FDA Executive Summary

Prepared for the July 30, 2014 meeting
of the Gastroenterology and
Urology Devices Panel

P130003
EDAP Technomed, Inc.

Ablatherm® Integrated Imaging
High Intensity Focused Ultrasound (HIFU)

Division of Reproductive, Gastro-Renal, and Urological Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

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List of Abbreviations Used

Abbreviation	Definition
AE	Adverse Event
AP	Anterior-Posterior
ASTRO	American Society for Therapeutic Radiation and Oncology
CFR	Code of Federal Regulations
CRYO	Cryotherapy
DRE	Digital Rectal Exam
EBRT	External Beam Radiotherapy
HIFU	High Intensity Focused Ultrasound
IDE	Investigational Device Exemption
IIEF	International Index of Erectile Function
IPSS	International Prostate Symptom Score
IRB	Institutional Review Board
ITT	Intent-to-Treat
MHz	Megahertz
PAS	Post-Approval Study
PG	Performance Goal
PIVOT	Prostate Cancer Intervention Versus Observation Trial
PMA	Premarket Approval
PSA	Prostate Specific Antigen
RP	Radical Prostatectomy
SPCG-4	Scandinavian Prostate Cancer Research Group-4 Trial
TRUS	Transrectal Ultrasound
TURP	Transurethral Resection of the Prostate
QoL	Quality of Life

1. Introduction

The purpose of this summary is to present information relating to the safety and effectiveness of the Ablatherm® Integrated Imaging High Intensity Focused Ultrasound (HIFU) system ("Ablatherm HIFU" or "Ablatherm"), manufactured by EDAP Technomed, Inc. (EDAP). This device is designed to thermally ablate the prostate gland (whole gland treatment) in cases of localized prostate cancer using HIFU energy. Treatment is delivered from an endorectal probe under ultrasound visualization. The PMA specifically indicates the device for use in the low risk prostate cancer population.

The information in this document comprises a summary of FDA's review of the premarket approval (PMA) application, P130003, highlighting areas where Panel expertise is being solicited. It includes a brief description of the device, and an overview of the preclinical and clinical studies conducted by EDAP.

Currently, there are no legally marketed HIFU devices for the treatment of prostate cancer. Therefore, an advisory panel is being convened to discuss the clinical data collected to demonstrate reasonable assurance of safety and effectiveness in support of PMA approval for this "first of a kind" device.

This Executive Summary for PMA P130003 contains a summary of the device in question, the Ablatherm HIFU, and of the pre-clinical and clinical data available.

This document, particularly the clinical section:

- Summarizes the study design, results, and conclusions derived from the clinical investigations performed;
- Provides a summary of FDA's evaluation of the proposed device's safety and effectiveness; and
- Discusses the Agency's concerns regarding this application, including:
    - the clinical meaningfulness of comparing Ablatherm HIFU effectiveness to the low risk subgroup of the radical prostatectomy arm of the PIVOT trial using metastasis rates at 8 years;
    - the impact of the positive biopsy and salvage therapy rates following Ablatherm HIFU on the ability to interpret the effectiveness data;
    - limitations in making cross-study comparisons; and
    - the safety profile and comparisons of this non-surgical device.

The questions to be discussed at the advisory panel meeting will address these fundamental concerns.

Note: Key for fonts used in FDA's Executive Summary:

Times New Roman is used for the general text and information obtained from the PMA submission.
Times New Roman bold italics is used for FDA's comments.
Times New Roman bold italics within a box is used to denote questions to the panel.
Times New Roman italics is used for text copied verbatim from the PMA application and published literature.

2. Proposed Indications for Use

The applicant proposes the following indications for use for Ablatherm HIFU:

"The Ablatherm® Integrated Imaging High Intensity Focused Ultrasound (HIFU) system is intended for the primary treatment of prostate cancer in subjects with low risk, localized prostate cancer."

The applicant is proposing that Ablatherm HIFU be approved for ablating the entire prostate gland to the extent of the device's technical capabilities (i.e., "whole gland" treatment), not focal therapy. "Low risk" is defined according to the D'Amico classification system for risk stratification as follows: prostate specific antigen (PSA) ≤ 10 ng/mL AND Gleason score ≤ 6 AND clinical stage T1 or T2a.

The panel will be asked to discuss whether the data from the clinical study support a reasonable assurance of safety and effectiveness for the Ablatherm HIFU in the context of the above proposed indication for use.

3. Clinical Background

Prostate cancer is the second most common cause of male cancer-related death in the U.S. It accounts for 3% of all male deaths and is currently the leading soft tissue malignancy in men, representing one third of incident cancer cases. In 2014, an estimated 233,000 new cases will be diagnosed and 29,480 men will die of prostate cancer in the U.S.[1] Among patients diagnosed

with prostate cancer, 46% are reported as being at low risk, 30% at moderate risk, and 24% at high risk, according to the D'Amico classification.[2] The widespread use of PSA screening in clinical practice has resulted in stage migration of the disease leading to an increased proportion of men being diagnosed at earlier stages and lower risk of morbidity and mortality of their disease.

The current choice for men with localized prostate cancer is either therapeutic intervention – consisting primarily of surgery (i.e., radical prostatectomy) or radiation (i.e., external beam radiotherapy (EBRT) or interstitial brachytherapy) – versus active surveillance (i.e., regular monitoring with delayed therapy if/when warranted). Other less frequently used therapeutic interventions in this patient population are cryotherapy and hormone therapy. There is increasing evidence that therapeutic intervention delays disease progression and disease-specific mortality as compared to active surveillance (or no treatment) but has little or no effect on overall survival regardless of risk strata. Despite this, the majority of patients with low risk prostate cancer still undergo therapeutic intervention either initially or after a relatively short period of active surveillance. Though "no treatment" might be an acceptable option for low risk disease in patients with limited life expectancy, it is widely accepted that there is currently no definitive way to determine which men require treatment and who can be safely managed on active surveillance.

The natural history of screen-detected prostate cancer remains poorly understood. Autopsy studies have revealed that 50% of men in the age group of 40–49 years harbor prostate cancer. Eighty percent of these cancers are of low volume (<0.5 cm^3) and low grade, and can be classified as "clinically insignificant." The advent of PSA testing and modified prostatic biopsy schemes have led to the diagnosis of cancers that would not otherwise have been diagnosed clinically during a patient's lifetime. There is continued research to develop biomarkers that more accurately characterize a patient's risk beyond that of the currently employed biomarkers of clinical stage, Gleason score, and PSA.[3]

At present, active therapeutic intervention of newly diagnosed prostate cancer remains the standard of care in the community, although there is increased uptake of active surveillance. Nevertheless, treatment, no matter which kind is chosen, is associated with significant morbidity and decreased quality of life. Using current methods of risk stratification, many clinicians are employing active surveillance with delayed, selective, or curative therapy for patients with low and even some with intermediate risk prostate cancer. It appears that only limited numbers of patients under active surveillance require additional treatment and with short follow-up, it appears that delayed treatment in these highly selected cases does not alter outcome. It is not clear whether the patients that appear to "progress" while on active surveillance had true progression or were wrongly stratified due to sampling error at the time of original diagnosis.

Despite all of this, many patients without "progression" discontinue active surveillance due to patient and/or physician anxiety. There are no current universally agreed upon criteria for selecting patients for active surveillance or intervention with curative intent of patients under active surveillance.

Clinical benefit is defined as an improvement in clinical management, patient health, and patient satisfaction in the target population, such as significantly improving patient management and quality of life, reducing the probability of death, aiding improvement of patient function, reducing the probability of loss of function, and providing relief from symptoms.[4] Localized prostate cancer has little impact on patient quality of life, symptoms, or function, other than the anxiety associated with the diagnosis, since patients are almost always asymptomatic at the time of diagnosis. In addition, there is significant debate whether low risk prostate cancer has any impact on overall survival. The long-term median survival times for patients with even high risk localized prostate cancer make overall survival an impractical endpoint for regulatory action for this disease. Metastasis-free survival is a variant of progression-free and disease-free survival, and has been utilized as an endpoint for regulatory action by the FDA for adjuvant therapies for breast and gastrointestinal malignancies. It is believed that an improvement of disease-free survival in a randomized trial of sufficient magnitude is predictive of clinical benefit. In general, however, comparison to historical controls or cross-study comparisons using a time-to-event endpoint, such as metastasis-free survival, are extremely problematic due to variations in both frequency and interpretation of imaging studies.

4. Regulatory History

4.1 IDE Study

The applicant initiated an IDE study (G050103) to assess the safety and effectiveness of Ablatherm HIFU in the U.S. for the treatment of low risk, localized prostate cancer. This study was designed as a pivotal study to support PMA approval. This study was planned as a multi-center, prospective, non-randomized, concurrently controlled clinical trial comparing Ablatherm HIFU to cryotherapy in patients with low risk, localized prostate cancer. The planned primary effectiveness endpoint was a composite consisting of (i) biochemical success, defined as a PSA nadir of ≤ 0.5 ng/mL and American Society for Therapeutic Radiation and Oncology (ASTRO) 1996 definition of biochemical recurrence-free survival[5] through 24 months, and (ii) a negative follow-up prostate biopsy at 24 months.

Due to accrual difficulties, particularly in the cryosurgery arm, this planned study was not completed. Of the planned 205 patients per arm, only 136 and 5 patients were recruited to the Ablatherm HIFU and cryosurgery arms, respectively.

All IDE subjects receiving Ablatherm HIFU were treated using the device version proposed in this PMA.

4.2 Premarket Approval Application

The applicant submitted the current original PMA (P130003) for Ablatherm HIFU on February 28, 2013. This application includes the data collected under IDE G050103, a systematic review and meta-analysis of the HIFU literature, and data collected from registries outside the U.S. (where Ablatherm HIFU is commercially available).

This Executive Summary is based on information submitted in the original PMA application, as well as information received from the applicant in response to a major deficiency letter issued by FDA.

5. Device Description

5.1 Overview of Components

The Ablatherm is a computer-controlled medical device intended to thermally ablate the prostate in cases of localized prostate cancer using transrectal high intensity focused ultrasound (HIFU) energy. The system consists of the following main components:

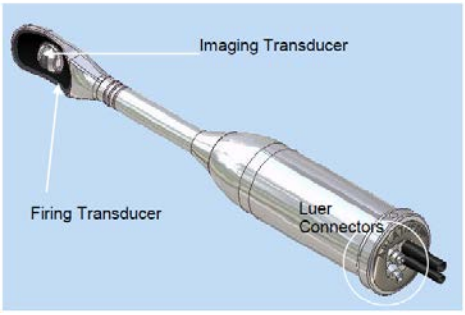
Treatment Module: The treatment module is a mobile unit with a padded bed on which the patient is positioned. The treatment module consists of the Ablapak holder, fluid cooling system, peristaltic pump, flow detector, endorectal probe holder, treatment probe and probe movement assembly, patient movement detector, cushions, support rail, keypad, and connections for the control module, mains power switch, emergency stop button, and a commercially available ultrasound scanner. The treatment module also houses an internal, "embedded" computer that communicates with the main computer on the control module. The probe movement assembly is capable of movement along five axes: longitudinal, transversal, vertical, angular, and rotational.

Ablatherm Treatment Module (left) and Control Module (right)

Control Module: The control module is a mobile unit that houses the computer and its peripherals (monitor, keyboard, mouse, CD burner, printer). The computer serves as the main interface for the operator and the device. It runs the main software program, and allows the user to monitor the treatment, monitor the device status, and maintain patient files. The control module is also used by EDAP engineers to maintain, check and calibrate the machine. The control module is permanently connected to the treatment module via a cable.

Endorectal Probe: The endorectal probe is attached to the probe movement assembly on the treatment module, and is inserted into the patient's rectum during treatment. The main functions of this component are to image the prostate before and during HIFU treatment using a 7.5 MHz array transducer, and to deliver HIFU energy within the prostate using a 3 MHz therapy transducer. These two ultrasound transducers are integrated into one component (with the imaging transducer located at the center of the therapy transducer). This component contains channels to circulate Ablasonic coolant/coupling fluid to and from a disposable latex probe cover (balloon), and a thermosensor to measure the temperature of this fluid. During treatment planning, the physician controls the movement of the endorectal probe to properly align it with respect to the prostate anatomy and to mark the treatment boundaries. During treatment, the system controls the endorectal probe's movement and HIFU output to create a spatial array of thermal lesions within the physician-defined prostate boundary. After treatment, the endorectal probe is disconnected from the probe movement assembly for reprocessing (i.e., cleaning and disinfection) and/or maintenance.

Endorectal Probe

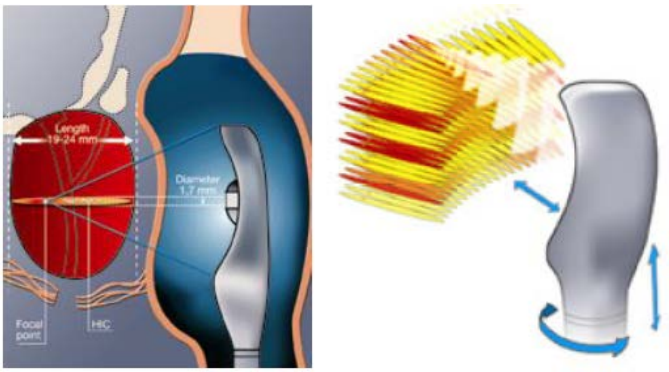


Ablapak: The Ablapak is a kit of single use, disposable accessories required to perform an Ablatherm treatment, consisting of: a pouch of Ablasonic coolant/coupling fluid, tubing set (including bubble trap, heat exchanger, and spike), syringe, ultrasound coupling gel (sterile), latex probe cover/balloon, silicone ligature (sterile), and patient movement reflector. The Ablasonic fluid is an aqueous solution that limits bubble formation while being continuously circulated between a heat exchanger (on the treatment module) and the therapy transducer (which is surrounded by a latex balloon). The purpose of this solution is to provide good ultrasound coupling between the therapy transducer and the rectum, as well as to cool the rectum. The ultrasound coupling gel, latex balloon, and silicone ligature are each cleared as stand-alone devices, and are provided to EDAP in final, finished form.

