provided from a randomized controlled trial with 2 years of follow-up. Finally, the totality of the primary and supportive evidence presented in the PMA provides a reasonable assurance of the safety and effectiveness of the Ablatherm® HIFU device for the treatment of low-risk, localized prostate cancer.

10 INTEGRATED SAFETY CONCLUSIONS

10.1 Introduction

For the principal assessment of safety, the safety of the HIFU IDE and HIFU Prospective Safety cohorts were compared to the PIVOT RP cohort. Supporting evidence of safety is provided by a comparison of the HIFU MA and CRYO MA cohorts.

10.2 Adverse Events Reported in the Literature

The median, interquartile range and range of adverse event rates reported the HIFU MA are presented in Table 61. The most frequently reported adverse event for the CRYO MA is erectile dysfunction. The median rate is higher in the CRYO MA (70.0) than in the HIFU MA (43.2). The median rates for obstruction are similar for the CRYO MA (14.8) and the HIFU MA (17.3). Likewise, the median rate of incontinence is 7.5 for the CRYO MA and 8.5 for the HIFU MA. The median rates of retention and stricture were higher in the HIFU MA (13.9 and 10.8) than in the CRYO MA (4.2 and 0). The median rate of fistula was 0.1 in the CRYO MA and 0 in the HIFU MA.

The incidence of urinary events, clinically manageable and usually transient, was higher in the HIFU MA cohort while the incidence of erectile dysfunction and fistula were higher in the CRYO MA cohort. The lower rate of erectile dysfunction following HIFU is a compelling factor in support of Ablatherm® HIFU treatment, especially to younger, sexually active men.

Table 61: Comparison of Adverse Event Rates, HIFU MA vs. CRYO MA

Adverse Events	HIFU MA			CRYO MA		
	Median [IQR] Rate (%)	Range	Articles Included	Median [IQR] Rate (%)	Range	Articles Included
Erectile Dysfunction	43.2 [36.3, 50.0]	13.0 – 77.1	9	70.0 [53.0, 89.8]	25.2 – 100	17
Incontinence	8.5 [6.2, 15.6]	0.0 – 20.0	12	7.5 [3.9, 17.2]	0.9 – 32.0	23
Retention	13.9 [7.4 – 19.3]	3.6 – 20.0	4	4.2 [2.2, 9.5]	0.0 – 22.0	12
Obstruction	17.3 [12.9, 20.2]	4.0 – 24.5	4	14.8 [11.9, 21.8]	9.0 – 28.7	3
Stricture	10.8 [7.3, 14.7]	3.2 – 21.7	6	0.0 [0.0, 5.2]	0.0 – 17.0	5
Fistula	0.0 [0.0, 0.6]	0.0 – 1.2	3	0.1 [0.0, 0.5]	0.0 – 1.9	15

10.3 HIFU Vs. Radical Prostatectomy

To assess safety, the adverse events from the HIFU Prospective Safety Cohort and HIFU IDE cohort were compared to the PIVOT RP Cohort. As shown in Table 62, a number of serious adverse events, including wound infection, sepsis, transfusion, myocardial infarction, bowel injury requiring surgical repair and 1 death were procedure-related and reported only in the radical prostatectomy cohort. The rates of the perioperative adverse events such as urinary tract infection, urinary catheter, urinary retention, dysuria and hematuria were higher in one or both of the HIFU Cohorts than the PIVOT RP Cohort. The 2-year postoperative adverse event rates of urinary incontinence unresolved at 2 years, erectile dysfunction and bowel injury were lower in both the HIFU Prospective Safety and HIFU IDE Cohorts than the PIVOT RP Cohort.

Table 62: Important Adverse Events Regardless of Relationship, HIFU IDE, HIFU Prospective Safety and PIVOT RP Cohorts

