SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Electrosurgical Device

Device Trade Name: AtriCure Synergy Ablation System

Applicant's Name and Address: AtriCure, Inc.
6217 Centre Park Drive
West Chester, OH 45069
USA

Date(s) of Panel Recommendation: October 26, 2011

Premarket Approval Application (PMA) Number: P100046

Date of FDA Notice of Approval: December 15, 2011

Expedited: Granted expedited review status on February 24, 2011 because we believe that this radio frequency ablation system for the treatment of patients with persistent or longstanding persistent atrial fibrillation who are undergoing open concomitant cardiac surgery may offer significant, clinically meaningful advantages over pharmacologic treatment or the open surgical Maze procedure. Also, the availability of the device may be in the best interest of patients.

II. INDICATIONS FOR USE

The AtriCure Synergy Ablation System is intended to ablate cardiac tissue for the treatment of persistent atrial fibrillation (sustained beyond seven days, or lasting less than seven days but necessitating pharmacologic or electrical cardioversion) or longstanding persistent atrial fibrillation (continuous atrial fibrillation of greater than one year duration) in patients who are undergoing open concomitant coronary artery bypass grafting and/or valve replacement or repair.

III. CONTRAINDICATIONS

The AtriCure Synergy Ablation System should not be used for contraceptive coagulation of the fallopian tubes. The device is not designed for safe and effective use for that purpose.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the AtriCure Synergy Ablation System labeling.

V. DEVICE DESCRIPTION

The AtriCure Synergy Ablation System devices included in this PMA are:

- AtriCure Synergy Ablation Clamps - Product Codes: OLL2, OSL2
- Ablation and Sensing Unit – ASU2 – RF Generator
- AtriCure Switch Box – ASB3 – allows user to connect multiple AtriCure devices to ASU2

System Description

The Synergy Ablation clamps are available in two models, the OLL2 (open long left curved) and OSL2 (open short left curved), to aid in accessing varying patient body habitus. The OLL2 and OSL2 are the same with the exception of jaw geometry and shaft length. The OSL2 jaws are slightly shorter than the OLL2's to provide surgeons with different options for accessing patient anatomy.

Synergy Ablation Clamp

The Synergy Ablation Clamps resemble standard surgical clamps and are always under the direct control of the surgeon. The devices include a syringe type grip handle/actuator, cylindrical shaft of varying lengths; varying jaw curvatures, lengths, and apertures, rounded jaw tips, and a cable that plugs into the ASB switch matrix and ASU RF generator (Figure 1).

The Clamp device handle is connected by a cylindrical shaft to a pair of grasping jaws with electrodes on each jaw. Each jaw contains two (2) linear electrodes located medially and axially on the centerline of each insulated jaw of the clamp type end effector (Figure 2). These directly opposing linear electrodes, two on each jaw, make up two electrode pairs. Within an electrode pair, energy flows from the electrode on the proximal or top jaw to the electrode on the distal or bottom jaw. To activate RF energy, the AtriCure Synergy Ablation Clamp is connected via an integral cable to the AtriCure Ablation and Sensing Unit (ASU2) and the AtriCure Switch Box (ASB3) (Figure 3).

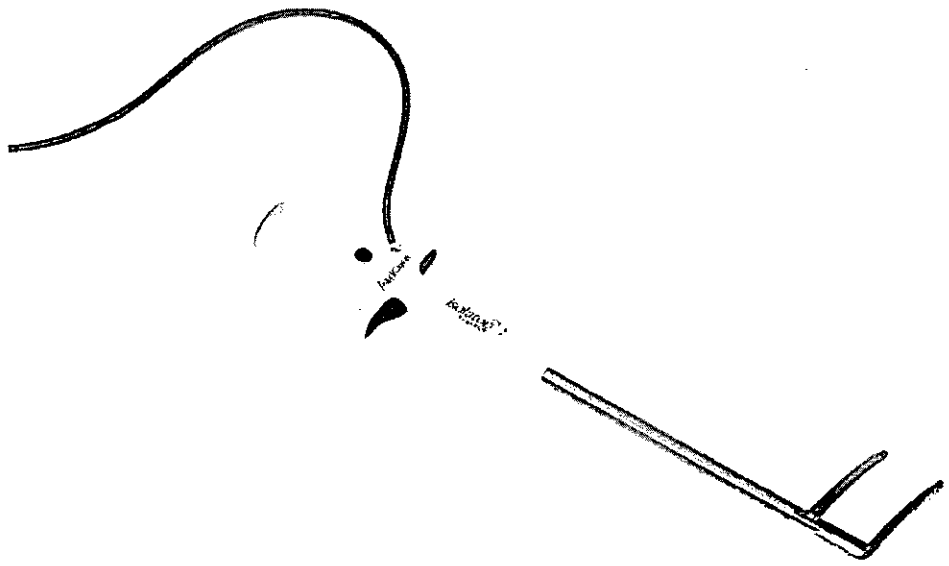

Figure 1. AtriCure Synergy Ablation Clamp (OLL2)