5.2 Principle of Operation

HIFU is a means of delivering ultrasound energy to a distant location (in this case, the prostate) in a controlled manner. This ultrasonic energy heats the target tissue to therapeutic levels (via tissue absorption) while minimizing the effect on surrounding structures. The Ablatherm delivers this therapeutic ultrasound energy via the endorectal probe, which also includes an integrated ultrasound imaging transducer for real-time ultrasound visualization/monitoring. The high intensity ultrasound waves from the therapy transducer propagate through the rectal wall and are focused within a portion of the prostate, generating intense heat (80-95°C) and causing the ablation of a volume of tissue at the focal area. The ablated tissue within a single focal area is called a HIFU lesion. In each lesion, heating begins at the therapy transducer's focal point, and spreads distally (away from the transducer) for 6 mm and proximally (toward the transducer) for 13-18 mm. Each resulting thermal lesion is 1.7 mm in diameter/width, and 19-24 mm in extent. This process is repeated in a stepwise fashion, under computer control, to create overlapping lesions to destroy the targeted tissues within the prostate. The goal of Ablatherm HIFU treatment is to ablate the entire prostate gland (to the extent possible). The apex, sphincter and rectum are preserved while prostate tissues are treated.

Diagrams showing spatial positioning of HIFU lesions



Neither the temperature nor lesion size is monitored during Ablatherm treatment. Rather the device uses a fixed HIFU frequency (3 MHz) and pulse ON/OFF duration (6 s ON, 4 s OFF, per the software requirements specifications), and modulates the electrical power to the therapy transducer to achieve the desired lesion size (i.e., a width of 1.7 mm and an extent that corresponds to the AP diameter of the prostate (i.e., prostate height) in that slice – must be between 19 and 24 mm). In bench and *in vivo* studies, these treatment parameters were empirically determined to result in these lesion sizes.

5.3 Clinical Usage

Prior to treatment, the patient positioned on the treatment module and is anesthetized (general or spinal anesthesia).

Treatment Module (with patient in position)

The endorectal probe is fitted with the latex balloon and ligature, filled with Ablasonic coupling liquid, coated with ultrasound coupling gel, and inserted into the patient's rectum.

Applying the balloon over the therapy transducer and filling with Ablasonic

Using the ultrasound imaging capabilities of the endorectal probe, the treating physician visualizes the prostate, and defines the contours of the gland and the boundaries of the target treatment volume (i.e., defining the longitudinal limits of treatment (apical and bladder neck), as well as reviewing the calculated positions of HIFU lesions on each transverse slice). During this treatment planning phase, all probe movement is controlled by the physician.

Once the physician has completed the treatment planning phase, the device automatically positions the endorectal probe (via encoded stepper motors) under computer control, and delivers the HIFU energy to regions within the defined treatment volume (energy successively applied to discrete positions within the treatment volume to create overlapping lesions). The ultrasound waves propagate through the rectal wall and are focused on a location (focal area) within the prostate. Intense heat is generated at this point causing ablation of tissue within the focal area (creating a single HIFU lesion). The device software divides the prostate into one or more blocks to allow inter-treatment planning during the procedure (allowing the user to adjust for possible edema of the prostate resulting from the treatment), and each block is treated by overlapping lesions within each transverse slice. The automated process is repeated in a stepwise fashion with the device successively repositioning the probe to create an array of HIFU lesions that cover the entire user defined treatment volume. Multiple targeted treatment volumes (typically several hundred) are required to ablate the entire prostate.

Throughout treatment, the system continuously monitors the position of the rectal wall (to verify that it remains a safe distance from the therapeutic transducer and the HIFU lesion), as well as patient motion. The typical duration of treatment is 1.5-3 hours.

5.4 Safety Features

The system incorporates a variety of safety features to prevent non-target tissue (particularly the rectal wall, the bladder, and the external urinary sphincter) from being heated to therapeutic levels. Below is a listing of important device features:

- Emergency stop button (located on the treatment module).
- Prior to treatment, the software reads the serial number of the endorectal probe (stored on EEPROM) to verify that it has been calibrated for use on this specific device (since transducer efficiency at converting electrical power to acoustic energy varies between transducers).
- Prior to treatment, the software requires the user to enter the code number printed on the Ablapak label (to verify that it has not previously been used to prevent reuse).
- The device cools Ablasonic coupling liquid in the heat exchanger and circulates it to the balloon surrounding the therapy transducer. Additionally, the temperature of the Ablasonic fluid is continuously monitored by the endorectal probe. This feature cools the rectal wall to minimize heating of this non-target tissue. If the temperature of this coolant rises too high, the system will suspend treatment.
- The system prohibits treating prostate tissue that is within 4 mm of the apex (as marked by the physician during treatment planning). This prohibition maintains a 4 mm safety distance from the external urinary sphincter.
- The distance from the transducer to the rectal wall is automatically measured prior to each HIFU lesion and compared to what was measured during treatment planning. If the difference is 1-4 mm, the probe position is automatically adjusted. If the difference exceeds 4 mm, treatment is suspended. This feature helps to avoid the rectal wall being included in the HIFU lesion.
- The system verifies the correct positioning of the encoded stepper motors that position the endorectal probe prior to each HIFU lesion, and halts treatment of the deviation is greater than 1 mm or 2 degrees.
- The system has a patient movement detector, consisting of a light emitter and sensor (on a mechanical arm that is positioned over the patient's hip) and a reflective sticker (that is placed on the patient's hip). If patient movement occurs during treatment (as indicated by the reflected light no longer being sensed), the system will suspend treatment.

5.5 Device Modifications

Development of the Ablatherm began in 1993, as summarized below:

- Initial prototypes: From 1993 to 2000, the following prototypes were developed and tested: (i) Experimental prototype, (ii) Prototype 1, and (iii) Prototype 2. These early versions were used to test the proof of concept of using HIFU for tissue ablation, and evaluated a variety of treatment parameters and resulting lesion characteristics, including various transducer designs and HIFU frequencies (typically 2.25 or 3 MHz).

- Ablatherm Maxis: Following these early prototypes, EDAP developed the Ablatherm Maxis. This version of the Ablatherm was in commercial use outside of the U.S. from 2000 to 2005. The therapy transducer of this device was similar in shape to that of the PMA device, and also operated at 3 MHz. For this reason, the lesion size produced by the Maxis version is similar. Also, the treatment planning procedure, in terms of how the physician marks the treatment boundary and how the system internally plans the lesion array within this boundary, is the same. A major difference is that this therapy transducer does not have an integrated ultrasound imaging transducer for visualizing the prostate during treatment. Instead, the Maxis therapy transducer is mounted to the endorectal probe on a hinge so that it can rotate to one side, and the core of the endorectal probe houses a standard transrectal ultrasound (TRUS) probe. With this design, imaging and therapy are performed sequentially (not simultaneously).
- Ablatherm Integrated Imaging: This is the version of the device that was studied in the IDE and is proposed in the PMA. To allow simultaneous imaging and therapy, as well as to enhance the reliability of the endorectal probe, shorten treatment duration, and better work within the physical constraints of the rectal anatomy, EDAP developed the Ablatherm Integrated Imaging version in 2005. Since that time, this is the version that has been commercially available outside the U.S. The primary difference from the Maxis version involves integrating the imaging transducer array into the therapy transducer (through a center hole), eliminating the need for a separate TRUS probe (and the associated motorized mechanisms for TRUS probe and therapy transducer movements) and enabling ultrasound visualization of the prostate during the HIFU procedure. Despite some loss of active transducer surface area to accommodate the imaging transducer array, the HIFU lesion produced is very similar to that of the Maxis version. This version is essentially the same as the Maxis with respect to treatment planning, HIFU ablation parameters and characteristics, and safety features.

FDA Comment: This information supports the applicability of the Ablatherm Maxis version in the submitted pre-clinical and clinical studies to the PMA device. While the use of the early prototype versions in the initial pre-clinical studies is justified, the applicability of clinical data on these early versions to the PMA version is uncertain.

Since the approval of the device for use in IDE G050103 for the purposes of clinical investigation, several device modifications have occurred. EDAP previously notified FDA of these changes and sought approval, when necessary, through the submission of supplements to the IDE. These device modifications are summarized in the PMA, and include minor updates to the system design, software, and manufacturing. The applicant concludes that none of these changes to the IDE version of the device impact our ability to use the clinical and performance data from the IDE version of the device to the evaluation of the PMA version of the device.

FDA Comment: ***None of these changes made during the IDE impact the HIFU output or other critical treatment parameters. They basically are minor upgrades/enhancements to modernize the system, replace obsolete components, improve manufacturability, or correct technical problems which either are not apparent to the user or have no change to the device's clinical use. While several of these changes included new or improved safety features, none invalidate the ability to use the data from the IDE version of the system in evaluating the safety and effectiveness of the PMA version proposed for approval.***

6. Pre-Clinical Studies

The applicant provides the following pre-clinical testing and information in support of the safety and effectiveness of Ablatherm HIFU:

6.1 Performance Testing and Characterization

The following tests were conducted to characterize the HIFU output from the Ablatherm:

Early bench and animal studies performed prior to 2000 using various prototypes of the Ablatherm. The purpose of these studies was to evaluate various therapy transducer designs and treatment parameters, to evaluate which to use in a clinical version of the device. The results of this series of tests led to the design of the Maxis version.

A series of bench and animal studies were performed after 2000 to characterize the Ablatherm Maxis and Integrated Imaging systems. Unlike the early testing described above, this testing is directly related to the PMA version of the device, since the test devices used the same transducer geometry and treatment parameters (e.g., HIFU frequency and power). The specific tests included in this section are as follows:

- Simulation studies (i.e., computer modeling of HIFU lesion geometry)
  - The results of these computer simulations defined the shot parameters for the Integrated Imaging transducer design, and predicted the lesion size/location. Specifically, this modeling was used to determine the treatment parameters that result in the Integrated Imaging transducer producing the same HIFU lesion as the previously studied Maxis transducer. These parameters were then used in subsequent *in vitro* and *in vivo* studies.
- *In vitro* studies (i.e., evaluation of lesion geometry in *ex vivo* calf liver)
  - The lesions induced by the Integrated Imaging probe were equivalent in terms of quality and volume to those induced by the Maxis probe. While small differences

were observed in lesion shape, these deviations were sufficiently small (~1 mm) to proceed to *in vivo* studies.

- *In vivo* studies (i.e., evaluation of lesion geometry in the rabbit liver model)
  - The lesions induced by the Integrated Imaging probe were equivalent in terms of quality, safety, and volume to those induced by the Maxis probe, and no more than 5% different in terms of shape. Testing at minimum shot depth, which creates a worst case scenario for damage to the anterior rectal wall, showed that damage was significantly less frequent with the Integrated Imaging probe than with the Maxis probe. This testing was used to support initiation of the G050103 clinical study.

The PMA summarizes the results of characterization and calibration tests performed on the Integrated Imaging system therapy transducer. Specifically, the following technical parameters were measured in this testing: transducer electrical impedance, transducer dimensions (i.e., diameter, truncated diameter, and focal length), ultrasonic beam profile (i.e., -6dB dimensions), acoustic intensity, acoustic power intensity and stability (via radiation force measurements), and transducer reference power (used to establish the relationship between the electrical power supplied to the transducer and the acoustical power provided to the tissue).

FDA Comment: FDA reviewers found this information adequate.

6.2 Biocompatibility Testing

Of the patient contacting components of the Ablapak, the following are legally marketed as stand-alone devices and do not require separate biocompatibility testing: the balloon, ligature, and ultrasound coupling gel. For the remaining components and accessories of the Ablatherm that have, or could potentially have, patient contact, the following biocompatibility tests were conducted and submitted for review:

Endorectal probe: • Cytotoxicity • Intracutaneous reactivity • Sensitization • Material-mediated pyrogenicity	Ablasonic coupling liquid: • Cytotoxicity • Intracutaneous reactivity • Sensitization	Reflector: • Cytotoxicity • Dermal irritation • Sensitization

FDA Comment: FDA reviewers found this information adequate.

6.3 Software Validation

The Ablatherm has two software programs, one running on the main computer of the control module, and the other controlling the embedded computer of the treatment module. These two programs share the control of the hardware systems used in treatment. Software verification and validation testing for each program was submitted by the applicant.

FDA Comment: FDA reviewers found this information adequate.

6.4 Electrical Safety and Electromagnetic Compatibility Testing

The applicant has provided information on the electrical safety and electromagnetic compatibility testing performed in accordance with IEC 60601 standards.

FDA Comment: FDA reviewers found this information adequate.

6.5 Sterilization and Shelf Life Validation

The following Ablapak components are provided sterile: Ablasonic coupling liquid, ligature, and ultrasound coupling gel. The ligature and coupling gel are legally marketed as stand-alone devices, and are provided to EDAP in final, packaged form with validated expiration dates. For the Ablasonic coupling liquid, the applicant provided information supporting autoclave sterilization and a 34-month shelf life.

FDA Comment: FDA reviewers found this information adequate.

6.6 Reprocessing Validation

Although the endorectal probe is covered with a new latex balloon prior to each treatment, there is still the potential for microorganisms to be transferred from the patient to the probe surface during the course of treatment or when the balloon is being removed. Therefore, the endorectal probe is labeled to be reprocessed between each use (manual cleaning, followed by high-level disinfection). To support the safety of endorectal probe reuse, the applicant has provided the reprocessing instructions, and cleaning and disinfection validation studies.

FDA Comment: This information has not yet been found to be adequate by FDA reviewers and is still under active review and discussion.

7. Clinical Studies

Clinical information regarding both long-term and intermediate-term follow-up were submitted in the PMA in support of the safety and effectiveness of Ablatherm HIFU.

7.1 Long-Term Clinical Information:

Overview

The primary clinical data submitted in support of PMA approval consists of long-term follow-up data obtained from a European registry on Ablatherm HIFU, which is compared to the low risk subgroup of patients in the radical prostatectomy (RP) arm of the U.S. Veterans Administration-based **P**rostate Cancer **I**ntervention **v**ersus **O**bservation **T**rial (PIVOT).[6] These long-term data were submitted to the PMA in response to FDA's major deficiency letter to address shortcomings with the IDE study and supporting clinical data (summarized below in "Intermediate-Term Clinical Information"), and are intended as the primary evidence in support of PMA approval.

HIFU Long Term / HIFU Long Term Refined Cohorts

EDAP presents two cohorts of subjects who underwent Ablatherm HIFU for the whole gland treatment of low risk, localized prostate cancer, referred to as the "HIFU Long Term Cohort" and the "HIFU Long Term Refined Cohort." These are multi-center, prospectively defined data collections of patients already treated with Ablatherm HIFU. Three institutions in Europe that recently reported 10-year outcomes following Ablatherm HIFU were selected for participation in this data collection. The sites, with reference to the corresponding publications, are the University of Regensburg, Regensburg, Germany,[7] Klinikum Harlaching, Munich, Germany,[8] and Edouard Herriot Hospital, Lyon, France.[9]

After screening out patients who did not receive Ablatherm HIFU as a primary, whole gland treatment for low risk, localized prostate cancer, the databases from the three European sites were combined into a single database for analysis, referred to as the HIFU Long Term Cohort (n=925). A subset of this cohort that more closely matches the inclusion and exclusion criteria of the IDE study is presented separately, and is referred to as the HIFU Long Term Refined Cohort (n=227). Specifically, subjects were excluded from the HIFU Long Term Refined Cohort subset if they had interventions to reduce prostate volume prior to HIFU (i.e., pre-HIFU or concomitant transurethral resection of the prostate (TURP), pre-HIFU hormone therapy) or had incidental prostate cancer that does not warrant intervention (i.e., stages T1a and T1b).