Adverse Events	HIFU IDE (n=135)	HIFU Prospective Safety (n=62)	PIVOT RP (n=280)[1] From Wilt et al 2012
Any	131 (97.0%)	39 (62.9%)	60 (21.4%)[2]
Erectile Dysfunction	91 (67.4%)	18 (29.0%)	Not Reported
Erectile Dysfunction unresolved at 2 years	60 (44.4%)	Not reported	231 (81.1%)[3]
Urinary Incontinence	52 (38.5%)	17 (27.4%)	Not Reported
Urinary Incontinence unresolved at 2 years	21 (15.6%)	Not reported	49 (17.1%)[4]
Urinary Obstruction	33 (24.4%)	0	Not Reported
Urinary Stricture	26 (19.3%)	0	Not Reported
Bladder Neck Contracture	24 (17.8%)	0	Not Reported
Urinary Retention resolved by day 30	12 (8.9%)	6 (9.7%)	Not Reported
Urinary Retention not resolved by day 30 or onset ≥ 30 days	28 (20.7%)	1 (1.6%)	6 (2.1%)[5]
Perioperative Death	0	0	1 (0.4%)[2]
Perioperative Wound Infection	0	0	12 (4.3%)[2]
Perioperative Sepsis	2 (1.5%)[6]	0	3 (1.1%)[2]
Perioperative Deep Vein Thrombosis	0	0	2 (0.7%)[2]
Perioperative Stroke	0	0	1 (0.4%)[2]
Perioperative Pulmonary	0	0	2 (0.7%)[2]

Adverse Events	HIFU IDE (n=135)	HIFU Prospective Safety (n=62)	PIVOT RP (n=280)[1] From Wilt et al 2012
Embolism			
Perioperative Myocardial Infarction	0	0	3 (1.1%)[2]
Perioperative Renal Failure or Dialysis	0	0	1 (0.4%)[2]
Perioperative Anal Tear/Rectal Wall Injury	4 (3.0%)	1 (1.6%)	Not Reported
Perioperative Bowel injury requiring surgical repair	0	0	3 (1.1%)[2]
Perioperative additional surgical repair	0	0	7 (2.5%)[2]
Perioperative Bleeding Requiring Transfusion	0	0	6 (2.1%)[2]
Perioperative Pneumonia	0	0	2 (0.7%)[2]
Urinary Tract Infection	46 (34.1%)	12 (19.4%)	7 (2.5%)[2]

[1]Any adverse events occurring within 30 days after surgery for the 280 subjects who completed RP.

[2]Within the perioperative period of 30 days.

[3]Erectile dysfunction was defined as the patient reported inability to have an erection or an erection sufficient for vaginal penetration two years following the procedure; n=285.

[4]Urinary incontinence was defined by patient reports ("have a lot of problems with urinary dribbling," "lose larger amounts of urine than dribbling but not all day," "have no control over urine," or "have an indwelling catheter") two years following the procedure; n=287.

[5]Catheterization ≥ 30 days

[6]Both cases of Sepsis were not related to ether the device or procedure (Table 30 of the PMA Application Clinical Study Report)

10.4 Quality of Life Measures

Summaries of quality of life parameters indicate that quality of life for the Ablatherm® HIFU subjects improve over time following HIFU treatment, although as expected for all definitive local therapies for prostate cancer, they never achieve the pre-treatment level.

10.5 Conclusions

The safety of the Ablatherm® device has been demonstrated by an analysis of the adverse events reported in the HIFU IDE. There were no deaths that were considered related to the investigational device or procedure. There was one adverse event of bladder neck contracture/urinary stricture that was reported by the investigator as a UADE, despite being

listed in the protocol as a potential complication. It was treated by the removal of a non-approved device used with the catheter. Of the adverse events reported as possibly, probably or definitely related to the Ablatherm® device or procedure, the vast majority (82%) resolved, and approximately half (51%) were of mild severity. None of the adverse events that were reported as possibly, probably or definitely related to the investigational device or procedure represented previously unknown risks, or new or different types of adverse events than those typically reported for HIFU and cryotherapy treatments for low-risk, localized prostate cancer. Based on the meta-analysis results, HIFU has higher potential risk of urinary events than cryotherapy; however, these events are usually clinically manageable and transient. These urinary events are not unexpected as the urethra, positioned in the center of the prostate, is intentionally ablated during HIFU treatment to ensure ablation of all cancer close to and in contact with the urethra. HIFU has a lower potential risk of erectile dysfunction, a longer-term, more permanent impairment than cryotherapy.