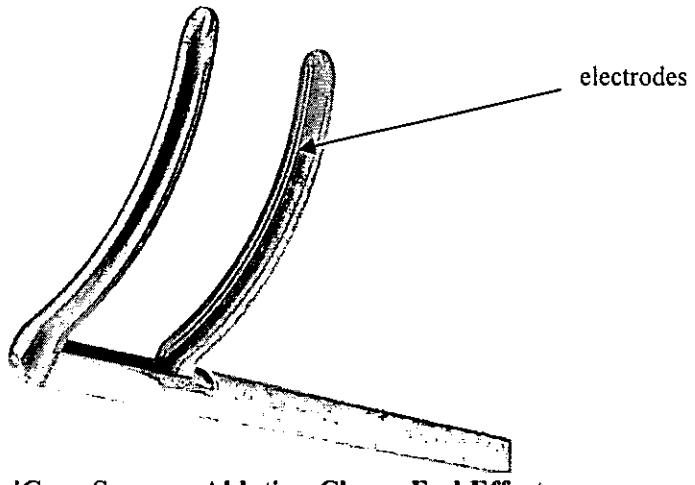

Figure 2. AtriCure Synergy Ablation Clamp End Effector

Ablation and Sensing Unit

The Ablation and Sensing Unit (ASU) is a radiofrequency (RF) generator used to power AtriCure Handpieces (Figure 3). The ASU is a portable reusable device that produces and delivers RF bipolar energy through the AtriCure Synergy Ablation Clamp to ablate cardiac tissue. The ASU limits the amount of voltage, current, and time for which the RF power is delivered to the Clamp. In addition, the ASU lights a visual indicator and sounds an audible tone signaling that the conditions for a complete ablation cycle have been satisfied. The footswitch is used to initiate (depress footswitch) and terminate (release footswitch) the RF energy delivery.

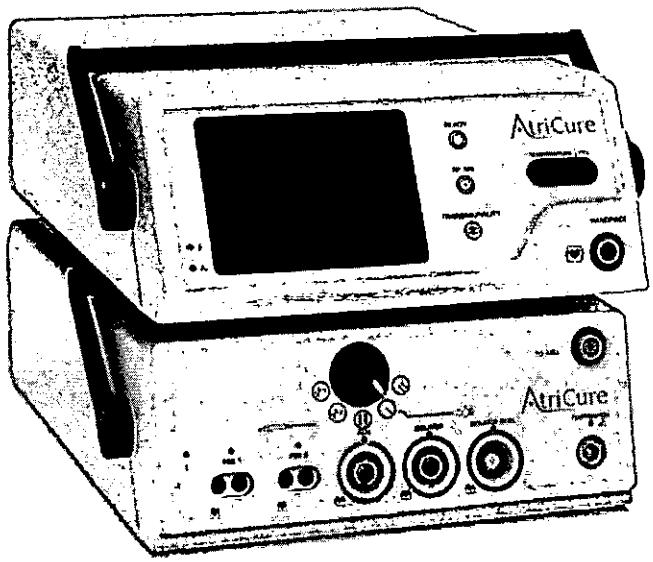

Figure 3. Generator- AtriCure Model ASU2/ASB3

AtriCure Switch Box
The ASU2 is used in conjunction with the AtriCure Switch Box (ASB3). The AtriCure Switch Box (ASB3) is an accessory interface module allowing various AtriCure ablative devices to connect to the RF generator (ASU2) (Figure 3). The ASB3 also provides the RF switching mechanism for the two electrode pairs in the AtriCure Synergy Ablation Clamps. The ASU2 and ASB3 are connected via a short cable. These units (ASU2/ASB3) are always outside of the sterile field and function to provide the RF energy (ASU2) and to direct the energy delivery to the Handpieces.

The ASB3 utilizes a mechanical switching system to allow the user to select a pathway for a specific source to communicate to a specific output. The operator can select which device will be activated via a rotating selection knob on the front of the ASB3. The operator is able to mechanically select and switch between ablation handpieces connected to the ASU2 RF generator.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction persistent or longstanding persistent AF: use of anti-arrhythmic and/or rate control medications and cardioversion (electrical and/or pharmacologic) Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The AtriCure Synergy Ablation System was cleared on January 26, 2007 (under a different trade name) via premarket notification K063630 for the following indication: The AtriCure Ablation System is intended to ablate soft tissues during general surgery

using radiofrequency energy. The indications for use for the AtriCure Synergy Ablation System was modified under K101174 (under a different trade name) to the following: The AtriCure Bipolar System including Isolator Synergy Dual Electrode Clamps is intended for the ablation of cardiac tissue during surgery. The AtriCure Synergy Ablation System first received the CE Mark in December 2005 for ablation of soft tissue, and thereby began commercial distribution in the European Union. In March 2009, the CE Mark approval was updated for the treatment of cardiac arrhythmias including atrial fibrillation. The list of countries where the AtriCure Synergy Ablation System is approved for commercial distribution is provided below:
United States, European Union, Canada, Japan, Lebanon, Colombia, Panama, Ecuador, Peru, China, Hong Kong, Argentina, Chile, Brazil, Thailand, Australia, Mexico, Turkey, Georgia, Azerbaijan, Russia, Norway, Taiwan, Costa Rica, Korea, Lithuania, and Malaysia.

The AtriCure Synergy Ablation System has not been withdrawn from marketing in any country for any reason

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The AtriCure Synergy Ablation system is indicated to treat persistent or longstanding persistent AF using radiofrequency ablation in patients undergoing a concomitant surgical procedure (coronary artery bypass grafting and/or valve replacement or repair). Below is a list of the potential adverse effects (e.g., complications) associated with the combined procedure

- Death
- Excessive bleeding related to the procedure which may require reintervention,
- Cardiac tamponade (if either open or catheter drainage is required),
- Pulmonary vein stenosis,
- Restrictive (constrictive) pericarditis,
- Infection which may include Sepsis or Endocarditis,
- Myocardial infarction (MI) per ACC guidelines,
- Stroke or Transient Ischemic Attack (TIA),
- Thromboembolism,
- Diaphragmatic paralysis,
- Esophageal-LA fistula or esophageal rupture,
- Atrial perforation or rupture,
- Ventricular perforation or rupture,
- Atelectasis,
- Pneumonia,
- Congestive Heart Failure,
- Cardiac Valve Injury,
- Persistent Pneumothorax (requiring intervention),
- Excessive Pain and Discomfort,
- Deep Sternal Wound Infection,
- Ventricular Arrhythmia (V. Tachycardia or V. Fibrillation),

- Drug Reaction,
- Perioperative heart rhythm/conduction disturbance (atrial and/or ventricular),
- Pericardial effusion or tamponade,
- Injury to the great vessels,
- Injury to unintended surrounding tissue structures, including tears and punctures,
- Extension of cardiopulmonary bypass.