The following table summarizes the derivation of the HIFU Long Term Refined Cohort from the European registry.

	Number Excluded	Number Remaining
Whole gland HIFU patients	--	4632
Not Low risk disease*	3707	925 [*HIFU Long Term Cohort*]
Adjuvant Hormone therapy	208	717
TURP	467	250
Incidental prostate cancer	23	227 [*HIFU Long Term Refined Cohort*]
*Also excluded were patients with prior radiation, prior prostate surgery within 1 year, prior orchiectomy or hormone therapy for > 6 months duration, metastatic disease (including lymph node and seminal vesicle involvement), prior rectal surgery within 1 year, and patients < 50 years old.		

Prior to creating these cohorts, EDAP prospectively developed the protocol and statistical data plan (summarized below) for data extraction and analysis.

- Design: Multicenter, prospectively-defined data collection of patients already treated with Ablatherm HIFU for localized prostate cancer. The three sites were in Germany and France.

- Objectives:
    - Primary: To document the long term freedom from metastasis rate following Ablatherm HIFU treatment.
        - Date imputed as the midpoint between the date of last assessment prior to diagnosis/death due to prostate cancer and the date of diagnosis/death.
        - Reported with descriptive statistics and 95% confidence limits.
    - Secondary: To document overall survival, prostate cancer specific survival, and freedom from salvage treatment following Ablatherm HIFU
        - Reported with descriptive statistics and 95% confidence limits.
    - Exploratory: To document the freedom from positive biopsy, PSA nadir success, and Phoenix* biochemical survival following Ablatherm HIFU
        - Reported with descriptive statistics and 95% confidence limits.
        - *According to the Phoenix definition, biochemical failure is defined as a PSA rise by 2 ng/mL or more above the nadir.[10]

FDA comment: Although the PMA refers to the primary effectiveness endpoint of freedom from metastasis as a "surrogate-free" endpoint, FDA regards it as a surrogate for the gold standard endpoint of overall survival.

- Methodology: The records of 4,632 registry subjects were screened with the inclusion/exclusion criteria for eligibility in the HIFU Long Term Cohort. All subjects meeting these criteria were included. Reasons for exclusion from the cohort were recorded.

- Inclusion Criteria (*for HIFU Long Term Cohort enrollment*):
    - Subject has undergone whole gland Ablatherm HIFU for the treatment of prostate cancer confirmed by PSA and pathologically;
    - Male subject, age ≥ 50 years at the time of HIFU procedure;
    - Organ-confined prostate cancer with a known stage;
    - Known PSA prior to the index Ablatherm HIFU procedure; and
    - Known Gleason score at the time of the Ablatherm HIFU procedure.

- Exclusion Criteria (*for HIFU Long Term Cohort enrollment*):
    - Any other prostate procedure prior to the index Ablatherm HIFU procedure with the exception of TURP;
    - Evidence of seminal vesicle involvement prior to the procedure;
    - Evidence of lymph node involvement or metastasis prior to the index Ablatherm HIFU procedure;
    - Any previous definitive local radiation treatment for prostate cancer, including EBRT or brachytherapy;
    - Previous surgery or procedure of the prostate (except prostate biopsy or HIFU) or urethra within 1 year prior to the index Ablatherm HIFU procedure;
    - Any hormone therapy lasting more than 6 months prior to HIFU or hormone therapy not discontinued at the time of HIFU;
    - Previous bilateral orchiectomy prior to the index Ablatherm HIFU procedure; and
    - Rectal surgery (other than hemorrhoidectomy) within 1 year prior to the index Ablatherm procedure, or history of rectal disease.

- Additional Exclusion Criteria (*for HIFU Long Term Refined Cohort enrollment*):
    - Subject has undergone TURP* prior to or at the time of the index Ablatherm HIFU procedure;
    - Subject has undergone hormone therapy* prior to the index Ablatherm HIFU procedure; and
    - Cancer stages T1a and T1b.

      *In Europe, TURP and hormone therapy are frequently used with Ablatherm HIFU to reduce the prostate volume to make whole gland treatment possible with HIFU (so ultrasound energy can reach the anterior region of the gland) and to lessen the potential for urinary obstruction following HIFU (due to post-treatment swelling and tissue sloughing). EDAP refers to this practice as "right-sizing."

FDA Comment: ***The results of the HIFU Long Term Cohort are not presented in the primary effectiveness analysis as a result of confounding (due to the prevalence of adjuvant TURP and hormone therapy) and the inclusion of a subset of subjects with incidental prostate cancer in***

who intervention is not warranted. Therefore, the remaining discussion of the long term Ablatherm HIFU data and the resulting effectiveness analyses pertain only to the HIFU Long Term Refined Cohort.

- Data Protection/Informed Consent: German and French laws/regulations were followed for confidentiality and use of patient data. The resulting HIFU Long Term Cohort database was anonymized during its creation, removing all potential patient identifying information. It was determined that patient informed consent was not needed to create this database.

- Collected Information:
  - Demographics: age, height, weight
  - History: cancer stage, uroflowmetry, International Prostate Symptom Score (IPSS), quality of life questionnaire (QoL) assessment
  - Baseline: days prior to index HIFU at evaluation, PSA, prostate volume, days prior to index HIFU at biopsy, results of TRUS-guided biopsy including Gleason score
  - Index HIFU procedure summary: year, device model, energy setting, procedure time, anesthesia (general vs. spinal), treatment adverse events
  - Post-treatment summary (each noting the days post-index HIFU): PSA, results of TRUS-guided biopsy including Gleason score, results of any record used to determine freedom from metastasis and cause specific mortality, adverse events and resolution, digital rectal exam (DRE), physical exam (for GI/GU body systems), uroflowmetry, IPSS, QoL, other prostate treatments

- Site Distribution of Patients:

Site	**HIFU Long Term Refined Cohort**
Lyon	71% (161)
Munich	18% (40)
Regensburg	11% (26)
Total	227

- Demographics/Baseline:

	HIFU Long Term Refined Cohort
Age	68 years (50-81)
PSA	5.7 ng/mL (0.1-10)
Gleason score	5.4 (2-6)
Cancer stage	T1c - 64.3% T2a - 35.7%
Prostate volume	26.7 cc (6-79)

- In accordance with FDA's PMA regulations (21 CFR 814.45), EDAP provides a justification for the comparability of this European cohort to the U.S. population. Although the European population is less ethnically diverse than the U.S., and the incidence and aggressiveness of prostate cancer varies in different ethnic groups, the aggressiveness and prognosis of the disease are dependent upon characteristics of the disease (i.e., PSA level, Gleason score, stage, and risk group) and not ethnicity. Given this, EDAP concludes that the difference in the rates of men of African descent (who have a higher prevalence of aggressive prostate cancer than other ethnic groups) between European and U.S. populations is not clinically relevant. In light of this information and other factors (i.e., (i) the study was conducted in accordance with the Helsinki Declaration and German and French laws/regulations regarding human subject protection, (ii) the data are applicable to U.S. medical practice, (iii) the studies were performed by clinical investigators of recognized competence, and (iv) the data are available for FDA inspection), FDA may rely on these foreign data in the review of this PMA.

- Ablatherm Model Used:
  - 19% were treated with an Ablatherm prototype (prior to 2000),
  - 41% were treated with the Ablatherm Maxis (during 2000-2004), and
  - 40% were treated with the Ablatherm Integrated Imaging (2005 and after).

- Follow-Up Duration: The median follow-up time (years from initial HIFU to date of last contact or death) is 6.6 years. Ninety-four of the 227 patients (41%) had follow up of 8 years or longer.

- Retreatment / Salvage Therapy: EDAP reports the proportions of subjects receiving "adjuvant HIFU" (defined as a repeat Ablatherm HIFU procedure occurring within 1 year of index Ablatherm HIFU) and "salvage therapy" (defined as repeat Ablatherm HIFU occurring after 1 year of index Ablatherm HIFU, and any radiotherapy, hormone therapy, or radical prostatectomy (RP)). Adjuvant HIFU is not categorized as a salvage therapy.
  - Adjuvant HIFU occurred in 15% (35/227)
  - Salvage therapy occurred in 34% (77/227)
    - 54/77 had a single salvage therapy vs. 23/77 had two or more.
    - The most common salvage therapy was repeat Ablatherm HIFU in 19%, followed by radiotherapy in 13%, hormone therapy in 10%, and RP in 2%.

PIVOT RP Cohort

To assess the outcomes of Ablatherm HIFU with respect to a standard of care using the long-term endpoint of metastasis-free survival, EDAP compares the results of the HIFU Long Term Refined Cohort with those of the low risk subgroup of the RP cohort from the PIVOT study. The PIVOT study was initiated by the Department of Veterans Affairs, National Cancer Institute, and the Agency for Healthcare Research and Quality, and is a randomized trial comparing RP to observation among men with localized prostate cancer who were diagnosed in the early PSA era (consistent with how patients are currently screened in the U.S.). Effectiveness data reported for these subjects includes overall survival, cancer-specific survival, and metastasis-free survival. The results of this study were published by Wilt et al.[6], from which the following relevant details were obtained:

- Enrollment Period: 1994-2002

- Sample Size:
    - Overall: 731 (364 RP, 367 observation)
    - Low risk subgroup: 296 (148 RP, 148 observation)

- Inclusion/Exclusion Criteria: Localized prostate cancer (T1-T2NxM0), PSA < 50 ng/mL, age ≤ 75, negative bone scan for metastatic disease, and life expectancy ≥ 10 years.

- Patient Population: Men diagnosed with clinically localized prostate cancer.
    - Age: Mean = 67 years
    - Race: 62% Caucasian, 32% African American (remainder = "Other")
    - PSA: Median = 7.8 ng/mL (mean = 10.2 ng/mL)
    - Stage: 50% T1c, 45% T2 (remainder were T1a/b, T3, or unknown)
    - Risk Strata: 40% low, 34% intermediate, 21% high (5% unknown)

- Treatment: 281/364 subjects randomized to RP actually underwent RP

- Salvage Therapy Rate: Not reported for the RP arm

- Follow-up: Study visit every 6 months; bone scans at 5, 10, and 15 years or at last visit, self-reported questionnaire for urinary, erectile, and bowel dysfunction at 2 years.

- Results (median 10-year follow-up):

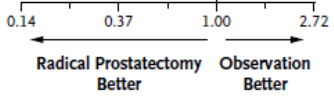
Overall population – all risk strata

	RP	**Observation**
Overall mortality	47.0%	49.9%
Prostate cancer mortality	5.8%	8.4%
Bone metastases	4.7%	10.6%

Subgroup analysis table (reproduced from page 208 of Wilt et al.)

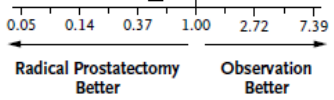
A Death from Any Cause

Subgroup	Observation	Radical Prostatectomy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/total no.			
Overall	183/367	171/364	0.88 (0.71–1.08)	
Age				0.85
<65 yr	50/131	43/122	0.89 (0.59–1.34)	
≥65 yr	133/236	128/242	0.84 (0.63–1.08)	
Race				0.81
White	119/220	117/232	0.84 (0.65–1.08)	
Black	53/121	46/111	0.93 (0.62–1.38)	
Other	11/26	8/21	0.85 (0.34–2.11)	
Charlson score				0.79
0	86/220	82/224	0.90 (0.66–1.21)	
≥1	97/147	89/140	0.84 (0.63–1.13)	
Performance score				0.66
0	146/310	139/312	0.89 (0.71–1.13)	
1–4	37/57	32/52	0.82 (0.51–1.31)	
PSA				0.04
≤10	101/241	110/238	1.03 (0.79–1.35)	
>10	77/125	61/126	0.67 (0.48–0.94)	
Risk				0.07
Low	54/148	62/148	1.15 (0.80–1.66)	
Intermediate	70/120	59/129	0.69 (0.49–0.98)	
High	49/80	42/77	0.74 (0.49–1.13)	
Gleason score				0.87
<7	125/261	113/254	0.86 (0.67–1.12)	
≥7	47/86	50/98	0.84 (0.56–1.25)	



B Death from Prostate Cancer

Subgroup	Observation	Radical Prostatectomy	Hazard Ratio (95% CI)	P Value for Interaction
	no. of events/total no.			
Overall	31/367	21/364	0.63 (0.36–1.09)	
Age				0.63
<65 yr	12/131	6/122	0.52 (0.20–1.39)	
≥65 yr	19/236	15/242	0.68 (0.34–1.33)	
Race				0.76
White	22/220	15/232	0.57 (0.30–1.10)	
Black	7/121	5/111	0.80 (0.25–2.54)	
Other	2/26	1/21	0.56 (0.05–6.17)	
Charlson score				0.63
0	19/220	14/224	0.69 (0.34–1.37)	
≥1	12/147	7/140	0.54 (0.21–1.38)	
Performance score				0.57
0	25/310	18/312	0.67 (0.37–1.23)	
1–4	6/57	3/52	0.41 (0.10–1.71)	
PSA				0.11
≤10	15/241	14/238	0.92 (0.44–1.91)	
>10	16/125	7/126	0.36 (0.15–0.89)	
Risk				0.11
Low	4/148	6/148	1.48 (0.42–5.24)	
Intermediate	13/120	6/129	0.50 (0.21–1.21)	
High	14/80	7/77	0.40 (0.16–1.00)	
Gleason score				0.57
<7	15/261	11/254	0.68 (0.31–1.49)	
≥7	15/86	10/98	0.51 (0.23–1.14)	



- Conclusions (from Wilt et al.):
    - Overall study population:
        - "*[A]s compared with observation, radical prostatectomy did not significantly reduce all-cause or prostate cancer mortality through at least 12 years among men with clinically localized prostate cancer that had been diagnosed in the era of PSA testing. Absolute differences in mortality between the study groups were less than 3 percentage points.*" (Reproduced from page 212 of Wilt et al.)
    - Low risk population:
        - "*Our findings support observation for men with localized prostate cancer, especially those who have low PSA value and those who have low-risk disease*." (Reproduced from page 211 of Wilt et al.)
        - "*Subgroup analyses suggested that surgery might reduce mortality among men with higher PSA values and possibly among men with higher-risk tumors, but not among men with PSA levels of 10 ng per milliliter or less or among men with low-risk tumors*." (Reproduced from page 212 of Wilt et al.)