Additionally, the safety of the Ablatherm® device has been demonstrated by an analysis of the adverse events reported in the long-term European HIFU experience (HIFU Prospective Safety cohort) compared to those reported in the radical prostatectomy arm of the PIVOT study (PIVOT RP cohort). Consistent with meta-analysis results, the HIFU IDE and HIFU Prospective Safety results indicate a higher potential risk of transient, clinically manageable urinary events and lower rate of longer-term, more permanent erectile dysfunction than radical prostatectomy. Of note, a number of potentially life-threatening adverse events that are observed following radical prostatectomy are not observed following HIFU due to the minimally-invasive nature of the Ablatherm® HIFU procedure. Specifically, no deaths were reported following HIFU treatment. Additionally, no device or procedure–related cases of wound infection, bleeding requiring transfusion, additional surgical repair, sepsis, deep vein thrombosis, stroke, pulmonary embolism, myocardial infarction, renal failure or bowel injury requiring surgical repair were reported in the HIFU IDE or HIFU Prospective Safety Cohorts.

Overall, the risk of more permanent and longer-term risks, such as erectile dysfunction, was reduced with the use of Ablatherm® HIFU device when compared to the use of a control device (cryotherapy) and a standard of care procedure (radical prostatectomy).

The consistency in the types of adverse events collected in the HIFU Cohorts affords assurance that the risks of the Ablatherm® HIFU are known.

The Ablatherm® HIFU is a minimally invasive treatment option for low risk prostate cancer that compares favorably in terms of erectile dysfunction to both cryotherapy and radical prostatectomy. For men for whom surgery is too risky or for whom the potential side effects of the currently available treatments are not attractive, the Ablatherm® HIFU provides an alternative treatment that is safe and effective.

11 RISK-BENEFIT ANALYSIS

The clinical data presented in this PMA includes intermediate-term results with a surrogate endpoint that is widely used in the scientific literature, the Phoenix definition of biochemical survival, at two years, and long-term results with a non-surrogate endpoint, metastasis free survival, at 8 years. Multiple data sources are presented and compared including an IDE study, prospective and retrospective data from European studies and databases and systematic reviews and meta-analyses of the literature. These data sets and their analyses form an internally consistent body of evidence supporting the safety and effectiveness of Ablatherm® HIFU upon which an assessment of risk-benefit can be made.

11.1 Assessment of Benefit

11.1.1 Benefit of a Minimally-Invasive Procedure

The minimally invasive Ablatherm® Integrated Imaging HIFU treatment is delivered in a single treatment and does not necessarily require hospital stay. Importantly, is not associated with the relatively rare but severe perioperative adverse events that are observed following radical prostatectomy. These include perioperative wound infection, sepsis, transfusion, myocardial infarction, bowel injury requiring surgical repair and death which were only observed in the radical prostatectomy cohort. There were no HIFU treatment or procedure related deaths reported in any of the data sources included in the PMA. HIFU offers convenience to the patient and avoidance of serious adverse events associated with radical prostatectomy.

11.1.2 Benefit of Precise Energy Delivery and Automated Safety Features

The Ablatherm® Integrated Imaging Device incorporates novel technology to treat localized, low-risk prostate cancer. Its transducer is sharply focused, allowing low intensity level at the transducer surface (5 watts/cm²) and high intensity level at the focus point (more than 5000 watts/cm²), thus preserving the intervening tissue. The small focal dimensions allow a precise thermal energy deposition with immediate, sharp delineation between treated and untreated tissue. The Ablatherm® Integrated Imaging has a number of safety features which include in line ultrasound monitoring which provides continuous visualization of the ultrasound beam path from the transducer to the focal point, a treatment planning tool, automatic detection of unintended probe movement prior to each ultrasound delivery, a patient movement detector and software driven controls. Thus, the product's novel technology and features, allow for the precise application of the HIFU technology for safe ablation of the prostate.

11.1.3 Benefit of Definitive Local Therapy

The American Urological Association recognizes both active surveillance and definitive treatment of low-risk localized prostate cancer (Thompson et al 2007[41]). The latter is, in part, a reflection of the understaging and undergrading of low risk prostate cancer. Although active surveillance may be an attractive treatment option for men with low risk prostate cancer, its choice carries the risk of not treating a cancer that is actually more aggressive than was diagnosed. HIFU is a definitive local therapy.