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF PRECLINICAL STUDIES

In vitro and *in vivo* testing was performed on the AtriCure Synergy Ablation System in bench and animal models and a summary is presented in this section.

A. Laboratory Studies

The following *in vitro* bench studies were performed to support the AtriCure Synergy Ablation System. Results for this testing was also submitted and reviewed in the 510k submissions under which the AtriCure Synergy Ablation System was cleared.

Table 1: Summary of Pre-Clinical Bench Testing

In Vitro Test	Overall Purpose and Description	Acceptance Criterion	Results & Conclusions
Drop Testing	To verify that the OLL2 and OSL2 devices do not present a safety hazard as a result of a free fall drop from a height of 1 meter onto a hard surface per EN60601-1:1990.	All Handpiece components shall maintain electrical and mechanical integrity and not dislodge from the instrument during the free fall.	Pass. The OLL2 and OSL2 devices met the safety requirement were not considered a safety hazard as a result of a free fall drop from a height of 1 meter onto a hard surface per EN 60601-1:1990 Section 21.5.
Strain Relief	To demonstrate the OLL2 and OSL2 cable meets the Cable Strain Relief Requirements as described in ANSI/AAMI HF 18:2001.	The handpiece cable must be capable of withstanding the mechanical stress of 40 N for 10 seconds and an impulse of 0.64 joules.	Pass. The OLL2 and OSL2 cable meets the Cable Strain Relief Requirements as described in ANSI/AAMI HF 18:2001 section 4.2.5.5.

In Vitro Test	Overall Purpose and Description	Acceptance Criterion	Results & Conclusions
Reliability Testing	To verify the reliability of the OLL2 and OSL2 Handpiece design per the product life profile using rate reliability testing and Weibull Analysis.	The OLL2 and OSL2 must demonstrate 99% reliability with 95% confidence. Failure of the device was defined as loss of mechanical function, loss of ability to create a transmural lesion, loss of mechanical integrity, loss or intermittent electrical power through the instrument, loss of electrical contact to the electrodes, insulation breakdown, adhesive failure, or EEPROM failure.	Pass. The OLL2 and OSL2 demonstrated 99% reliability with 95% confidence. The OLL2 meets the reliability target and lesion performance criteria.
Bench Ablations Comparison	To investigate the ablation performance of the OLL2 and OSL2 on different types of tissue on bench testing.	OLL2: All ablated lesions must be transmural as evidenced by tissue sectioning and visual inspection and lesions must be wider than predicate device. OSL2: All lesions are transmural as evidenced by gross examination and average lesion width is no more than 5 mm.	Pass. The OLL2 and OSL2 successfully created lesions on bench tissue. All lesions were 100% transmural. No adverse tissue effects were observed with the OLL2 and OSL2.
Dielectric Withstand	To verify the OLL2 and OSL2 meet electrical safety requirements specified in the product specification and IEC 60601-2-2 and AAMI HF-18.	The devices must meet electrical safety requirements specified in the product specification and IEC 60601-2-2 and AAMI HF-18.	Pass. The OLL2 and OSL2 met electrical safety requirements specified in the product specification and IEC 60601-2-2 and AAMI HF-18.
Surface Tempera-ture	To verify the handpieces meet the External Surface Temperature Requirements per EN 60601-1 Section 42.	The temperature of the shaft must be less than or equal to 60° C.	The handpieces meet the External Surface Temperature Requirements per EN 60601-1 Section 42. Thirty (30) instruments demonstrated 90% reliability with 95% confidence.

In Vitro Test	Overall Purpose and Description	Acceptance Criterion	Results & Conclusions
Closing Force	To verify the OLL2 and OSL2 (post 2x EtO Sterilization) meets the Closing Force requirements has a maximum force of 10 lbf and maximum momentary force spike of 25 lbf through the device range of motion.	The Handpiece maximum force is less than or equal to 10.0 lbf throughout the range device's of motion and the Handpiece maximum momentary force spike is less than or equal to 25.0 lbf.	Pass. The OLL2 and OSL2 (2x EtO Sterilization) meet the Closing Force requirements.
Closure Latch	To verify the OLL2 and OSL2 meet the Closure Latch unlatching requirement after exposure to 2x EtO sterilization.	Force to unlatch must be between 2.0 and 4.0 lbf.	Pass. The OLL2 and OSL2 meet the Closure Latch unlatching after exposure to 2x EtO sterilization.
Tip Splay/ Lateral Alignment	To verify the OLL2 and OSL2 meet the lateral alignment requirement after 2x EtO sterilization.	The proximal jaw lateral motion is less than or equal to 0.60 inches (to the right and left, i.e. 0.120 inches total) and displacement less than or equal to 0.010 inches (both measurements at the midpoint of the jaw) when a load of 1.0±0.1 lbf is applied laterally at the midpoint of the jaw.	Pass. The OLL2 and OSL2 meet the lateral alignment requirement set forth in the product specification after 2x EtO sterilization.
Shaft Stiffness	To verify that the OLL2 and OSL2 meet shaft stiffness as evidenced by retaining the ability to open and close under loading.	The jaws open to 1.00±0.2 inches and will be able to be closed and latched while under top and side loads of 4.0±0.2 lbf.	Pass. The OLL2 and OSL2 met shaft stiffness specifications.
Force Testing	To verify that the OLL2 and OSL2 meet jaw force specifications.	OLL2: The instrument return spring rate must be 19.81±3.5 and the 2 mm differential must be ≤3.0 and the return force at 2 mm (2mm return stroke compression) must be 6.59±1.17. OSL2: The instrument spring rate must be 14.59±3.5 lbf/in. The maximum differential at 2 mm load must be 3.9 lbf. The 2 mm return force must be 4.85±0.78.	Pass. The OLL2 device met jaw force specifications.