As an additional, supplemental comparator, EDAP also presents the results from the recently published SPCG-4 trial.[11] The SPCG-4 (i.e., **S**candinavian **P**rostate **C**ancer **G**roup Study Number **4**) trial is a randomized study comparing RP to watchful waiting among men with localized prostate cancer who were diagnosed before the PSA era, and, thus, had more advanced disease at the time of diagnosis.

FDA Comment: Although the SPCG-4 trial also reports the long-term metastasis-free survival rate following RP and is similar in size to the PIVOT study (n=695 total men enrolled), the findings are not representative of contemporary prostate cancer patients diagnosed in the PSA era, who typically have earlier stage disease. Therefore, the results of the SPCG-4 trial are not presented in this Executive Summary.

Effectiveness Comparisons

The PMA effectiveness analyses consist of cross-study comparisons, primarily between the between the HIFU Long Term Refined Cohort and the low risk subgroup of the PIVOT study RP arm. The table below lists some of the known confounders that may affect the interpretability of this amendment. Some of the factors such as clinical stage and age would favor the PIVOT trial cohort while others such as PSA and follow-up favor the Ablatherm HIFU cohort. The impact of these prognostic variables on the effectiveness analyses is unknown.

	HIFU Long Term Refined Cohort	**PIVOT low risk RP subgroup**
N	227	148
Median age (years)	68	67*
Median PSA (ng/mL)	5.7	7.8*
Median follow-up (years)	6.6	10
Salvage therapy rate	34%	Not reported
Pathological evaluation	Local	Central
Cancer stage	Excludes T1a & T1b	Includes T1a & T1b
Bone scan schedule	At physician discretion	Prospectively defined (i.e., at 5, 10 and 15 years, or at last visit for subjects with less than 15 years of follow-up)
Disease-specific survival adjudication	Not reported	Independently adjudicated

*Only reported for the entire RP arm (all risk strata), not the low risk subgroup.

FDA Comment: ***Cross-study comparisons are complicated by known and unknown confounders that likely introduce bias. One of the key factors in this comparison is the rigor with which the primary endpoint data were collected. The PIVOT study was prospectively designed and the patient assessments, such as bone scans, were performed according to a pre-specified schedule. In contrast, for the HIFU Long Term Refined Cohort were followed per standard of care for prostate cancer. Data were obtained from existing clinic records, by contacting referring urologists, and sending mail-survey/letters directly to patients that queried PSA measurements, biopsies and metastatic status. For Ablatherm HIFU subjects lost to follow-up, additional information was sought from registration offices to determine cause specific survival. In all subjects, the amount of missing data is unknown. For Ablatherm HIFU subjects that died of non-prostate cancer causes, the last known PSA and metastatic status was used.***

The PMA clinical report makes comparisons across studies as if they were different arms of a randomized trial. Multiple problems arise when making such comparisons. One common difficulty with cross-study comparisons arises from differences in the frequency and timing of key follow-up measures between the two groups. For instance, while PIVOT RP subjects had regular bone scans at 5, 10, and 15 years, or at last visit for subjects with less than 15 years of follow-up, the comparator Ablatherm HIFU subjects underwent bone scans at physician discretion only. This difference could lead to under reporting of metastases for Ablatherm HIFU. Another problem in such comparisons is that patients in different groups may differ in

prognostic variables, such as age, baseline PSA, cancer stage, and tumor size. Failure to adjust for such differences can bias the observed difference between two treatment groups when estimating the treatment effect. In the PMA, the comparisons between Ablatherm HIFU and PIVOT RP do not include adjustments for prognostic variables, as such information is not available to the applicant. The panel will be asked to discuss the adequacy and interpretability of the PMA effectiveness conclusions in this cross-study comparison.

Primary Effectiveness Analysis:

- Long Term Freedom from Metastasis

The primary analysis in support of Ablatherm HIFU effectiveness is a descriptive (i.e., non-statistical) comparison of the 8-year estimate of metastasis-free survival in the HIFU Long Term Refined Cohort and the subset of low risk subjects from the RP arm from the PIVOT study.

Metastases were reported at any time following Ablatherm HIFU in 1.3% (3/227) of HIFU Long Term Refined Cohort subjects, for a Kaplan-Meier 8-year freedom from metastasis rate of 98.2% (94.4, 99.4%). In the PIVOT low risk RP subgroup patients, metastases were reported at any time following surgery in 4.1% (6/148) of subjects (Kaplan-Meier freedom from metastasis rate not reported).

The following table shows that these cohorts qualitatively had similar cumulative risk estimates of metastasis at 8 years:

Cohort	**Cumulative risk* at 8 years**	**95% Confidence Interval**
HIFU Long Term Refined	1.1%	0.1, 2.0%
PIVOT low risk RP subgroup	1.4%	0.4, 4.8%

*In this comparison, the cumulative risk estimate is a competing risks analysis that treats death due to causes other than prostate cancer as a competing risk. This rate differs from the Kaplan-Meier estimate reported above that treats death due to other causes as a censoring event.

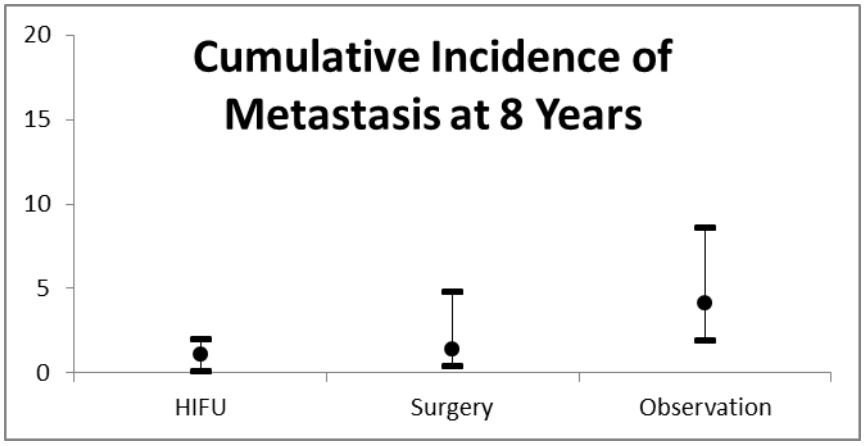
Although no formal statistical analysis was planned or performed, the comparison is essentially a non-inferiority comparison to RP.

<u>FDA Comment</u>: A key underlying principle of any non-inferiority analysis is that the active therapy used as the control is efficacious in that trial, which is known as "assay sensitivity." If assay sensitivity is not conserved, an ineffective or potentially detrimental therapy may be approved. Normally, one has to rely on historical data or a third arm using placebo or sham to assure assay sensitivity. In this case, however, we have the third arm of "placebo/sham" (i.e., observation) in the PIVOT trial. As reported by Wilt et al. and summarized above, in an

exploratory analysis the PIVOT trial failed to detect a difference between observation and RP for the endpoint of bone metastasis rate in the low risk population. Key data regarding this finding are summarized below:

Bone metastasis	***RP***	***Observation***	***Absolute Risk reduction***	***Relative Risk***	***P-value***
Overall	*17 (4.7%)*	*39 (10.6%)*	*6% (2.1 to 9.9)*	*0.44 (0.25 to .76)*	*0.001*
Low risk	***6 (4.1%)****	***9 (6.1%)***	***2.0% (-3.3 to 7.6)***	***0.67 (0.24 to .83)***	***0.39***
Intermediate risk	*6 (4.7%)*	*19 (15.8%)*	*11.2% (3.7 to 19.2)*	*0.29 (0.12 to .71)*	*0.002*
High risk	*4 (5.2%)*	*11 (13.8%)*	*8.6% (-0.9 to 8.3)*	*0.38 (0.13 to .14)*	*0.03*

*In comparison, 3 (1.3%) HIFU Long Term Refined Cohort subjects reported metastases.
Note: The above risk stratifications are based on the local pathology findings.



***FDA Comment*: In light of the PIVOT study conclusions and the use of the low risk RP subgroup as the comparator to Ablatherm HIFU, the clinical benefit of the subject device in the treatment of the low risk population is unclear.**

The PIVOT trial failed to establish the superiority of RP to observation in the intention to treat population including all risk strata. An exploratory subgroup analysis of low risk patients revealed no significant difference between RP and observation for either survival or metastasis rates, although observation was numerically superior for survival and inferior for metastasis rate. Even though metastasis-free survival is a potentially useful endpoint in prostate cancer,

the use of this endpoint is challenging due to the low event rate in the low risk group. The panel will be asked to discuss whether the comparison of Ablatherm HIFU to the low risk subgroup of the PIVOT RP arm using metastasis rates at 8 years support the effectiveness of this new treatment.

Secondary Effectiveness Analyses:

- Overall Survival

In the HIFU Long Term Refined Cohort, a total of 7.9% (18/227) subjects died following treatment (any time), for a Kaplan-Meier 8-year overall survival estimate of 89.4% (82.3, 93.7%). In the PIVOT low risk RP subgroup, 41.9% (62/148) of subjects died at some time during the study period (Kaplan-Meier survival rate not reported).

The following table compares the cumulative incidence of death between these two cohorts:

Cohort	**Cumulative risk at 8 years**	**95% Confidence Interval**
HIFU Long Term Refined	9.0%	6.2, 11.6%
PIVOT low risk RP subgroup	25.0%	18.7, 32.6%

FDA Comment: The clinical significance of this descriptive comparison is unclear given the natural history of low risk prostate cancer and the PIVOT study conclusions.

- Prostate Cancer Specific Survival

In the HIFU Long Term Refined Cohort, 0.4% (1/227) of subjects died from prostate cancer following treatment (any time), for a Kaplan-Meier 8-year cancer-specific survival estimate of 99.2% (94.2, 99.9%). In the PIVOT low risk RP subgroup, 4.1% (6/148) of subjects died from prostate cancer at some time during the study period (Kaplan-Meier survival rate not reported).

The following table compares the cumulative incidence of death from prostate cancer between these two cohorts:

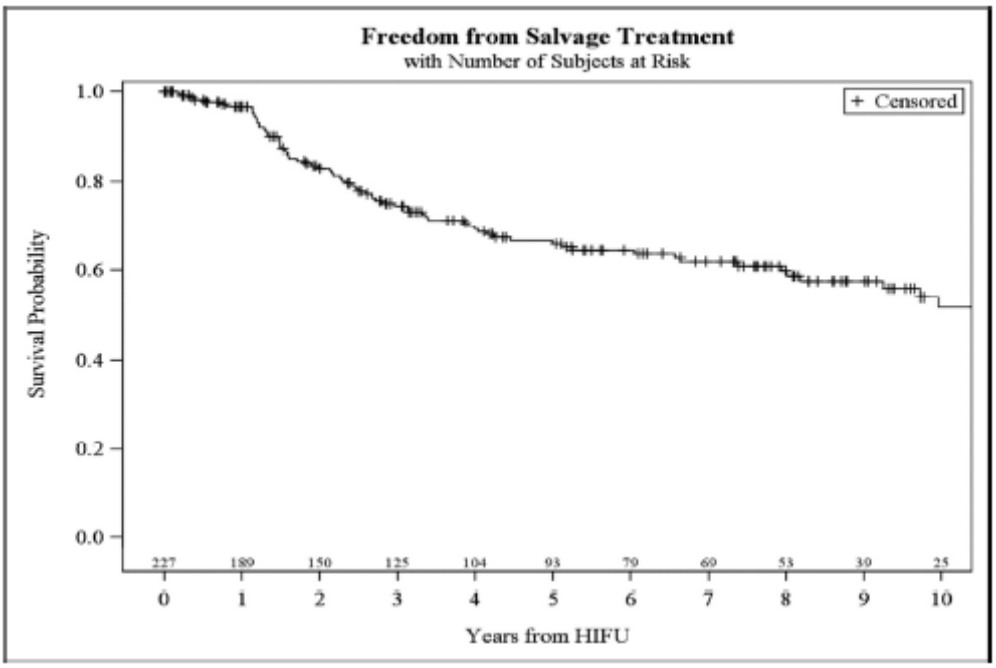
Cohort	**Cumulative risk at 8 years**	**95% Confidence Interval**
HIFU Long Term Refined	0.4%	0.0, 1.0%
PIVOT low risk RP subgroup	1.4%	0.4, 4.8%

FDA Comment: The clinical significance of this descriptive comparison is unclear given the natural history of low risk prostate cancer and the PIVOT study conclusions.

- Freedom from Salvage Therapy

In the HIFU Long Term Refined Cohort, a total of 34% (77/227) of subjects had a salvage therapy following Ablatherm HIFU (any time), for a Kaplan-Meier 8-year freedom from salvage therapy estimate of 59.8% (51.6, 67.1%). These salvage therapies exclude adjuvant HIFU procedures performed within 1 year of index Ablatherm HIFU (i.e., this incidence of salvage therapy is in addition to the incidence of adjuvant HIFU procedures). The Kaplan-Meier plot of freedom from salvage therapy versus time is provided in the figure below:

Freedom from Salvage Treatment – HIFU Long Term Refined Cohort



In the PIVOT trial, no information is reported on the salvage therapies experienced in the RP arm. Therefore, no comparison of salvage therapy rates between these Ablatherm HIFU and RP cohorts is possible.

Based on biopsy results and other clinical information, European Ablatherm HIFU cohort subjects received repeat Ablatherm HIFU within 1 year (i.e., "adjuvant HIFU") in 15% of cases, and salvage therapy (i.e., repeat Ablatherm HIFU > 1 year, radiotherapy, hormone therapy, or RP) in 34% of cases. The Kaplan-Meier 8-year estimate of freedom from salvage therapy is 60%. While it would be meaningful to compare this information to the RP dataset, this information is not reported in the PIVOT study. The panel will be asked to discuss the clinical meaningfulness of the metastasis rate comparison between Ablatherm HIFU and the PIVOT RP arm given the available information regarding the rate salvage therapy following Ablatherm HIFU and the inability to compare this information to the RP control.

Exploratory Effectiveness Analyses:

- Freedom from Positive Biopsy

In the HIFU Long Term Refined Cohort, post-HIFU biopsy was only performed at physician discretion (not routinely performed). Overall, 20% (45/227) of subjects had a positive biopsy within 10 years of whole gland Ablatherm HIFU. Kaplan-Meier estimates for positive biopsy were 13%, 24%, and 27% at 2, 8, and 10 years (respectively) following index Ablatherm HIFU treatment.