11.1.4 Benefit of Cancer Control

Clinical evaluation of the EDAP Ablatherm® Integrated Imaging HIFU device for the treatment of low-risk, localized prostate cancer showed a comparable biochemical survival (Phoenix definition, surrogate endpoint) as compared to a control procedure (cryotherapy) in the intermediate-term assessment (2 years post procedure) and a high freedom from metastasis rate (non-surrogate endpoint) comparable to a standard of care procedure (radical prostatectomy) in the long-term assessment (8 years post procedure). Results from the analyses and comparisons of secondary endpoints for the assessment of prostate cancer treatment success demonstrate consistency with the analysis of the intermediate and long-term principal endpoints. Thus, the EDAP Ablatherm® Integrated Imaging HIFU device is effective in providing cancer control, as compared to a control procedure or the standard of care, for the treatment of low-risk localized prostate cancer.

11.1.5 Benefit of Preserving Erectile Function

Comparing adverse events in the literature demonstrated the incidence of erectile dysfunction following HIFU to be lower than the incidence following cryotherapy. Comparison of prospective cohorts demonstrated the incidence of erectile dysfunction is also lower following HIFU in comparison to radical prostatectomy. The lower rate of erectile dysfunction following HIFU is a compelling factor in support of Ablatherm® HIFU treatment, especially to younger, sexually active men.

11.1.6 Benefit of Preservation of Treatment Options

Disease recurrence is possible following all prostate cancer therapies. Treatment with HIFU, however, does not result in a therapeutic impasse as subsequent definitive local therapy with other standard of care treatments such as cryotherapy, brachytherapy, external beam radiation therapy and radical prostatectomy remain viable options.

11.2 Assessment of Risk

The Ablatherm® Integrated Imaging (or its very similar prior models) has been used outside of the U.S. for over 15 years with more than 40,000 HIFU treatments administered. The literature search conducted for the HIFU MA cohort found 13 peer-reviewed articles on well-controlled studies of HIFU treatment in men with localized, low-risk prostate cancer. The safety of this device is well documented and understood.

11.2.1 Risk of adverse events

All therapeutic procedures for the treatment of prostate cancer have their own set of risks. There was a higher potential risk of urinary events, such as incontinence, retention, obstruction and stricture, reported with the use of Ablatherm® HIFU device when compared to the use of a control device (cryotherapy) and a standard of care procedure (radical prostatectomy). However, these urinary events are clinically manageable and usually transient. The increased urinary adverse events following HIFU in comparison to cryotherapy are likely related to the ablation of the urethra and adjacent tissue. During cryotherapy, the urethra is preserved with a warming device which may also preserve periurethral tissue which often harbors cancer. The is also a potential risk of long-term erectile dysfunction but this was lower following HIFU treatment compared to cryotherapy and radical prostatectomy.

11.3 Conclusions

In the intermediate-term, the Phoenix biochemical survival rate in subjects treated with HIFU was comparable to cryotherapy. Additionally, the HIFU results from the IDE study were found to be consistent with the results from a literature review and meta-analysis as well as a European HIFU registry. The longer-term the freedom from metastasis rate of subjects treated with HIFU is similar to that of radical prostatectomy. Based on the totality of evidence, the EDAP Ablatherm® Integrated Imaging HIFU device is effective in providing cancer control, as compared to a control procedure or the standard of care, for the treatment of low-risk localized prostate cancer. There are several benefits to HIFU which include the preservation of future treatment options if needed due to local recurrence, the precise energy delivery and automated safety features of the Ablatherm® HIFU device, the minimally invasive nature of the procedure resulting in an avoidance of serious surgical adverse events and the reduced rates of erectile dysfunction.

The potential risks of HIFU include higher rates of clinically manageable, usually transient urinary events. There is also a potential risk of long-term erectile dysfunction but this was lower following HIFU treatment compared to cryotherapy and radical prostatectomy.

The consistency in the types of adverse events collected in the HIFU IDE and HIFU Prospective Safety cohorts with those reported in the literature affords assurance that the risks of the Ablatherm® HIFU are known.

There is a need for a treatment for low-risk prostate cancer that provides equivalent effectiveness to standard treatments, avoids serious perioperative surgical adverse events and preserves erectile function. The Ablatherm® HIFU is a minimally invasive treatment option for low risk prostate cancer that compares favorably in terms of erectile dysfunction to both cryotherapy and radical prostatectomy. For men for whom surgery is too risky or for whom the potential side effects of the currently available treatments are not attractive, the Ablatherm® HIFU provides an alternative treatment that is safe and effective. The probable benefits of Ablatherm® HIFU outweigh the probable risks.