B. Animal Studies

The AtriCure Synergy Ablation System was tested in acute and chronic animal studies. The studies were performed to verify cardiac ablation safety and performance in a clinically relevant *in vivo* environment. In all studies, device efficacy was assessed by gross examination of tissue after staining with 2,3,5,-triphenyl-tetrazolium chloride (TTC). The ablation was considered successful if the ablation was transmural (full thickness). All charring lesions were also examined for any signs of adverse tissue effects such as tissue charring, tissue perforation, and lateral thermal spread.

One chronic (30 day) study was conducted in accordance with Good Laboratory Practices (GLP) per 21 CFR Part 58. The ablation lesions in this study were assessed for effectiveness by pacing and by histologic evaluation. All lesions were 100% transmural. The remaining five studies were non-GLP studies performed for product development in accordance with test facility standard operating procedures. Of these five studies, one was chronic (28 + 2 days) and four were acute studies.

In addition to effectiveness, all studies were evaluated for safety by examining the lesions grossly for adverse tissue effects such as charring or perforation and monitoring the health of the animals over the duration f the two chronic studies. In both acute and chronic studies, the animals demonstrated no adverse effects specifically associated with ablation energy delivery. Although not formally assessed in the acute studies, there were no instances of thrombosis observed in any animal studied. In the chronic study, animals survived to the terminal surgery with no complications attributed to the ablation protocol. A summary of all animal studies is provided below in Table 2.

Table 2: Summary of *In Vivo* Animal Testing and Results

Chronic or Acute, # of Animals	Purpose and Description	Key Assessment Criteria	Key Outcomes
Study Title: Evaluation of the AtriCure Synergy Ablation Technology in the Porcine DCR-2538			
GLP, Chronic (30 d -2 ± 7 d) n= 9 pigs: 1 control 7 studied 1 reserve	To evaluate the safety and performance of the AtriCure Synergy Ablation System in a porcine model 30 days post procedure, in compliance with Good Laboratory Practices (21CFR, Part 58). Following median sternotomy, the surgeon ablated the left atrial appendage (LAA), right atrial appendage (RAA), and left pulmonary vein (LPV); the control pig had sham surgery.	• Endpoints used to evaluate the safety of the devices included: 1) baseline and post-surgical CT scans; 2) gross pathology of heart, brain, liver, lung, kidneys, bowel, and spleen; and 3) histopathology of the tissue of the ablation site to assure no signs of thromboembolic events attributed to the devices. • The device performance was evaluated by verification of conduction block across the right atrial appendage, left atrial appendage, and left pulmonary vein ablations via pacing, and the assessment of clinical observations.	• Conduction block was achieved in all ablation lesions performed at time of surgery, and the electrical block was maintained at study endpoint (30 d-2, + 7) • The OLL2 ablations did not result in pulmonary vein stenosis, regurgitation at mitral/ tricuspid valves, no decrease in LV ejection fraction, or endocardial thrombus as verified by CT scans. • Histopathology of the ablation lesions showed 100% transmurality at 1-month follow-up. • No clinical observations or events were attributed to ablation energy delivery.

Chronic or Acute, # of Animals	Purpose and Description	Key Assessment Criteria	Key Outcomes
Study Title: Performance Evaluation of the Dual Electrode System for Cardiac Ablation in a Chronic Porcine Model DCR-1181			
Non-GLP Performance Study Chronic (28 ± 2 d) n=6 pigs	To verify the performance of the AtriCure Synergy Ablation Clamp (model OLL2) for ablation of cardiac tissue using a Maze III surgical procedure. Cardiopulmonary bypass (CPB) was not used due to concerns regarding survivability post-CPB. Instead, RF lesions were created either by placing a purse-string incision at the targeted area or clamping the cardiac structure. The study also compared the AtriCure OLL2 Clamp to data from previous generation Handpieces for the following variables: RF time, energy delivered, lesion width.	• At necropsy the hearts were treated with a special stain (TTC) to allow visual examination and assessment of ablation line lesions for lesion transmurality, width (lateral thermal spread), presence or absence of thrombus, charring, and pulmonary vein stenosis. • Selected microscopic slides were sent to a veterinary pathologist for histological assessment of the ablation lesions and to confirm the gross visual assessment of lesion transmurality. • Engineering analysis of energy delivery: total energy delivery, duration of application.	• The OLL2 device can isolate cardiac tissue in one application but requires more time and energy. • The OLL2 device can create ablations that are discreet and visible to the naked eye via use of a special stain (TTC) without damaging adjacent structures. • Evidence of tissue charring, thrombus, or pulmonary vein stenosis was not observed. • A total of 63 slides with 244 cross-sections were examined; 212/244 cross-sections showed clearly demarcated ablation lesions. The remaining sections (35) were not reviewed for a variety of reasons including poor tissue staining and/or inability to locate the ablation lesion. All defined ablation lesions (209/209 sections) were 100% transmural from the epicardium to the endocardium at 28 days survival.

Chronic or Acute, # of Animals	Purpose and Description	Key Assessment Criteria	Key Outcomes
Study Title: OLL2 Acute Animal Lab DCR-1273			
Non-GLP Verification Study -- Acute n=2 pigs	To verify that the AtriCure Synergy Ablation Clamp (OLL2) functions as required in live tissue following EtO sterilization. Two OLL2 devices were used: one at maximum tissue pressure and one set at minimum tissue pressure. Assessment included: device must be atraumatic to tissue (i.e. free of pinch surfaces, sharp edges, snags) to prevent unintended damage during tissue interface; must be able to operate device with one hand; the device must be able to access and create transmural lesions on the porcine LAA, RAA, IVC, SVC. A comparison of the OSL2 device to previous AtriCure Handpieces (OLL1) was also performed to verify performance.	• At necropsy the hearts were treated with a special stain (TTC) to allow visual examination and assessment of ablation lesions: visual examination of lesions for transmurality, width (lateral thermal spread), presence or absence of thrombus, or charring. • Pacing to confirm electrical isolation following creation of ablation lesions. • Intraoperative device use was observed to determine whether the device was atraumatic to tissues. • A baseline ablation lesion was first created with the OLL1 device for lesion comparison.	• Blood was observed pooling between the jaws in the heel of both the OLL1 and OLL2 devices which extended the time of ablation. • The OLL2 devices created 100% transmural lesions as evidenced by gross examination and measurement. Lesions did not exhibit thrombus or charring. • The OLL2 devices appeared to be atraumatic to tissue as visual observation of tissue revealed no evident tissue damage following tissue interface. • The surgeon was able to operate the device with one hand. • The OLL2 device appeared to function as well as the previous generation OLL1AtriCure Handpiece.