In the PIVOT trial, no comparable information is reported for RP subjects. Therefore, no comparison of positive biopsy rates between these Ablatherm HIFU and RP cohorts is possible.

Routine biopsies were not performed in the HIFU Long Term Refined Cohort. Even so, the Kaplan-Meier estimates of positive biopsy following Ablatherm HIFU in this population were 13% and 24% at 2 and 8 years, respectively. As described later in this Executive Summary, in the IDE study where the protocol required repeat prostate biopsy in all subjects at 2 years, 28% of subjects were documented to have a positive biopsy. There is no comparator available for this information. The panel will be asked to discuss the clinical meaningfulness of the metastasis rate comparison between Ablatherm HIFU and the PIVOT RP arm given the available information regarding the rate of positive biopsy following Ablatherm HIFU.

- PSA Nadir

In the HIFU Long Term Refined Cohort, PSA measurements were generally performed per physician discretion and patient availability (i.e., not performed according to a standard follow-up schedule). The PSA nadir following Ablatherm HIFU was calculated as the lowest PSA achieved within 6 months of the final Ablatherm HIFU treatment. A subject was considered a success for this endpoint if a PSA < 0.5 ng/mL was achieved. PSA nadir was indeterminate for subjects in whom no PSA data was collected during this 6-month period.

Of the 214 subjects with PSA nadir data, 57% met the criteria for PSA nadir success.

In the PIVOT trial, no comparable information is reported for RP subjects. Therefore, no comparison of PSA nadir success rates between these Ablatherm HIFU and RP cohorts is possible.

<u>FDA Comment</u>: The clinical significance of this single-arm PSA-based outcome is unclear.

- Biochemical Failure (Phoenix definition) at 2, 5, and 10 years

In the HIFU Long Term Refined Cohort, PSA measurements were generally performed per physician discretion and patient availability (i.e., not performed according to a standard follow-up schedule). While there are no validated definitions of biochemical failure following HIFU, this analysis is based on the Phoenix definition (i.e., PSA nadir + 2 ng/mL) as this is the most commonly used definition in the clinical literature. Freedom from biochemical failure was estimated using Kaplan-Meier analyses with subjects censored at the time of the latest available post-HIFU PSA or at the time of salvage treatment. Subjects with an indeterminate nadir PSA are excluded from the analysis.

Kaplan-Meier estimates for Phoenix biochemical failure were 11%, 30%, and 50% at 2, 5, and 10 years (respectively) post-HIFU.

In the PIVOT trial, no comparable information is reported for RP subjects. Therefore, no comparison of biochemical failure between these Ablatherm HIFU and RP cohorts is possible.

FDA Comment*: *The clinical significance of this single-arm PSA-based outcome is unclear.

Safety Comparisons

To evaluate the safety of Ablatherm HIFU relative to RP, EDAP analyzed a subgroup of the HIFU Long Term Cohort that consists of subjects who were prospectively followed for adverse event collection within one of three prior studies between 2003 and 2013. This subgroup is referred to as the "HIFU Prospective Safety Cohort." Although EDAP also collected detailed, prospective adverse event information in a cohort of Ablatherm HIFU subjected treated under IDE G050103 (detailed under "Intermediate-Term Clinical Information," below), the HIFU Prospective Safety Cohort was created to assess the safety profile of Ablatherm HIFU in a population that underwent similar rates of adjuvant HIFU and salvage therapy as the Ablatherm HIFU cohort evaluated for effectiveness (i.e., the HIFU Long Term Refined Cohort). (IDE subjects were not permitted to have either adjuvant HIFU or salvage therapy, and, thus, may result in a "best case scenario" that could lead to a biased safety analysis for the benefit-risk assessment.)

The HIFU Prospective Safety Cohort consists of 62 subjects who were enrolled into one of three different studies (identified below) conducted at Lyon, France. While each of these single arm studies occurred at different times and had unique objectives, all followed subjects prospectively following Ablatherm HIFU for a defined period of time for adverse events.

- Cohort Study Distribution:
    - Study 1 ("HIFU-INT-06.01"):

- N=17 subjects
- 2006-2007
- Follow-up through 6 months
- Safety endpoints: Thickness of the preserved rectal wall by MRI; adverse events collected at all follow-up visits.

o Study 2 ("HIFU-F-02.5"):
- N=27 subjects
- 2003-2005
- Follow-up through 3 months
- Safety endpoints: Frequency, severity and resolution of adverse events occurring during and after HIFU treatment.

o Study 3 ("HIFU-F-05.02"):
- N=18 subjects
- 2007-2013
- Follow-up through 12 months
- Safety endpoints: Nature, intensity and frequency of adverse events; thickness of the preserved rectal wall by MRI, description of the prostate size modifications between treatment start and end; IPSS, IIEF-5, EORTC QLQ-C30, and continence questionnaires.

- Total Follow-Up Duration:
  - Median = 5 years

FDA Comment: ***There are several limitations with the HIFU Prospective Safety Cohort. First, the number of subjects (n=62) is low for a primary analysis of safety. Additionally, subjects were followed prospectively for safety for different durations of time (ranging from 3 to 12 months), depending on which study there were in. Only 84% of the pooled cohort was followed for 2 years or more.***

- Demographics/Baseline:

	HIFU Prospective Safety Cohort	**HIFU Long Term Refined Cohort**
Age	70 years (53-78)	68 years (50-81)
PSA	5.9 ng/mL (0.3-10)	5.7 ng/mL (0.1-10)
Gleason score	5.8 (4-6)	5.4 (2-6)
Stage	T1a -1.6% T1b – 3.2% T1c – 61.3% T2a – 33.9%	 T1c - 64.3% T2a - 35.7%
Prostate volume	26.1 cc (12-43)	26.7 cc (6-79)

- Ablatherm Model Used:
    - 29% were treated with the Ablatherm Maxis (during 2000-2004), and
    - 71% were treated with the Ablatherm Integrated Imaging (2005 and after).

- Treatment Characteristics:
    - Most subjects had a procedure to right-size the prostate:
        - 63% received prior/concomitant TURP, and
        - 11% received prior hormone therapy.
    - HIFU Prospective Safety Cohort subjects were similar to HIFU Long Term Refined subjects with respect to index HIFU treatment parameters/characteristics.
    - Procedures after the index HIFU treatment:
        - 11% underwent adjuvant HIFU, and
        - 47% underwent salvage therapy.

FDA Comment: ***The HIFU Prospective Safety Cohort differs from the HIFU Long Term Refined Cohort utilized for the effectiveness analyses in several important ways including age (safety cohort patients were older), concomitant therapies at the time of the index HIFU procedure (11% received prior or concomitant hormone therapy, and 63% underwent TURP), and salvage therapy (47%). The collective impact of these differences is unknown.***

- Safety Results – Adverse Events:
    - A total of 75 adverse events were reported in 63% (39/62) of subjects.
        - Device relatedness: 61% of adverse events were device-related (mainly erectile dysfunction, UTI, urinary incontinence, retention, and dysuria), and 3% were unrelated (remainder were not evaluable/unknown).
        - Severity: 27% were "high intensity" (half of which were erectile dysfunction), 36% were "moderate," and the remainder were "low" or unknown.

The following table summarizes all adverse events (regardless of relationship) occurring in two or more HIFU Prospective Safety Cohort subjects:

Adverse Event	Number of Events	Number (%) of Subjects
Any	75	39 (63%)
Erectile Dysfunction	19	18 (29%)
Urinary Tract Infection	16	12 (19%)
Urinary Incontinence (grade 1)	15	15 (24%)
Urinary Retention	7	7 (11%)
Dysuria	4	4 (6%)
Hematuria	2	2 (3%)

Urinary Incontinence (grade 2)	2	2 (3%)

*Clinically relevant events occurring in 1 subject each were: rectal lesion seen on MRI, rectal wall injury, and urethral stenosis.

Most (79%) of these adverse events were reported within 3 months of the index HIFU procedure, and most (57%) resolved. Notable exceptions were:

- Erectile dysfunction ongoing in 13/19 events.
- Incontinence (grade 1) ongoing in 6/15 events.
- Incontinence (grade 2) ongoing in 2/2 events.

These Ablatherm HIFU adverse events are compared to those reported for the RP arm of the PIVOT study. Since the PIVOT study report does not stratify the RP arm safety data by D'Amico category, data from the entire cohort of RP subjects (n=280) are reported.

The PIVOT study stratifies adverse events by the following three categories: surgical events, perioperative events (i.e., occurring within 30 days), longer-term events (i.e., ongoing urinary incontinence, erectile dysfunction, and bowel dysfunction at 2 years post-treatment). The following tables, reproduced from Wilt et al., summarize (i) the surgical and perioperative events, and (i) the long-term events, respectively, for RP arm subjects:

Table 1. Adverse Events Occurring within 30 Days after Surgery.*

Event	Patients (N = 280)
	no. (%)
Any	60 (21.4)
Pneumonia	2 (0.7)
Wound infection	12 (4.3)
Urinary tract infection	7 (2.5)
Sepsis	3 (1.1)
Deep-vein thrombosis	2 (0.7)
Stroke	1 (0.4)
Pulmonary embolism	2 (0.7)
Myocardial infarction	3 (1.1)
Renal failure or dialysis	1 (0.4)
Bowel injury requiring surgical repair	3 (1.1)
Additional surgical repair	7 (2.5)
Bleeding requiring transfusion	6 (2.1)
Urinary catheter present >30 days after surgery	6 (2.1)
Death	1 (0.4)
Other	28 (10.0)

* Of the 364 men randomly assigned to the radical-prostatectomy group, radical prostatectomy was completed in 280. Multiple events may have occurred in a single patient.

Table 2. Patient-Reported Urinary, Erectile, and Bowel Dysfunction at 2 Years, According to Study Group.*

Dysfunction	Radical Prostatectomy	Observation	P Value
	no./total no. (%)		
Urinary incontinence†	49/287 (17.1)	18/284 (6.3)	<0.001
Erectile dysfunction‡	231/285 (81.1)	124/281 (44.1)	<0.001
Bowel dysfunction§	35/286 (12.2)	32/282 (11.3)	0.74

* The values reported are the number of men reporting the dysfunction and the total number of men who responded to the question.
† 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").
‡ Erectile dysfunction was defined as the inability to have an erection or an erection sufficient for vaginal penetration.
§ Bowel dysfunction was defined by patient reports that it was a "moderate" or "big" problem.

Since HIFU Prospective Safety Cohort subjects were not routinely assessed for ongoing urinary incontinence, erectile dysfunction, and bowel dysfunction at 2 years post-treatment, EDAP states that "*comparison of 2-year urinary incontinence, erectile dysfunction and bowel dysfunction between the HIFU Prospective Safety Cohort and the PIVOT RP Cohort is not appropriate*." As a result, the primary analysis of safety involves a comparison of (i) the HIFU IDE Cohort (the characteristics of which are detailed under "Intermediate-Term Clinical Information," below), (ii) the HIFU Prospective Safety Cohort, and (iii) the PIVOT RP arm. As described below, the HIFU IDE Cohort safety data are reflective of subjects who did not undergo any adjuvant HIFU or salvage therapy. The adverse event information (regardless of relationship to Ablatherm HIFU or RP) from these three study groups are summarized in the following table:

Adverse Events	HIFU IDE (n=135) From Table 29, PMAA CSR	HIFU Prospective Safety (n=62) From Table 26, Long Term CSR	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%)	231 (81.1%)[3] Unresolved at 2 years
Urinary Incontinence	52 (38.5%)	17 (27.4%)	49 (17.1%)[4] Unresolved at 2 years
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]
Death	0	0	1 (0.4%)[2]
Wound Infection	0	0	12 (4.3%)[2]
Sepsis	2 (1.5%)[6]	0	3 (1.1%)[2]
Deep Vein Thrombosis	0	0	2 (0.7%)[2]
Stroke	0	0	1 (0.4%)[2]
Pulmonary Embolism	0	0	2 (0.7%)[2]
Myocardial Infarction	0	0	3 (1.1%)[2]
Renal failure or dialysis	0	0	1 (0.4%)[2]
Bowel Injury	4 (3.0%)[7]	1 (1.6%)[8]	Not Reported
Bowel injury requiring surgical repair	0	0	3 (1.1%)[2]
Additional surgical repair	0	0	7 (2.5%)[2]
Bleeding requiring transfusion	0	0	6 (2.1%)[2]
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 considered to be related to ether the device or procedure (Table 30 of the PMA Application Clinical Study Report)
[7]4 Anal tears
[8]Rectal wall injury

***FDA Comment**: Several of the separately-reported adverse event categories are related, and may be more clinically meaningful for interpretation when combined, as follows: "voiding symptoms" (e.g., bladder/urinary urgency, urinary frequency, hesitancy, incomplete bladder emptying, irritative symptoms, nocturia, lower urinary tract symptoms, etc.), "urinary retention" (e.g., urinary restriction, retention, obstruction, etc.), "stricture" (e.g., urinary stricture, urethral stenosis, bladder neck contracture, etc.), "bowel dysfunction" (e.g., constipation, diarrhea, hemorrhoidal pain, nausea, vomiting, ischemic bowel, rectal bleeding, etc.), and "urethral injury" (e.g., urethral perforation, sloughing, submucosal hematoma, etc.). From the HIFU IDE Cohort, the incidence rates associated with these general categories are: voiding symptoms in 55%, urinary retention in 49%, stricture in 35%, bowel dysfunction in 21%, and urethral injury in 15%. Given the uncertainty discussed above regarding whether clinical benefit has been demonstrated for Ablatherm HIFU, it is unclear whether the observed morbidity profile is appropriate.*

***FDA Comment**: In the above table, please note that the PIVOT RP safety cohort was not limited to the low risk subgroup of the surgery arm, but rather included all of the patients in the surgery arm (i.e., all risk subgroups).*

***FDA Comment**: In general, cross-study comparison of safety is challenging due to differences in safety adverse event definitions, as well as the timing and frequency of data collection. These factors are particularly important for quantification of erectile dysfunction and urinary incontinence, both of which change over time following these procedures and have varying definitions. Certain perioperative complications (such as urinary retention, dysuria, and hematuria) appear not to have been collected in the PIVOT study, possibly due to their expected nature following RP.*

A safety analysis of Ablatherm HIFU in both the HIFU IDE Cohort and the HIFU Prospective Safety Cohort demonstrate significant morbidity of the HIFU procedure, although not worse than that reported for RP. Common adverse events (from the HIFU IDE Cohort) were erectile dysfunction, voiding symptoms (e.g., bladder/urinary urgency, urinary frequency, hesitancy, incomplete bladder emptying, irritative symptoms, nocturia, lower urinary tract symptoms, etc.), urinary retention (e.g., urinary restriction, retention, obstruction, etc.), urinary incontinence, urinary tract infection, stricture (e.g., urinary stricture, urethral stenosis, bladder neck contracture, etc.), bowel dysfunction (e.g., constipation, diarrhea, hemorrhoidal pain, nausea, vomiting, ischemic bowel, rectal bleeding, etc.), and urethral injury (e.g., urethral perforation, sloughing, submucosal hematoma, etc.). While this safety information from the HIFU IDE Cohort does not take into account the likely increased morbidity associated with the repeat and salvage therapies that occurred in the various European registry cohorts, these safety data are likely the most accurate due to the rigorous prospective follow-up received by HIFU IDE subjects. Comparison of Ablatherm HIFU safety

to the PIVOT RP arm is provided, although there are differences in the event definitions, reporting, and timing of follow-up, as well as in key patient characteristics (i.e., age, concomitant therapies, and salvage treatment). Comparison to the observation arm of the PIVOT trial is neither performed nor possible since the PIVOT study does not report this information. Given the Ablatherm HIFU adverse event profile and the issues surrounding cross-study comparisons to the RP arm of the PIVOT study, the panel will be asked discuss the appropriateness and interpretability of this safety analysis.