12 APPENDICES

Appendix 1: Listing of all Adverse Events

Table 63: Device/Procedure Related Adverse Events by Severity and Status, HIFU IDE Cohort

			Severity						Status						Severity for Ongoing					
	Overall (N=135)		Mild		Moderate		Severe		Resolved		Ongoing		Perm. Dis./Imp.		Mild		Moderate		Severe	
Adverse Event	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.
Any Adverse Event	755	95.6% (129)	386	80.7% (109)	273	72.6% (98)	96	34.1% (46)	616	93.3% (126)	137	59.3% (80)	2	1.5% (2)	61	28.1% (38)	59	37.0% (50)	17	11.9% (16)
Erectile Dysfunction	93	66.7% (90)	21	14.8% (20)	48	35.6% (48)	24	17.0% (23)	34	24.4% (33)	58	43.0% (58)	1	0.7% (1)	8	5.9% (8)	36	26.7% (36)	14	10.4% (14)
Incontinence	57	35.6% (48)	43	28.1% (38)	12	8.9% (12)	2	1.5% (2)	42	28.9% (39)	15	11.1% (15)	0	0	11	8.1% (11)	2	1.5% (2)	2	1.5% (2)
Urinary Retention	49	25.9% (35)	4	3.0% (4)	18	12.6% (17)	27	13.3% (18)	46	24.4% (33)	3	2.2% (3)	0	0	0	0	3	2.2% (3)	0	0
Perineal/Penile/ Rectal/Prostate Pain	46	25.2% (34)	29	18.5% (25)	16	9.6% (13)	1	0.7% (1)	43	23.7% (32)	3	2.2% (3)	0	0	2	1.5% (2)	1	0.7% (1)	0	0
Hematuria	43	28.9% (39)	34	24.4% (33)	9	5.9% (8)	0	0	43	28.9% (39)	0	0	0	0	0	0	0	0	0	0
Urinary Tract Infection	42	25.2% (34)	19	12.6% (17)	23	12.6% (17)	0	0	42	25.2% (34)	0	0	0	0	0	0	0	0	0	0
Bladder Urgency	38	24.4% (33)	23	15.6% (21)	13	9.6% (13)	2	1.5% (2)	28	18.5% (25)	10	7.4% (10)	0	0	7	5.2% (7)	3	2.2% (3)	0	0
Other	37	23.7% (32)	20	14.1% (19)	14	9.6% (13)	3	2.2% (3)	28	17.8% (24)	9	6.7% (9)	0	0	4	3.0% (4)	4	3.0% (4)	1	0.7% (1)
Urinary Stricture	36	18.5% (25)	5	3.7% (5)	24	14.1% (19)	7	4.4% (6)	33	17.8% (24)	2	0.7% (1)	1	0.7% (1)	1	0.7% (1)	1	0.7% (1)	0	0
Slow Stream	35	23.0% (31)	30	20.0% (27)	5	3.7% (5)	0	0	29	19.3% (26)	6	4.4% (6)	0	0	6	4.4% (6)	0	0	0	0

			Severity						Status						Severity for Ongoing					
	Overall (N=135)		Mild		Moderate		Severe		Resolved		Ongoing		Perm. Dis./Imp.		Mild		Moderate		Severe	
Adverse Event	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.
Bladder Neck Contracture	34	17.8% (24)	10	4.4% (6)	12	8.1% (11)	12	7.4% (10)	33	17.0% (23)	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0
Dysuria	27	17.8% (24)	17	11.1% (15)	10	6.7% (9)	0	0	26	17.0% (23)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0
Bladder Spasms	26	17.8% (24)	17	11.9% (16)	8	5.9% (8)	1	0.7% (1)	26	17.8% (24)	0	0	0	0	0	0	0	0	0	0
Obstruction (2-17 days Post Op)	25	17.0% (23)	7	4.4% (6)	11	8.1% (11)	7	5.2% (7)	25	17.0% (23)	0	0	0	0	0	0	0	0	0	0
Urinary Frequency	23	15.6% (21)	14	10.4% (14)	8	5.9% (8)	1	0.7% (1)	14	10.4% (14)	9	6.7% (9)	0	0	5	3.7% (5)	4	3.0% (4)	0	0
Nocturia	17	11.1% (15)	12	8.9% (12)	5	3.7% (5)	0	0	9	6.7% (9)	8	5.9% (8)	0	0	6	4.4% (6)	2	1.5% (2)	0	0
Urethral Sloughing	17	12.6% (17)	13	9.6% (13)	2	1.5% (2)	2	1.5% (2)	13	9.6% (13)	4	3.0% (4)	0	0	4	3.0% (4)	0	0	0	0
Scrotal Swelling	12	8.1% (11)	9	6.7% (9)	3	2.2% (3)	0	0	12	8.1% (11)	0	0	0	0	0	0	0	0	0	0
Perineal/Penile/Rectal /Prostate Discomfort	11	8.1% (11)	9	6.7% (9)	2	1.5% (2)	0	0	10	7.4% (10)	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0
Bladder Outlet Obstruction	9	6.7% (9)	1	0.7% (1)	6	4.4% (6)	2	1.5% (2)	8	5.9% (8)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0
Blood at tip of penis / urethral bleeding	7	5.2% (7)	7	5.2% (7)	0	0	0	0	7	5.2% (7)	0	0	0	0	0	0	0	0	0	0
Constipation	7	5.2% (7)	1	0.7% (1)	6	4.4% (6)	0	0	6	4.4% (6)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0
Incomplete Bladder Emptying	7	5.2% (7)	6	4.4% (6)	1	0.7% (1)	0	0	6	4.4% (6)	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0