Chronic or Acute, # of Animals	Purpose and Description	Key Assessment Criteria	Key Outcomes
Study Title: OLL2 Animal Lab DCR-1346			
Non-GLP Verification Study -- Acute n=2 pigs	To verify the ablation performance of the AtriCure Synergy Ablation Clamp (OLL2) device on various anatomical locations (IVC, small bowel, thigh muscle, diaphragm) in an *in vivo* porcine model. The study also compared the AtriCure OLL2 clamp to a previous generation AtriCure Handpiece (EML1) to verify performance.	• Assessment criteria included: Comparison of lesion width created with the OLL2 clamp to lesions created with the EML1 clamp and average maximum tissue temperature outside the insulated OLL2 jaw measured at thermo-couple position T4. • Ablation line visual assessment: 1) examination of lesions for transmurality, width (lateral thermal spread), and presence or absence of thrombus, or tissue charring. • Energy delivered per unit volume of tissue ablated and time to transmurality was also evaluated.	• Ablation times and energy delivered per unit volume to the tissue were comparable between the OLL2 and the previous generation EML1 AtriCure Handpiece. • All ablation lesions were 100% transmural with the exception of two (one for each device) per visual inspection post-mortem. • Lesions created with OLL2 Handpiece were wider compared to lesions created with the EML1 Handpiece. • Visual gross examination of ablation lesions did not exhibit thrombus or charring. No tissue damage beyond that intended by the ablation process was visible. • Tissue was not submitted for microscopic evaluation. • The average maximum temperature outside of the jaw was less than 50°C on all tissue types.

Chronic or Acute, # of Animals	Purpose and Description	Key Assessment Criteria	Key Outcomes
Study Title: OSL2 Animal Lab DCR-1579			
Non-GLP Verification Study -- Acute n=1 pig	To verify the ablation performance of the OSL2 Handpiece on cardiac tissue in an in vivo porcine model. Assessment included: 1) device must be atraumatic to tissue (i.e. free of pinch surfaces, sharp edges, snags) to prevent unintended damage during tissue interface; 2) must be able to operate device with one hand; 3) the device must be able to access and create as many transmural lesions on the LAA and RAA as possible. Evaluation of the study also compared the OSL2 Handpiece to a previous generation Handpiece (LHP2) for the following variables: RF time, energy delivered, lesion width.	• Ablation line gross visual examination and assessment of lesions for: 1) transmurality, 2) width (lateral thermal spread), and 3) presence or absence of thrombus, or charring. • Evaluation of energy delivered per unit volume of tissue ablation and time to achieve transmurality • Intraoperative device use was observed to determine whether the device was atraumatic to tissues.	• The OSL2 device can create ablations that are discreet and visible to the naked eye without visual evidence of damage to adjacent structures. • Neither charring nor thrombus was observed with the OSL2 ablations. • Gross visual examination of the lesions indicated 100% transmurality of the ablation lesions. • Tissue was not submitted for microscopic evaluation. • The OSL2 devices appeared to be atruamatic to tissue interface as visual observation of tissue post-mortem revealed no evident tissue damage. •

C. Biocompatibility

The biocompatibility of the patient contacting materials of the AtriCure Synergy Ablation Clamp have been assessed and tested according to ISO 10993-1:2003, *Biological evaluation of medical devices*, and the applicable subparts of Required Biocompatibility Training and Toxicology Profiles for Evaluation of Medical Devices May 1, 1995 (FDA Bluebook Memorandum G95-1) with 100% passing results. The device is typically used epicardially on the perfused heart or epi/endocardially in an evacuated heart (on cardiopulmonary bypass). As such, the AtriCure Synergy Ablation Clamps (OLL2, OSL2) are categorized as externally communicating devices that are intended for bone/tissue contact for limited contact duration (less than 24 hours).

Required testing was determined from ISO 10993 and with the independent contract biocompatibility test labs that AtriCure works with for biocompatibility testing. All test methods, sample sizes, and sample preparation are determined and performed by the contract laboratories that operate according to GLPs, ISO 10993, and other applicable standards. A summary of biocompatibility testing performed is included in Table 3.

Table 3: Summary of Biocompatibility Testing and Results

Biological effect category	Test Methods	Results
Sensitization	Maximization Sensitization Test ISO 10993-10	Pass
Systemic Toxicity	Systemic Injection USP/ISO	Pass
Cytotoxicity	ISO 10993-5 Elution Test (MEM Extract)	Pass
Intracutaneous Reactivity	(Intradermal) Reactivity Test ISO 10993-10	Pass
Hemocompatibility	Hemolysis ISO 10993-4 ASTM Method Complement Activation C3a and Sc5b-9	Pass
Material Mediated Pyrogenicity	ISO 10993-11:2006	Pass
Genotoxicity	AMES reverse bacterial mutation	Pass

D. Sterilization

The OLL2 and OSL2 are packaged at AtriCure Inc. and are ethylene oxide sterilized by a contract sterilizer in compliance with ISO 11135, EN550, and AAMI TIR 16. The AtriCure Synergy Ablation Clamps (models OLL2, OSL2) are the only devices in the AtriCure Synergy Ablation System that are provided sterile. The ASU generator and ASB switch box are used outside of the sterile field at all times. All validations follow ISO 11135, EN550 and AAMI TIR 16 regulations to ensure 10^{-6} SAL and include: bioburden analysis, a minimum of 3 half-cycles (including consideration for a half-cycle using a refrigerated truck to simulate cold shipping conditions and a minimum load half-cycle study), and a full cycle study to examine EtO residuals.