7.2 Intermediate-Term Clinical Information:

Overview

To supplement the long-term clinical data discussed above, the PMA contains the results of several intermediate-term clinical datasets.

The initial clinical dataset originally as the primary evidence to support PMA approval was designed and begun under IDE G050103. For reasons described below, the G050103 clinical study was ultimately terminated early and not completed per the protocol. As presented in detail elsewhere in this Executive Summary, EDAP's termination of the IDE study led them to develop a series of alternate datasets to support the safety and effectiveness of Ablatherm HIFU, beginning with the intermediate-term clinical information comparing Ablatherm HIFU (derived from the IDE, a European registry, and meta-analyses of the published literature) to cryotherapy (detailed below), followed by long-term clinical information comparing Ablatherm HIFU (derived from newly available European registry results) to the RP arm of the PIVOT study.

The development of the intermediate-term clinical information is described below.

IDE G050103 Summary

The IDE study was for a non-randomized, concurrently controlled clinical study to demonstrate that the safety and effectiveness of Ablatherm HIFU is equivalent to (i.e., non-inferior) to cryotherapy at 2 years. The IDE's primary effectiveness endpoint for assessing non-inferiority was a composite consisting of (i) biochemical success, defined as a PSA nadir of ≤ 0.5 ng/mL within 6 months and the ASTRO 1996 consensus definition of biochemical recurrence-free survival* through 2 years, and (ii) a negative follow-up prostate biopsy at 2 years. This endpoint is referred to in the PMA as 2-year "Nadir/ASTRO/Biopsy survival."

*According to the ASTRO 1996 consensus definition, biochemical failure is defined as three consecutive PSA rises after the nadir.[5]

Protocol Summary

- Purpose: To demonstrate that Ablatherm HIFU is non-inferior with respect to safety and effectiveness to standard, whole gland cryotherapy (CRYO) in the treatment of low risk, localized prostate cancer.

- Study Design: Multicenter, non-randomized, concurrently controlled, clinical trial involving 27 U.S. sites (15 HIFU, 12 CRYO) and 410 subjects (205 HIFU, 205 CRYO). To minimize bias due to patient self-selection of treatment arm, HIFU and cryotherapy sites were geographically separated by at least 100 miles.

- Patient Population: Adult males, presenting for primary treatment of low risk, localized prostate cancer.

- Inclusion Criteria:
    - Diagnosis of prostate cancer confirmed by PSA and prostate biopsy;
    - Male subject, age ≥ 50 years;
    - Organ-confined prostate cancer, clinical stage T1a, b, or c 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 (Note: a subject with a histological grading of primary 4 will not be permitted for study enrollment);
    - Prostate volume ≤ 40 cc;
    - Prostate AP diameter < 25 mm (HIFU arm) / ≤ 30 mm (CRYO arm);
    - Normal rectal anatomy and rectal mucosa;
    - Maximum rectal wall thickness 6 mm;
    - The investigator has completed a medical history and a physical examination to assure that the subject meets all study enrollment criteria;
    - The subject is willing and able to read, understand and sign the study specific informed consent form; and
    - The subject agrees to comply with study protocol requirements, including HIFU or cryotherapy treatment and all follow-up visit requirements through 24 months following treatment and annual study visits until device approval or study termination.

- Exclusion Criteria:
    - Evidence of seminal vesicle involvement;
    - Evidence of 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 1 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 Ablatherm endorectal probe insertion difficult;
- Anatomic anomaly of the rectum or anomaly of the rectal mucus 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;
- Concurrent illness, disability or geographical residence would hamper attendance at required study visits;
- Known latex hypersensitivity;
- Current participation in another clinical investigation of a medical device or drug or has participated in such a study within 30 days prior to study enrollment; and
- The investigator believes that the subject will be unwilling or unable to comply with study protocol requirements, including the HIFU or cryotherapy procedure and study-related follow-up visit requirements.

- Endpoints:
  - *Effectiveness (primary)* – Nadir/ASTRO/Biopsy survival at 2 years.
  - *Effectiveness (secondary)* –
    - achievement of a PSA nadir of < 0.5 ng/mL by 6 months post-treatment;
    - overall survival rate;
    - disease-specific survival rate;
    - change in UCLA Prostate Cancer Index;
    - change in International Prostate Symptom Score (IPSS);
    - PSA stability/cancer recurrence beyond 2 years;
    - Phoenix biochemical survival;
    - time to first positive biopsy; and

    - time to salvage therapy.
  - *Safety* – Analysis of adverse events (including sexual function information from the UCLA Prostate Cancer Index).

- Statistical Analysis Plan:
  - *Hypothesis / Primary Effectiveness Endpoint Analysis*: The primary effectiveness analysis was a test of non-inferiority of Ablatherm HIFU treatment (as measured by the proportion of patients meeting the primary effectiveness endpoint) to cryotherapy, with a delta of < 10% and assumed success rate of 80% and 79.5% for the HIFU and cryotherapy study arms, respectively. Specifically,

    H_o: $\Pi_C - \Pi_A = 0.10$ versus
    H_A: $\Pi_C - \Pi_A < 0.10$,

    where Π_C and Π_A are the population response rates for cryotherapy and Ablatherm HIFU, respectively.

    From the primary effectiveness endpoint, success is defined as attainment of a PSA nadir of < 0.5 ng/mL within 6 months post-treatment and stability of PSA according to ASTRO criteria through 24-month follow-up without a positive biopsy. Any subject who has a positive biopsy, retreatment, or alternate treatment during the 24-month post-treatment period will be categorized as a "failure."

    The data were to be analyzed using an intent-to-treat (ITT) approach, in which any missing PSA value will be imputed as a "rising" value. Since the study is non-randomized, the primary analysis was to be a stratified analysis that uses propensity scores to form five strata from the baseline variables.

  - *Secondary Effectiveness Endpoint Analyses*: Analyses of the primary effectiveness endpoint were to be repeated using (i) other methods to impute missing data (as sensitivity analyses), and (ii) a per-protocol analysis using only available data.

  - *Safety Endpoint Analysis*: The frequencies of adverse events were to be presented and compared (using Fisher's Exact Test) between Ablatherm HIFU and cryotherapy arms.

- Sample Size: Assuming a type I error of 0.05 and a power of 80%, 184 subjects in each arm were calculated to be necessary to test the study hypothesis. Assuming a loss to follow-up rate of 10%, a total of 205 subjects per arm were targeted for enrollment.

Protocol Modifications

The following modifications to the protocol, incorporated into the above summary, occurred during the IDE study:

- G050103/S018 (9/17/2007) – Increase in the minimum subject age for study inclusion to 60 years; allow prostate AP diameters of up to 30 mm in the cryotherapy arm; add Phoenix biochemical survival as a secondary effectiveness endpoint; allow the Galil Medical CRYO-HIT cryotherapy system to be used in the control arm (in addition to the Endocare CRYOcare system); increase in the number of cryotherapy sites from 6 to 12; and eliminate the separate cohort of Ablatherm training subjects from the study.

- G050103/S022 (2/4/2009) – Decrease in the minimum subject age for study inclusion to 50 years; replace the 5-day follow-up visit with a telephone call; remove alpha blockers and saw palmetto from the exclusion criteria; increase in the number of HIFU sites from 12 to 15; extend the window for the timing of the baseline evaluations prior to treatment; and add the exclusion of subjects with acute prostatitis.

IDE Termination – Alternate Study Plan

Due to a variety of factors, the IDE study was not completed. By 2010, EDAP had experienced poor enrollment (<70%) in the HIFU arm, and essentially no enrollment in the cryotherapy arm. In the clinical report, EDAP describes the efforts that they made to complete the study, concluding that the G050103 study was not possible to complete for a variety of reasons, most notably: (i) inability of subjects seeking cryotherapy to meet the IDE inclusion criteria regarding prostate size, (ii) patient unwillingness to consent for post-treatment biopsies in the absence of elevated PSA (particularly in the control arm), and (iii) shifts in the clinical use of cryotherapy (increasingly being used in conjunction with hormonal therapy and off-label for focal therapy). EDAP evaluated the other existing treatment alternatives for use as a control in this non-inferiority study, and concluded that none were practical or meaningful with this effectiveness endpoint.

Based on their conclusion that the only control option that is clinically meaningful and practically feasible is a retrospective cryotherapy cohort, EDAP decided in 2010 to terminate IDE enrollment, and to obtain comparative cryotherapy data from an ongoing U.S. cryotherapy registry. EDAP developed a prospective protocol to use to select a minimum of 125 registry patients, using inclusion/exclusion criteria that mirror those of the IDE protocol. The primary effectiveness endpoint specified for this comparison was the same as stated in the IDE protocol – Nadir/ASTRO/Biopsy survival at 2 years.

Screening the CRYO registry resulted in the enrollment of only 67 subjects, far below the pre-specified minimum requirement of 125. As a result, EDAP developed a second alternative plan to perform a meta-analysis of the cryotherapy literature to use as the primary comparator for the HIFU IDE data. For the primary effectiveness analysis of these intermediate-term results, EDAP derived a performance goal (i.e., "HIFU PG") from the meta-analysis of the cryotherapy literature against which to compare the HIFU IDE effectiveness results (superiority analysis). Since the only effectiveness endpoint reported in each of these cryotherapy studies is biochemical survival (i.e., routine biopsies not performed), EDAP changed the primary effectiveness endpoint from "Nadir/ASTRO/Biopsy survival at 2 years" to "Phoenix survival** at 2 years." At the same time, since early termination of the IDE study prevented the collection of substantial long-term (i.e., > 2-year) data, EDAP (i) analyzed a retrospective group of men treated with the Ablatherm as part of a European registry, and (ii) performed a meta-analysis of the HIFU literature. As with the cryotherapy meta-analysis, these alternate HIFU data sources also only report effectiveness in terms of Phoenix biochemical survival.

**According to the Phoenix definition, biochemical failure is defined as a PSA rise by 2 ng/mL or more above the nadir.[10]

As a result of the difficulties experienced with the IDE study and alternate sources of clinical data, EDAP reports the following clinical data sources to supplement the long-term data in support of PMA approval:

- HIFU IDE: 136 HIFU subjects enrolled at 13 sites (12 U.S., 1 Canada) under IDE G050103
- HIFU Registry: 199 HIFU subjects obtained from a European registry (outcome data on 115 subjects at 3 sites)
- HIFU MA: Meta-analysis of the HIFU literature (13 articles selected)
- CRYO Retro: 67 cryotherapy subjects obtained from a U.S. registry (outcome data on 64 subjects at 5 sites)
- CRYO MA: Meta-analysis of the cryotherapy literature (25 articles selected)

For completeness, the PMA also summarizes the results from the CRYO IDE cohort (n=5 subjects; not presented in this Executive Summary).

The table below summarizes the endpoints and comparisons being presented in the alternate statistical plan.

Primary Effectiveness Comparison		
	Endpoint	**Time Point**
HIFU IDE vs. HIFU PG	Phoenix Biochemical Survival	2 years
Additional Safety and Effectiveness Comparisons		
	Endpoint	**Time Point**
HIFU IDE vs. CRYO Retro	Phoenix Biochemical Survival PSA Nadir ≤ 0.5 ng/mL	2 years Within 6 months
HIFU Registry vs. CRYO MA	Phoenix Biochemical Survival	2 years and 5 years
HIFU MA vs. CRYO MA	Phoenix Biochemical Survival	2 years and 5 years
HIFU IDE vs. CRYO MA	Safety	
HIFU IDE vs. CRYO Retro	Safety	
HIFU MA vs. CRYO MA	Safety	

HIFU IDE Cohort Overview

Between May 2006 and June 2010, 13 investigational sites treated a total of 135 HIFU IDE cohort subjects. Per the protocol, all subjects were followed a minimum of 2 years. The table below summarizes the subject accountability information by follow-up visit:

	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	136	136	136	136	136	136	136	136	136	136	136
Not Treated[1]	1	1	1	1	1	1	1	1	1	1	1
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

[1]Although subject 121-006 was not treated, he was followed through the Month 1 visit

From the above table, 113/135 subjects were evaluated at 2 years. Of the 22 not evaluated at 2 years:

- 16 withdrew either voluntarily or to seek alternate treatment,
- 4 missed the 24 month visit but did not exit the study, and
- 2 died (due to atherosclerotic cardiovascular disease and lung cancer, respectively).

A total of 389 protocol deviations were documented in 115 subjects. These consisted of "missed study procedure" (n=212), "follow up visit completed out of window" (n=98), "deviation from protocol" (n=18), "enrolled ineligible subject" (n=5), and "other" (n=56). The specific reasons for these deviations are explained by EDAP, which demonstrate that the majority are unlikely to significantly impact assessment of the key safety and effectiveness endpoints, and indicate that this high overall number of deviations is due to investigator thoroughness. Although the "missed study procedure" included 8 cases of missed 2-year biopsy and 7 cases of missed 2-year PSA, the applicant developed an imputation plan to minimize bias. The cases of "enrolled ineligible subject" involved 3 subjects who were upgraded from Gleason 6 to 7 by the core lab after treatment, 1 subject whose prostate AP diameter was below 25 mm at screening but found to be slightly greater than 25 mm at treatment, and 1 subject who had one of two pre-treatment PSAs greater than 10 ng/mL (deemed an artifact due to prior digital rectal exam).