			Severity						Status						Severity for Ongoing					
	Overall (N=135)		Mild		Moderate		Severe		Resolved		Ongoing		Perm. Dis./Imp.		Mild		Moderate		Severe	
Adverse Event	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.
Urinary Obstruction	5	3.0% (4)	2	1.5% (2)	2	1.5% (2)	1	0.7% (1)	5	3.0% (4)	0	0	0	0	0	0	0	0	0	0
Anal Tear	4	3.0% (4)	4	3.0% (4)	0	0	0	0	4	3.0% (4)	0	0	0	0	0	0	0	0	0	0
Back Pain	4	3.0% (4)	4	3.0% (4)	0	0	0	0	4	3.0% (4)	0	0	0	0	0	0	0	0	0	0
Fatigue	4	3.0% (4)	3	2.2% (3)	0	0	1	0.7% (1)	4	3.0% (4)	0	0	0	0	0	0	0	0	0	0
Urinary Hesitancy	4	2.2% (3)	3	1.5% (2)	0	0	1	0.7% (1)	4	2.2% (3)	0	0	0	0	0	0	0	0	0	0
Abdominal Pain/discomfort	3	1.5% (2)	1	0.7% (1)	2	1.5% (2)	0	0	3	1.5% (2)	0	0	0	0	0	0	0	0	0	0
Bladder stone	3	2.2% (3)	1	0.7% (1)	1	0.7% (1)	1	0.7% (1)	3	2.2% (3)	0	0	0	0	0	0	0	0	0	0
Catheter Discomfort / Incision Pain	3	2.2% (3)	2	1.5% (2)	1	0.7% (1)	0	0	3	2.2% (3)	0	0	0	0	0	0	0	0	0	0
Diarrhea	3	2.2% (3)	2	1.5% (2)	1	0.7% (1)	0	0	3	2.2% (3)	0	0	0	0	0	0	0	0	0	0
Epididymitis	3	2.2% (3)	0	0	3	2.2% (3)	0	0	3	2.2% (3)	0	0	0	0	0	0	0	0	0	0
Penile Tip Irritation or Redness	3	1.5% (2)	2	0.7% (1)	1	0.7% (1)	0	0	3	1.5% (2)	0	0	0	0	0	0	0	0	0	0
Urinary Urgency	3	2.2% (3)	3	2.2% (3)	0	0	0	0	1	0.7% (1)	2	1.5% (2)	0	0	2	1.5% (2)	0	0	0	0
Catheter Clog / Malfunction	2	1.5% (2)	0	0	1	0.7% (1)	1	0.7% (1)	2	1.5% (2)	0	0	0	0	0	0	0	0	0	0