E. Packaging Design and Shelf Life

The OLL2 and OSL2 are packaged in a thermoformed tray and sealed with a Tyvek® lid. Qualification testing was performed for packaging design performance, packaging shelf-life, and device shelf-life for the OLL2 and OSL2. A three year shelf-life has been established for the OLL2 and OSL2.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study *to establish a reasonable assurance of safety and effectiveness of radiofrequency ablation with the AtriCure Synergy Ablation System for the treatment of persistent and longstanding persistent AF* in the US under IDE # G070080. Data from this clinical study were the primary basis for the PMA approval decision. In addition to the data collected under the pivotal IDE study, the applicant provided additional post-hoc data to support approval of their device. These included data

from a previous terminated IDE study (G020237), data from two institutional databases, and data from an ongoing registry. These are described briefly in Section XI. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between February 8, 2008 and June 12, 2009. The database for this PMA/PMA supplement reflected data collected through November 17, 2010 and included 55 patients. There were 9 investigational sites.

The ABLATE ("AtriCure Synergy Bipolar RF Energy Lesions for Permanent Atrial Fibrillation Treatment during Concomitant, On-Pump, Endo/Epicardial Cardiac Surgery") trial was a prospective, multi-center, one-arm, non-randomized clinical study. The study was designed to evaluate the safety and effectiveness of the AtriCure Synergy Ablation System in the treatment of permanent[1] AF in the concomitant surgical setting. This pivotal study was based on a Bayesian adaptive design. The performance goal endpoints for the study were based on historical data reported in the clinical literature and the applicant's data from a previous abandoned IDE study (G020237), the RESTORE trial discussed below. Therefore, control subjects were not used in this study. Candidates for treatment with the study device included subjects of both genders undergoing certain concomitant open-heart surgeries, such as coronary artery bypass grafting and/or valve repair or replacement. All subjects were followed through discharge, at 30 days, 3 months, 6 months, 12 months, 18 months, 2 years and annually for five years thereafter.

Statistical Aspects of the ABLATE Study

Statistical evaluation of primary outcomes was performed using Bayesian methodology for all analyses (interim, for sample size determination, and final). These are described briefly below.

Primary Safety Analysis

The primary safety endpoint was the rate of major adverse events (MAEs), which included death, stroke, myocardial infarction (MI), transient ischemic attack (TIA) or bleed, occurring within the initial 30 days post procedure or discharge (whichever was later).

The statistical hypothesis for safety is

$$q_T < 0.1895,$$

1 The ABLATE study protocol specified the target population to be those with "permanent" AF per the 2006 ACC/AHA/ESC Guidelines (Fuster, 2006). However, the definition of the AF classification "permanent" has changed with the publication of the 2007 HRS consensus statement (Calkins, 2007). Therefore, the current indication has translated this target population to those with "persistent" or "longstanding persistent" AF per the 2007 HRS consensus statement definitions.

where the treatment adverse event rate is labeled q_T. The primary safety endpoint would be considered met if the posterior probability that q_T is less than 0.1895 exceeds 0.95, i.e.

$$\Pr(q_T < 0.1895 \mid \text{Trial Results}) \geq 0.95.$$

The prior distribution for the primary safety endpoint is Beta (1,1). The choice for the performance goal 0.1895 is discussed below.

Primary Effectiveness Analysis
The primary effectiveness endpoint is the rate of subjects that achieved successful obliteration of atrial fibrillation while off of any antiarrhythmic medication (Class I or III) evaluated at six months post procedure. The statistical hypothesis is

$$p_T \geq 0.60,$$

where p_T is the probability of being a success for effectiveness. The primary effectiveness endpoint would be considered met if the posterior probability that p_T is greater than 0.60 exceeds 0.975, i.e.,

$$\Pr(p_T > 0.60 \mid \text{Trial Results}) \geq 0.975.$$

A uniform prior distribution is assigned for the unknown probability of success, $p_T \sim$ Beta(1,1). The choice for the performance goal 0.60 is discussed below in Section

Interim Monitoring and Adaptive Design
The Applicant used a Bayesian adaptive approach to sample size selection. The minimum total sample size was 50 patients and the maximum was 100.

The first interim look was to be made when 50 patients had been enrolled in the study and 20 patients had reached their 6-month endpoint, whichever occurred later. This was to be repeated after every five patients were enrolled until the threshold for enrollment cessation was achieved, for a maximum of 10 interim analyses.

At each interim analysis the Applicant was to calculate the predictive probability of meeting the primary safety and the primary effectiveness endpoint at the end of the trial. The predictive probability of meeting the effectiveness endpoint and the safety endpoint is calculated two ways: first assuming accrual stops and all currently enrolled patients are followed to six months, second assuming enrollment continues to the maximum sample size, 100 patients, and all are followed to six months. Because the final outcomes of some enrolled subjects were not yet known at the time of the interim look, they were predicted, using information from the subjects with known outcomes, in combination with a beta-binomial distribution for modeling the transition from either baseline or 3-month outcomes to the 6-month outcomes. The predictive probability was used to decide whether (1) to stop accruing patients, wait 6- months, and then do the final analysis, (2) to stop the trial for futility, or (3) to

continue enrolling subjects into the trial. The predictive probability thresholds for stopping enrollment began at 90%, and then decreased gradually to 80% as the maximum sample size was reached. The futility thresholds began at 5% and increased to 10%.

Note that predictive probability is only used to decide whether to stop enrollment or stop for futility. It is not used for making a decision about the final analysis. The final analysis will use 6-month data from all enrolled patients, with no predicted patients.