Demographic and baseline information is summarized below:

- Age: mean = 64 years; range = 51-80
- Race: Caucasian (82%), African American (13%), Other (5%)
- PSA: mean = 4.6 ng/mL; range = 0.3-9.9
- Prostate height: mean = 22.4 mm; range = 1.8-25.0
- Digital rectal exam (DRE) findings: nodules present = 12%
- Gleason score: 6 (all 3+3) in 98.5%, 7 (all 3+4) in 1.5%
- Stage: T1a (2%), T1b (2%), T1c (81%), T2a (14%)

Ablatherm HIFU treatment information is summarized below:

- All subjects underwent whole gland Ablatherm HIFU, with intentional ablation of the lateral margins of the prostate in each subject (i.e., nerve sparing <u>not</u> attempted)
- Procedure time: mean = 139 minutes; range = 61-257
- Anesthesia type: General (85%), Spinal (15%), Sedation/Versed (7%)
- Prostate volume treated: mean = 28.3 cc; range = 10.5-48.4
- Total number of HIFU lesions: mean = 516; range = 69-739
- Concomitant procedures performed in 8% (consisting of cystoscopy, proctoscopy, Foley catheter in suprapubic position)
- Malfunctions/interruptions occurred in 31 cases
    - all were error codes designed to ensure safe and effective treatment (i.e., system responding as designed),

- all but 4 treatment interruptions were transient and were resumed,
- the remaining 4 treatment interruptions were classified as device operating errors, all resulted in treatment being suspended and were resolved by rebooting the system (for 3 communication errors) or by replacing a faulty power amplifier and implementing a software update (for 1 power delivery error), and
- all treatments were successfully completed.

HIFU Registry Cohort Overview

To enhance the HIFU IDE data and to provide longer-term (5 year) HIFU results, EDAP reports data on a cohort of subjects enrolled in an EDAP-sponsored European HIFU registry. This information is also expected to provide "real life" information regarding the use of HIFU in clinical practice (i.e., outside of the investigational setting). To minimize bias in the selection process, EDAP developed a prospective protocol to standardize subject inclusion/exclusion, data abstraction, and data analysis. EDAP was blinded from the treatment outcome data during the selection process. All clinical centers* with a minimum of 25 cases meeting the inclusion criteria were selected, and a sample size of 300 was planned. Out of 8,508 patients treated since the start of the registry, 199 subjects from 3 sites were enrolled. Key reasons for being excluded included: the subject was younger than 50 years, did not undergo "whole gland" Ablatherm HIFU, did not have low risk disease, did not have a baseline positive biopsy, had a prior prostate procedure (other than TURP), and had a previous treatment for prostate cancer.

*These are the same European centers that contributed data to the HIFU Long Term Refined Cohort. However, the HIFU Registry cohort is smaller due to more restrictive inclusion/exclusion criteria.

Like the HIFU IDE cohort, these 199 subjects all had low risk, localized prostate cancer. However, unlike the HIFU IDE cohort, many of these subjects had a surgical or hormonal treatment immediately prior to HIFU to "right-size" the prostate, and some may have had HIFU retreatment. Most of the HIFU Registry subjects were treated with the Ablatherm Maxis instead of the Ablatherm Integrated Imaging.

The specified primary effectiveness endpoint is Nadir/ASTRO/Biopsy survival, consistent with the G050103 protocol. However, this was later replaced by Phoenix survival due to the lack of routine biopsy data in the absence of rising PSA.

Of the 199 subjects enrolled into the HIFU Registry cohort, only 115 had sufficient PSA data to enable assessment of 2-year Phoenix biochemical survival (i.e., one PSA prior to 6 months and another at or after 2 years, or are known failures prior to 2 years due to salvage therapy). Of

these 115, 76 have sufficient data to assess 5-year Phoenix survival. This missing information is to be expected, given that these subjects were not treated as part of a standard protocol.

Demographic and baseline information for these 115 subjects are summarized below:

- Age: mean = 68 years; range = 49-79
- Race: not reported (likely predominantly Caucasian at these European sites)
- PSA: mean = 5.5 ng/mL; range = 0.1-9.9
- Gleason score: 6 (50%), remainder were below 6
- Stage: T1a (7%), T1b (10%), T1c (48%), T2a (35%)

Of the 115 subjects:

- 39 (34%) had retreatment, involving:
    - 32 HIFU retreatments,
    - 10 radiotherapy treatments,
    - 6 hormone therapy treatments,
    - 1 cryotherapy procedure, and
    - 1 radical prostatectomy.

HIFU MA Overview

To further enhance the HIFU IDE data and to provide additional long-term (5 year) HIFU data, EDAP performed a meta-analysis of the HIFU literature. This literature-based meta-analysis estimated biochemical survival rates at 2 and 5 years. The search involved all English language literature published from 1997 to 2012. Criteria for inclusion in the meta-analysis included prospective or retrospective cohort studies of patients with low risk, localized prostate cancer treated with HIFU. Reports on focal HIFU and salvage HIFU were excluded, as were duplicative reports. Thirteen (13) studies (on 1,193 pooled subjects) were identified and included in the meta-analysis.

The purpose of this meta-analysis is to provide additional 2 and 5-year HIFU outcome data as supportive evidence for the PMA (i.e., Phoenix survival estimates, and adverse events). The estimated biochemical survival rates were obtained using random-effects linear regression models. Disparate definitions of biochemical survival were aggregated.

In addition to the above meta-analysis, EDAP also submitted literature articles from a broader, less-restrictive search of the HIFU literature (n=27 articles; Section 8), with the intent of providing all information known regarding the safety and effectiveness of HIFU in the treatment of localized prostate cancer. The search includes all articles published between 1997-2012 that report prospective/retrospective studies of whole gland HIFU, excluding case reports/series.

CRYO Retro Cohort Overview

As described above, EDAP retrospectively collected the CRYO Retro cohort with the intention of using it as a replacement for the CRYO IDE cohort. Data from these retrospective subjects were from a U.S. registry ("COLD Registry"). To minimize bias in the selection process, EDAP developed a prospective protocol to standardize subject inclusion/exclusion, data abstraction, and data analysis. EDAP was blinded from the treatment outcome data during the selection process. A total 1,883 subjects were screened. Unfortunately, enrollment into the CRYO Retro cohort also proved difficult due to the exclusion of subjects who had undergone previous hormone therapy and the prevalent use of off-label focal cryotherapy. Also, the plan to obtain post-treatment biopsies in CRYO Retro subjects was a deterrent to subjects consenting to enrollment. Ultimately, the CRYO Retro cohort only consented and enrolled a total of 67 subjects – short of the target enrollment goal of 125.

Like the HIFU IDE cohort, these 67 subjects all had low risk, localized prostate cancer. All received conventional, whole gland cryotherapy (i.e., using cleared cryotherapy systems, a double freeze technique, at least 5 cryoprobes, and a cleared urethral warmer). One third of the cohort received treatment prior to 2005.

The specified primary effectiveness endpoint is Nadir/ASTRO/Biopsy survival, consistent with the G050103 protocol. However, this was later replaced by Phoenix survival due to the lack of routine biopsy data in the absence of rising PSA.

Of the 67 subjects enrolled into the CRYO Retro cohort, only 64 (at 5 sites) had at least 24 months of follow-up. Of these 64, only 62 had sufficient PSA data for both nadir and 2-year Phoenix survival assessment.

Demographic and baseline information for these 67 subjects are summarized below:

- Age: mean = 70 years; range = 55-80
- Race: Caucasian (87%), African American (7%), not specified (6%)
- PSA: mean = 5.3 ng/mL; range = 1.0-9.7
- Gleason score: 6 (all 3+3) in 95.5%, remainder were < 6 or not specified
- Stage: T1a (0%), T1b (0%), T1c (84%), T2a (13%), not specified (3%)
- Prostate volume: mean = 30.7 cc
- Pre-existing erectile dysfunction: 70%

CRYO MA Overview

Following the inability to enroll an adequate number of subjects into the CRYO Retro cohort, EDAP developed a new statistical plan to compare the HIFU IDE results to a meta-analysis of literature-reported cryotherapy results (CRYO MA). This literature-based meta-analysis estimated biochemical survival rates at 2 and 5 years associated with contemporary, whole gland cryotherapy. The search involved all English language literature published from 1997 to 2012. Criteria for inclusion in the meta-analysis included prospective or retrospective cohort studies of patients with low risk, localized prostate cancer treated with HIFU. Reports on focal HIFU and salvage HIFU were excluded, as were duplicative reports. Twenty-five (25) studies (on 1,864 pooled subjects) were identified and included in the meta-analysis.

EDAP's stated 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 the effectiveness of Ablatherm HIFU. Also, this meta-analysis provides 2 and 5-year cryotherapy outcome data as supportive evidence for the PMA (i.e., Phoenix survival estimates, and adverse events). The estimated biochemical survival rates were obtained using random-effects linear regression models. Disparate definitions of biochemical survival were aggregated.

From analysis of the literature used for the CRYO MA, the estimated 2-year Phoenix survival rate for contemporary, whole gland cryotherapy is 87% with a range of 69% to 96%. EDAP set the lower bound performance goal (i.e., the HIFU PG) at 5% lower than the estimated cryotherapy biochemical survival rate to (i) allow for variability in the literature based estimate as well as in the HIFU estimate and (ii) provide the basis for the conclusion that the HIFU biochemical survival rate is similar to cryotherapy biochemical survival rate. For these reasons, the stated HIFU PG is 82%. In their revised statistical analysis plan, EDAP proposes to demonstrate that Ablatherm HIFU is superior to HIFU PG with respect to 2-year Phoenix survival.

Effectiveness Comparisons

As previously described, the primary effectiveness endpoint and the comparator differ from that specified in the G050103 study protocol: (i) the primary effectiveness endpoint has changed from "Nadir/ASTRO/Biopsy survival at 2 years" to "Phoenix survival at 2 years," and (ii) the primary comparator has changed from the concurrent CRYO IDE cohort (non-inferiority analysis) to the HIFU PG performance goal (superiority analysis). Although the IDE statistical analysis plan specified the use of the ITT population for the primary effectiveness analysis, EDAP states that the most appropriate analysis population for comparison to the HIFU PG is the 24-month completers (n=116).

As summarized below, the 2-year Phoenix survival rate in the HIFU IDE cohort was found to be superior to the HIFU PG:

Cohort	Phoenix Biochemical Survival Rate @ 2 Years*	95% Confidence Limits	p-value
HIFU IDE	90.5%	85.2, 95.8%	0.009
HIFU PG	82%	n/a	

*Based on the population of 24-month completers.

***FDA Comment**: The Phoenix biochemical survival endpoint was developed in context of radiotherapy only, and is not a validated endpoint for HIFU. Neither Phoenix survival nor any other PSA-based endpoint has been validated as a surrogate for the gold standard endpoint of overall survival; therefore, it is challenging to draw clinical conclusions based on analysis of these results.*

***FDA Comment**: The use of a performance goal as the primary comparator in the context of this clinical indication creates challenges for data interpretation. Performance goals are usually used in situations where the disease condition is well understood and treatment response is highly homogeneous. If the treatment response is heterogeneous (i.e., heavily dependent on certain characteristics of individual patients and/or medical practice), using a performance goal can introduce serious bias into the effectiveness comparison. In this PMA, the reported outcomes of the various HIFU and cryotherapy cohorts suggest that treatment response is highly heterogeneous for prostate cancer, which casts doubt on the appropriateness of the performance goal approach in the present situation. Additionally, the CRYO MA results, upon which this performance goal is based, may be difficult to interpret and subject to bias (due to different patient selection, device/treatment parameter variations, extent and timing of treatment, potential retreatments, etc.). Furthermore, the specific performance goal that was chosen (i.e., Phoenix survival at 2 years of 82%) lacks a statistical justification and a meaningful clinical interpretation.*

Based on EDAP's revised analysis plan, the following descriptive comparisons are presented as secondary effectiveness endpoints:

Cohort	Phoenix Biochemical Survival Rate @ 2 Years*	PSA Nadir ≤ 0.5 ng/mL within 6 months**
HIFU IDE	90.5% (85.2, 95.8%)	74.1% (66.7, 81.5%)
CRYO Retro	95.2% (90.0, 100.0%)	80.6% (61.1, 90.1%)

*Based on the population of 24-month completers.
**Based on the ITT populations.

Cohort	Phoenix Biochemical Survival Rate @ 2 Years*	Phoenix Biochemical Survival Rate @ 5 Years*
HIFU Registry	94.4% (90.0, 98.8%)	82.9% (74.4, 91.4%)
CRYO MA	87% (range: 69-96%)	81% (range: 49-93%)

*Based on the population of evaluable subjects.

Cohort	Phoenix Biochemical Survival Rate @ 2 Years*	Phoenix Biochemical Survival Rate @ 5 Years*
HIFU MA	92% (range: 74-98%)	83% (range: 66-88%)
CRYO MA	87% (range: 69-96%)	81% (range: 49-93%)

*Based on the population of evaluable subjects.

From the HIFU IDE data, there was no statistical evidence that baseline covariates (age, prostate volume, Gleason score, cancer stage) are associated with 2-year Phoenix survival. Subjects with lower baseline PSA had a higher likelihood of 2-year Phoenix survival.

FDA Comment: No hypotheses were proposed or are tested for these secondary effectiveness endpoint comparisons, and no statistical conclusions are possible. The clinical significance of these PSA-based outcomes is unclear.

FDA Comment: Limitations with the HIFU Registry cohort are that this dataset includes subjects with "right-sizing" and retreatment, both of which confound the effectiveness results. Additionally, these subjects were not treated and followed according to a uniform, prospective protocol, further complicating the comparisons.

FDA Comment: Limitations with the CRYO Retro cohort include (i) the baseline and demographic characteristics of these subjects being too dissimilar to those of the HIFU IDE subjects to allow for a propensity score adjusted comparison of the endpoints, (ii) only 18% of CRYO Retro subjects had a biopsy on or before 24 months and none of the others would consent to a post-treatment biopsy in the absence of rising PSA (making it impossible to assess

the Nadir/ASTRO/Biopsy survival endpoint used in the IDE), and (iii) the questionnaire data (i.e., QoL, IPSS) that were sought were unavailable for most subjects. Also, subjects who had previously expired could not be included due to the inability to obtain informed consent. The value of this cohort as a control population is limited due to small sample size, missing and uncollected information, and dissimilar baseline and demographic characteristics.