			Severity						Status						Severity for Ongoing					
	Overall (N=135)		Mild		Moderate		Severe		Resolved		Ongoing		Perm. Dis./Imp.		Mild		Moderate		Severe	
Adverse Event	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.
Hemorrhoidal Pain	2	1.5% (2)	2	1.5% (2)	0	0	0	0	2	1.5% (2)	0	0	0	0	0	0	0	0	0	0
Irritative Urinary Voiding Symptoms	2	1.5% (2)	1	0.7% (1)	1	0.7% (1)	0	0	2	1.5% (2)	0	0	0	0	0	0	0	0	0	0
Nausea	2	1.5% (2)	1	0.7% (1)	1	0.7% (1)	0	0	2	1.5% (2)	0	0	0	0	0	0	0	0	0	0
Pelvic Pain	2	1.5% (2)	1	0.7% (1)	1	0.7% (1)	0	0	1	0.7% (1)	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0
Rectal Bleed	2	1.5% (2)	1	0.7% (1)	1	0.7% (1)	0	0	2	1.5% (2)	0	0	0	0	0	0	0	0	0	0
Hernia	1	0.7% (1)	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Penile Discharge	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Penile Numbness	1	0.7% (1)	1	0.7% (1)	0	0	0	0	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0

The 37 adverse events described as “Other” are summarized in Table 64. With the exception of pyuria with 2 reported events, the remaining adverse events described as “Other” were each reported only once during the IDE study. More than half (20) were mild in severity, 28 resolved and none resulted in permanent impairment or death.

Table 64: Device/Procedure Related Adverse Events - Other, HIFU IDE Cohort

	Overall (N=135)		Severity						Status						Severity for Ongoing					
			Mild		Moderate		Severe		Resolved		Ongoing		Perm. Dis./Imp.		Mild		Moderate		Severe	
Adverse Event	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.
Any Other Event	37	23.7% (32)	20	14.1% (19)	14	9.6% (13)	3	2.2% (3)	28	17.8% (24)	9	6.7% (9)	0	0	4	3.0% (4)	4	3.0% (4)	1	0.7% (1)
Pyuria	2	1.5% (2)	1	0.7% (1)	0	0	1	0.7% (1)	1	0.7% (1)	1	0.7% (1)	0	0	0	0	0	0	1	0.7% (1)
Bloody Stool	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Buttock/Leg/ Thigh Pain	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Chills	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Clots	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Deep Pelvic Pain on Standing	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Discomfort in Penis at Start of Urination	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Early Detumescence	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0
Fever	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Granulomatous Prostatitis	1	0.7% (1)	1	0.7% (1)	0	0	0	0	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0
Increased Rectal Prostatic Space	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
: Inflammation	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Irritated bowel movement	1	0.7% (1)	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
L Side Flank Pain	1	0.7% (1)	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
LUTS	1	0.7% (1)	1	0.7% (1)	0	0	0	0	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0
Malaise	1	0.7% (1)	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0

			Severity						Status						Severity for Ongoing					
	Overall (N=135)		Mild		Moderate		Severe		Resolved		Ongoing		Perm. Dis./Imp.		Mild		Moderate		Severe	
Adverse Event	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.
Meatal Stenosis	1	0.7% (1)	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Narrowing distal prostatic urethra	1	0.7% (1)	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Occasional Pain Post-Coitally	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Penoscrotal Edema	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Peyronie's disease	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0
Prostate Obstruction	1	0.7% (1)	1	0.7% (1)	0	0	0	0	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0
Prostatic Atrophy	1	0.7% (1)	1	0.7% (1)	0	0	0	0	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0
Prostatic Inflammation with Calculi	1	0.7% (1)	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
R Hip Pain	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Rash (Allergy to Antibiotic)	1	0.7% (1)	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Recurrent Prostate Cancer	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0
Rising PSA	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0
Submucosal Hematomas in Prostatic Urethra	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Swelling of Foreskin	1	0.7% (1)	0	0	0	0	1	0.7% (1)	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0

			Severity						Status						Severity for Ongoing					
	Overall (N=135)		Mild		Moderate		Severe		Resolved		Ongoing		Perm. Dis./Imp.		Mild		Moderate		Severe	
Adverse Event	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.	# AEs	% Subj.
Tissue flap in left distal prostate urethra	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Unable to Empty Bladder	1	0.7% (1)	1	0.7% (1)	0	0	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Urethral Perforation	1	0.7% (1)	0	0	0	0	1	0.7% (1)	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Urethral tissue inflammation	1	0.7% (1)	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Urinary restriction	1	0.7% (1)	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0
Vomiting	1	0.7% (1)	0	0	1	0.7% (1)	0	0	1	0.7% (1)	0	0	0	0	0	0	0	0	0	0

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