Study Oversight

The ABLATE trial utilized an independent core laboratory to read all of the Holter, permanent pacemaker (PPM), and ECG results. In addition, an independent cardiac surgeon not involved with the clinical study reviewed all adverse events through one year. A Data and Safety Monitoring Board (DSMB) was established for the trial and reviewed data periodically to ensure safety of subjects. The DSMB is still being utilized for the active clinical registry study that is ongoing (ABLATE AF) to maintain their role of ensuring safety of subjects.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the ABLATE study was limited to patients who met the following inclusion criteria:

   - Subject is greater than or equal to 18 years of age.
   - Subject has history of permanent atrial fibrillation (AF in which cardioversion (electrical and/or pharmacologic) has failed or has not been attempted) as defined by the 2006 ACC/AHA/ESC Guidelines.
   - Subject is scheduled to undergo elective cardiac surgical procedure(s) to be performed on cardiopulmonary bypass including open-heart surgery for one or more of the following: Mitral valve repair or replacement. Aortic valve repair or replacement. Tricuspid valve repair or replacement, and Coronary artery bypass procedures.
   - Left Ventricular Ejection Fraction > 30% (determined by echocardiography performed within 60 days of enrollment as documented in patient medical history, or intra-operatively at the time of treatment).
   - Subject is willing and able to provide written informed consent.
   - Subject has a life expectancy of at least 1 year.
   - Subject is willing and able to return for scheduled follow-up visits.

   Patients were not permitted to enroll if they met any of the following exclusion criteria:

   - Stand alone AF without indication(s) for concomitant coronary artery bypass grafting (CABG) and/or valve surgery.
   - Previous atrial ablation, AV-nodal ablation, or surgical Maze procedure.
   - Wolff-Parkinson-White syndrome.
   - Prior cardiac surgery (Redo).

- Patients requiring surgery other than CABG and/or cardiac valve surgery and/or patent foramen ovale repair, and/or atrial septal defect repair.
- Class IV NYHA heart failure symptoms.
- Prior history of cerebrovascular accident within 6 months or at any time if there is residual neurological deficit.
- Documented MI within the 6 weeks prior to study enrollment.
- Need for emergent cardiac surgery (i.e. cardiogenic shock).
- Known carotid artery stenosis greater than 80%.
- LA size greater than or equal to 8 cm.
- Current diagnosis of active systemic infection.
- Severe peripheral arterial occlusive disease defined as claudication with minimal exertion.
- Renal failure requiring dialysis or hepatic failure.
- A known drug and/or alcohol addiction.
- Mental impairment or other conditions which may not allow the subject to understand the nature, significance and scope of the study.
- Pregnancy or desire to get pregnant within 12-months of the study treatment.
- Preoperative need for an intra-aortic balloon pump or intravenous inotropes.
- Requires anti-arrhythmic drug therapy for the treatment of a ventricular arrhythmia.
- Patients who have been treated with thoracic radiation.
- Patients in current chemotherapy.
- Patients on long term treatment with oral or injected steroids (not including intermittent use of inhaled steroids for respiratory diseases).
- Patients with known connective tissue disorders.

2. Study Treatment

Along with their concomitant surgery, investigators were required to perform the Maze IV procedure using the investigational system. This procedure includes both right and left pulmonary vein isolation as well as a series of ablation lines to create "the box lesion" on the posterior left atrial free wall. Lesions to the mitral annulus and the left atrial appendage are also performed. On the right side of the heart lesions include a right atrial anterior free wall appendage lesion as well as a lesion from the appendage to the tricuspid annulus. Confirmation of pulmonary vein exit block was done to demonstrate effective isolation. The following table indicates which lesions required the use of the investigational device per the protocol.

Table 4: Protocol Required Device Use for Lesion Set Creation

Lesion	Device Recommended
Left-sided lesions	
Right and Left Pulmonary Vein	Synergy Ablation Clamp only
Roof Line	Synergy Ablation Clamp only
Floor Line	Synergy Ablation Clamp only
Mitral Valve Connecting	Initiated with Synergy Ablation Clamp, completed with AtriCure Transpolar Pen or cryo-surgical device
Left Atrial Appendage to Pulmonary Vein	Synergy Ablation Clamp only
Right-sided Lesions	
Right Tricuspid Valve	Synergy Ablation Clamp, AtriCure Transpolar Pen, or a cryo-surgical device
Superior Vena Cava (SVC) to Inferior Vena Cava (IVC)	Synergy Ablation Clamp only
Free Wall Appendage	Synergy Ablation Clamp only
Right Atrial Appendage to Tricuspid Annulus	Synergy Ablation Clamp, AtriCure Transpolar Pen or cryo-surgical device
Septal Lesion (optional)	Any technique

After surgery, subjects were placed on either a Class I or Class III anti-arrhythmic drug (AAD) immediately. They received anti-coagulation according to the clinician's preference and clinical indications.

3. Follow-up Schedule

Subjects were followed through discharge, at 30 days, 3 months, 6 months, 12 months, 18 months, 2 years and annually for five years thereafter. Follow-up at discharge was to be completed no more than 48 hours prior to hospital discharge. Other visits at or before 6 months had post-visit windows of 7 days (30 days and 2 months) or 14 days (3 months and 6 months) for completion of follow-up. The clinical assessments included a targeted history and physical exam as well as an assessment of medications and ECG. At two months an optional clinical assessment was encouraged as a means of evaluating the subject's AF status while on antiarrhythmic agents. All subjects were required to have a clinic visit at three and six months.

At the 3-month visit, the subjects were to discontinue their antiarrhythmic medications in an effort to allow evaluation of treatment efficacy while off drugs at

6 months (the primary efficacy time point). In an effort to wash out a drug at least five half-lives before the 6-month assessment, amiodarone was stopped 12 weeks earlier and other drugs four weeks earlier. Cardioversions were permitted up to the 6-month assessment and recommended by the protocol at any visit at which a subject was in AF or atrial flutter, if tolerated.

At each clinic visit, subjects were evaluated for safety.