FDA Comment: The HIFU and CRYO meta-analysis results are difficult to interpret and likely subject to bias (due to different patient selection, device/treatment parameter variations, extent and timing of treatment, potential retreatments, collection and reporting of results, etc.).

Since biopsy data at 2 years were only collected in the HIFU IDE cohort, no comparison to cryotherapy is possible. The results of this single-arm analysis are summarized below:

- 118/135 subjects had a post-treatment biopsy at or before 2 years:
  - 38 were positive, and
  - 80 were negative.
- Based on the evaluable subjects, the observed rate of positive biopsy 2 years following a single Ablatherm HIFU was 32% (38/118). Assuming that all 17 subjects who did not undergo biopsy were cancer-free (best-case scenario), the 2-year rate of positive biopsy is 28% (38/135).

FDA Comment: A 28% rate of positive biopsy rate at 2 years appears high for a definitive therapy.

Safety Comparisons

Due to the fact that HIFU IDE subjects had regular, prospective follow-up for 2 years, they provide the primary source of safety data for Ablatherm HIFU.

Overall, a total of 1,012 adverse events were reported in 131 subjects. Of these, 811 resolved, 192 were ongoing, and 5 resulted in death (none related to Ablatherm HIFU or prostate cancer). Approximately half of the adverse events (531) were rated as mild, 352 were moderate, and 129 were severe. Seven hundred fifty-five (755) of the events were deemed device/procedure related.

The overall HIFU IDE event rates (regardless of relationship to Ablatherm HIFU) were presented previously in comparison to the HIFU Prospective Safety and PIVOT RP cohorts under "Long-Term Clinical Information." The HIFU IDE device/procedure related adverse events reported in > 3% of HIFU IDE subjects are summarized in the following table:

Adverse Event	Any Occurrence	Unresolved at 24 Months
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%
Slow Stream	23.0%	4.4%
Urinary Stricture	18.5%	1.4%
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%
Urethral Sloughing	12.6%	3.0%
Nocturia	11.1%	5.9%
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%
Includes device and/or procedure related adverse events occurring with a frequency >3%. Percentages on the same row are not additive.		

Rectal fistula, which was actively monitored in the HIFU IDE cohort using proctoscopy, was not observed.

Although the primary safety analysis in the PMA is the comparison of the HIFU IDE cohort to the RP arm of the PIVOT study (presented earlier under “Long-Term Clinical Information”), EDAP also compares HIFU IDE cohort adverse events to those of cryotherapy since both of these therapies cause tissue ablation. The cryotherapy data summarized in the table below were obtained from the following sources: the CRYO Retro cohort, and the cryotherapy arm of the randomized study (versus EBRT) reported by Donnelly et al.[12]:

Adverse Event	CRYO Retro (n=67 subjects)	Donnelly et al. (n=117 subjects)
Erectile Dysfunction	24%	70%*
Urinary Incontinence (any)	18%	32%
Urinary Retention	9%	22%
Urinary/Bladder Outlet Obstruction	6%	
Urinary Stricture	2%	
Sloughing	3%	
Urinary Urgency	15%	65%
Urinary Frequency	13%	
Hematuria	16%	Not reported
Urinary Tract Infection	12%	Not reported
Nocturia	9%	Not reported
Dysuria	6%	Not reported
GU Pain	5%	10%
GI Pain		16%
Fecal Incontinence	0%	8%
Rectal Fistula	0%	0%

*Unresolved at 24 months with or without medical therapy.

EDAP states that the CRYO Retro adverse event profile appears to be underreported, relative to the published report by Donnelly et al.

***FDA Comment*: It is difficult to make valid cross-study comparisons of safety between the HIFU IDE cohort and these cryotherapy cohorts. The CRYO Retro results are retrospective data obtained from subjects who were not prospectively followed according to a standard protocol. While the Donnelly et al. article provides a more rigorous assessment of adverse events following cryotherapy, it is questionable whether this information is suitable for comparison to HIFU IDE as these cryotherapy subjects were older and from a higher risk strata, and received neoadjuvant hormone therapy. For both of the cryotherapy datasets, it is unknown whether comparable definitions were used to categorize the adverse events. A separate limitation of this supplementary safety analysis is that the PMA does not contain an effectiveness analysis comparing HIFU to cryotherapy using a valid, clinically meaningful endpoint, making it difficult to develop a balanced benefit-risk analysis for this safety comparison.**

8. Post-Approval Study Considerations

FDA Comment: ***The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The issues noted below are FDA's comments regarding potential post-approval studies (if FDA finds the device approvable), for the Panel to include in the deliberations.***

If the Ablatherm HIFU device were to be approved, FDA believes a post-approval study (PAS) is necessary. Through review of the premarket data, the FDA review team has identified the following potential post-market concerns that may need to be addressed:

- Evaluation of acute and long term outcomes associated with the device safety.
- Evaluation of long term device performance with regards to effectiveness.

The applicant is proposing to conduct a PAS in which the overall goal is to generate long term clinical data from the use the Ablatherm HIFU device in the United States to assess the metastasis free survival rate. The applicant submitted a protocol outline interactively on April 24, 2014. An overview of the PAS outline is provided in the table below, followed by FDA's assessment.

8.1 Overview of Applicant's PAS Proposal

The following table presents the applicant's PAS protocol outline.

Study Component	**Description**
Study Objective	To follow a cohort of subjects treated with whole gland Ablatherm HIFU in the United States to assess the freedom from metastasis rate.
Study Design	This is an on label prospective, uncontrolled (single arm), multicenter study. A total of 15 US sites will participate in the study. IDE and non-IDE sites will be needed to complete the target subject enrollment.
Study Population	IDE active (not previously withdrawn) subjects who are willing to sign a new consent form will be included in the study and will be followed clinically following this study protocol. Non-IDE subjects will be needed and it is expected that additional non-IDE study sites will be required in order to complete the target subject enrollment. All males 50 years old and older diagnosed with low risk prostate cancer will be considered eligible for study participation and will be enrolled in the study based on the study entry criteria.

Study Component	**Description**
Sample Size (Patients and Sites)	No formal statistical hypotheses will be tested. Rather the sample size of 500 subjects was chosen to provide sufficient precision in the estimation of the primary and secondary endpoints. An expected 8 year metastasis free survival estimate (from the EU HIFU cohort) of 98.2% survival, an accrual period of 3 years, a minimum follow-up of 8 years and an annual lost to follow-up rate of up to 5%. A sample size of 500 subjects will provide approximately 300 subjects with follow-up through 8 years and 7 metastasis events. There is a >90% probability the precision of the 8 year metastasis free survival rate will be less than 2.25% and a >99% probability the precision will be less than 2.5%.
Endpoints	**Primary Endpoint** The occurrence of prostate cancer metastasis at eight years post Ablatherm HIFU procedure. This "surrogate-free" endpoint incorporates clinically relevant safety and effectiveness outcomes. **Secondary endpoints** • Overall survival following Ablatherm HIFU • Cancer specific survival following Ablatherm HIFU • Freedom from salvage treatment following Ablatherm HIFU • Morbidity at 2 years • Adverse events (AEs) and device- and procedure-related AEs
Evaluation Endpoints	On the yearly visits, PSA levels will be obtained and, based on evaluation of clinical risk associated with rising PSA levels, prostate biopsy and bone scans will be conducted in order to determine prostate cancer metastasis. The standardized criteria for the requirement of biopsy and bone scans will be developed prior to study initiation and clearly described in the final study protocol. Subject not diagnosed with metastatic prostate cancer prior to the 8-year follow-up interval will be subjected to a bone scan at eight years post procedure in order to assess the primary endpoint of freedom from metastasis. All adverse events will be evaluated at each follow-up visit. This will include specific documentation of those known to be possible following the HIFU procedure including but not limited to: • erectile dysfunction, • hematuria,

Study Component	**Description**
	• perineal/penile/rectal/prostate pain or discomfort, • bladder urgency • urinary stricture • urinary retention • urinary incontinence • urinary frequency • urinary sloughing • urinary obstruction • urinary hesitancy • dysuria • nocturia • urinary tract infection • bladder neck contracture • bladder outlet obstruction • bladder spams The International Prostate Symptom Score (IPSS), the International Index of Erectile Function (IIEF) and quality of life questionnaires utilized will assess and provide patient reported incidence of short and long term erectile, urinary and bowel dysfunction.
Follow-up Visits and Length of Follow-up	Patients will be followed for a total of 8 years after Ablatherm HIFU treatment. Subjects will be examined and evaluated according to the following schedule of visits. The timing of the visits will be calculated from the original date of Ablatherm HIFU treatment in the premarket or in the post-market for newly enrolled patients. • Pre-treatment • Post-treatment assessment 10 ± 5 days • 1, 3, 6, 12, 18, 24, 36, 48, 60, 72, 84 and 96 months post-op
Statistical Plan	Baseline characteristics including age, baseline PSA, baseline cancer stage, Gleason score and procedure parameters will be summarized as mean, standard deviation and range for continuous parameters and frequency and percent for categorical. All endpoints will be evaluated using Kaplan-Meier estimates. Subjects free from event will be censored at the last available assessment date.

Study Component	**Description**
	The number of subjects at risk, the number with metastasis and the Kaplan Meier estimate with associated 95% confidence limits will be reported at yearly intervals. Additionally, a competing risks analysis will evaluate the rate of prostate cancer metastasis in the presence of the competing risk of death due to other causes. Salvage treatments following HIFU will be summarized as the number of subjects requiring salvage treatment and the number and type of salvage treatments used. Adverse events will be summarized as the number of events and number and percent of subjects with event overall and by the categories of event type, relationship to device and/or procedure, severity, seriousness and the timing of the event relative to HIFU treatment.
Study Timeline	It is expected that, once the study protocol is finalized and approved by FDA, it would take EDAP approximately six to nine months to enroll all the study sites, to train all investigators on the study protocol and use of the device, and to obtain IRB approval for all sites. Subject enrollment is expected to be completed in approximately three years and all study subjects will be followed for 8 years.

8.2 FDA Assessment of the PAS Proposal

The applicant has proposed to combine extended follow-up of the premarket cohort, with new enrollment of subjects, to follow patients for a total of 8 years post-HIFU treatment. Patients from the IDE study completed 24 month study visits; therefore, an extended follow-up of the IDE cohort is necessary to assess the longer-term performance of the device. Additionally, newly enrolled patients (non-IDE) will be included to achieve approximately 300 subjects with follow-up through 8 years. The primary endpoint is the occurrence of prostate cancer metastasis at eight years post Ablatherm HIFU procedure. Secondary endpoints include: overall survival, cancer specific survival, freedom from salvage treatment, morbidity at 2 years, and AEs and device- and procedure-related AEs. There is no formal statistical hypothesis to be tested. There are potential limitations with the proposed study, as discussed below:

1. The primary effectiveness endpoint is the metastasis-free survival rate. Given the study population with low risk, localized prostate cancer, this endpoint may not be appropriate to evaluate long-term performance because of the extremely low rate that is expected.

The panel will be asked to discuss the appropriateness of metastasis-free survival as the primary endpoint, and to recommend any other effectiveness endpoints that should be included as primary or secondary.

2. Safety issues will be measured as secondary endpoints including morbidity at 2 years, and device and procedure-related adverse events.

The panel will be asked to discuss if there are specific primary or secondary safety endpoints to be evaluated.

3. There is no comparator group in the applicant's PAS proposal.

The panel will be asked to discuss if a comparator group is needed, and if so, to provide recommendations on the appropriate comparator for the low risk prostate cancer patient population.

9. References

1. National Cancer Institute. Accessed at: http://www.cancer.gov/cancertopics/types/prostate

2. D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, Broderick GA, et al.; Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer; JAMA; 1998 Sep 16; 280(11):969-974.

3. Rodrigues G, Warde P, Pickles T, Crook J, et al.; Pre-treatment risk stratification of prostate cancer patients: A critical review; Can Urol Assoc J; 2012 Apr; 6(2):121-127.

4. "Guidance for Industry and Food and Drug Administration Staff: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and *De Novo* Classifications." Accessed at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM296379.pdf

5. American Society for Therapeutic Radiology and Oncology Consensus Panel; Consensus statement: Guidelines for PSA following radiation therapy; Int J Radiat Oncol Biol Phys; 1997; 37:1035-1041.

6. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, Fox S, Gingrich JR, Wei JT, Golhooly P, Grob BM, Nsouli I, Iyer P, Cartagena R, Snider G, Roehrborn C, Sharifi R, Blank W, Pandya P, Andriole GL, Culkin D, Wheeler T; Prostate cancer intervention versus observation trial (PIVOT) study group; Radical prostatectomy versus observation for localized prostate cancer; N Engl J Med; 2012 Jul 19; 367(3):203-213.

7. Ganzer R, Fritsche HM, Brandtner A, Bründl J, Koch D, Wieland WF, Blana A; Fourteen-year oncological and functional outcomes of high-intensity focused ultrasound in localized prostate cancer; BJU Intl; 2013 Aug; 112(3):322-329.

8. Thüroff S, Chaussy C; Evolution and outcomes of 3 MHz high intensity focused ultrasound therapy for localized prostate cancer during 15 years; J Urol; 2013 Aug;190(2):702-710.

9. Crouzet S, Chapelon JY, Rouvière O, Mege-Lechavallier F, Colombel M, Tonoli-Catez H, Martin X, Gelet A; Whole-gland ablation of localized prostate cancer with high-intensity focused ultrasound: Oncologic outcomes and morbidity in 1002 patients; Eur Urol; 2013 (http://www.hifu.ca/Crouzet_et_al_1002_Primary_Eur_Urol_2013_1.pdf).

10. Roach M, Hanks G, Thames H, Schellhammer P, Shipley W, Sokol G, Sandler H; Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix consensus conference; Int J Radiat Oncol Biol Phys; 2006; 65:965-974.

11. Bill-Axelson A, Holmberg L, Ruutu M, Garmo H, Stark JR, Busch C, Nordling S, Häggman M, Andersson SO, Bratell S, Spångberg A, Palmgren J, Steineck G, Adami HO, Johansson JE; SPCG-4 Investigators; Radical prostatectomy versus watchful waiting in early prostate cancer; N Engl J Med; 2011 May 5; 364(18):1708-1717.

12. Donnelly BJ, Saliken JC, Brasher PM, Ernst SD, Rewcastle JC, Lau H, Robinson J, Trpkov K; A randomized trial of external beam radiotherapy versus cryoablation in patients with localized prostate cancer; Cancer; 2010 Jan 15; 116(2):323-330.