Upon completion of the primary efficacy endpoint evaluation at 6 months post procedure, subjects are entered into a long-term surveillance phase. The study originally outlined a surveillance plan that consisted of a phone call assessment with the subjects at twelve months and then annually thereafter for a total of five years, with an allowed window of 28 days around each target visit date. A supplemental rhythm status at 12 months or greater was added to provide more insights on the durability of the procedure ABLATE study subjects.

The key time points are shown below in the table summarizing the schedule of events.

Table 5. Overall Schedule of Events

Assessment	Baseline	Procedure	Pre-Discharge	30 days	2 mo[2]	3 mo	Interim Visit[3]	6 mo	12 & 18 mo	Years 2 - 5
Informed Consent	X									
Medical History	X									
Adverse Event Evaluation			X	X	X	X	X	X		
Physical Exam	X		X	X	X	X	X	X		
NYHA Class	X			X	X	X	X	X		
Medications	X		X	X	X	X	X	X		
AAD Adjustment			X	X	X	X	X	X		
12 lead ECG	X		X	X	X	X	X	X[4]		
Holter Monitor 24hr/48 hr								X	X[xvii]	
RBC, WBC, HGB, HCT, Platelets	X		X							
INR[5]	X		X	X		X	X	X		
Pregnancy Test[6]	X									
Echocardiogram (transthoracic)	X[7]							X[8]		

2 2 month visit is optional
3 Interim visit is not required.
4 Assess from 24 hour Holter monitor
5 For anticoagulated patients only.
6 Females of childbearing potential
7 Cardiac Catheterization/Coronary angiogram can be used
8 Optional to assess left atrial transport function (LATF)

Echocardiogram (transesophageal)		X[9]								
AtriCure lesion set		X								
Pacing Study [10]		X								
Concomitant Surgical Procedure		X								
Cardioversion[11]			X	X	X	X	X			
Telephone FU									X	X

4. Clinical Endpoints

Primary Safety Endpoint

With regards to safety, the primary safety endpoint was the rate of Major Adverse Events (MAEs) occurring within the initial 30 days post procedure or discharge (whichever was later). The MAEs consisted of: death, excessive bleeding (defined as > 2 units of RBCs with reoperation), stroke, TIA or MI. The Applicant derived a historical safety rate of 13.95% from the reported experience with the "cut and sew" Cox Maze III procedure. A performance goal of 18.95% was used for hypothesis testing. The primary safety endpoint would be considered met if the Bayesian posterior probability that the rate of MAE is less than 18.95% exceeded 0.95.

Secondary Safety Endpoints

The following secondary safety endpoints were evaluated:

- Composite six month post procedure major adverse event rate
- Overall adverse event rate at six months

Primary Effectiveness Endpoint

With regard to effectiveness, the primary effectiveness endpoint was defined as the rate of subjects that are free of AF while off of any antiarrhythmic medication (Class I or III) evaluated at six months post procedure via 24-hour Holter monitor assessment (or permanent pacemaker interrogation in the case of those subjects that have a pacemaker implanted). The Applicant identified a reference rate of 70% based on surgical ablation procedures performed using RF ablation technology in the setting of concomitant surgery as found in historical literature, as well as its own RESTORE IDE study. A performance goal of 60% was used for hypothesis testing. The primary effectiveness endpoint would be considered met if the Bayesian posterior probability that the six-month success rate is greater than 60% exceeded 0.975.

Freedom from AF was defined as episodes < 5 minutes duration and no more than 1 hour total AF duration in 24 hours.

9 Can be used to access eligibility criteria if an echocardiogram (or cardiac catheterization) has not been performed within 60 days

10 For subjects in whom sinus rhythm has been restored intraoperatively, and as determined by physician discretion.

11 At physician discretion per standard of care at institution

[xvii] 48 hour Holter monitor to be performed at 12 months or later

Secondary Effectiveness Endpoints

The following secondary effectiveness endpoints were prospectively defined:

- The proportion of patients who are free of atrial fibrillation (episodes < 5 min. duration and no more than 1 hr total AF duration in 24 hrs monitoring) independent of the need for anti-arrhythmic drugs (Class I and Class III) as determined by a 24-hour Holter recording at 6 months
- Effectiveness of pulmonary vein isolation to produce acute electrical conduction block
- Reduction of overall AF burden as measured on 24 hour Holter at 6 months

In addition, the following secondary endpoints were added to the investigational plan after enrollment was completed based on discussions with FDA:

- The proportion of patients in who are free of atrial fibrillation (episodes < 5 min. duration and no more than 1 hr total AF duration in a 24 hr timeframe) independent of the need for anti-arrhythmic drugs (Class I and Class III) as assessed by a 48-hour Holter recording performed at a minimum of 12 months post procedure.
- The proportion of patients in the treatment group who are free of atrial fibrillation (episodes < 5 min. duration and no more than 1 hr total AF duration in a 24 hr timeframe) and off Class I and III antiarrhythmic drugs as assessed by a 48-hour Holter recording performed at a minimum of 12 months post procedure.
- Overall atrial fibrillation burden measured on a 48 hour Holter recording at 12 months or after.

B. Accountability of PMA Cohort

1. Interim Analysis

The Applicant conducted the first interim look when 55 patients had been enrolled and all had provided the 30-day safety outcome. The pre-specified safety performance goal was met; therefore, the predictive probability of meeting the safety endpoint with the current sample size was 100%. There were 50 patients for the effectiveness interim analysis, and there were 24 effectiveness successes out of 29 patients providing 6-month data. After calculation, the predictive probability of meeting the effectiveness endpoint with the current sample size was 98.8%, which exceeded the stopping boundary. Thus the trial accrual was stopped per the pre-specified stopping rules.

2. Patient Disposition

At the time of database lock, of 55 patients enrolled and treated in the PMA study, 50 patients are available for analysis at the 6-month post-operative visit.

The following chart presents patient accountability.

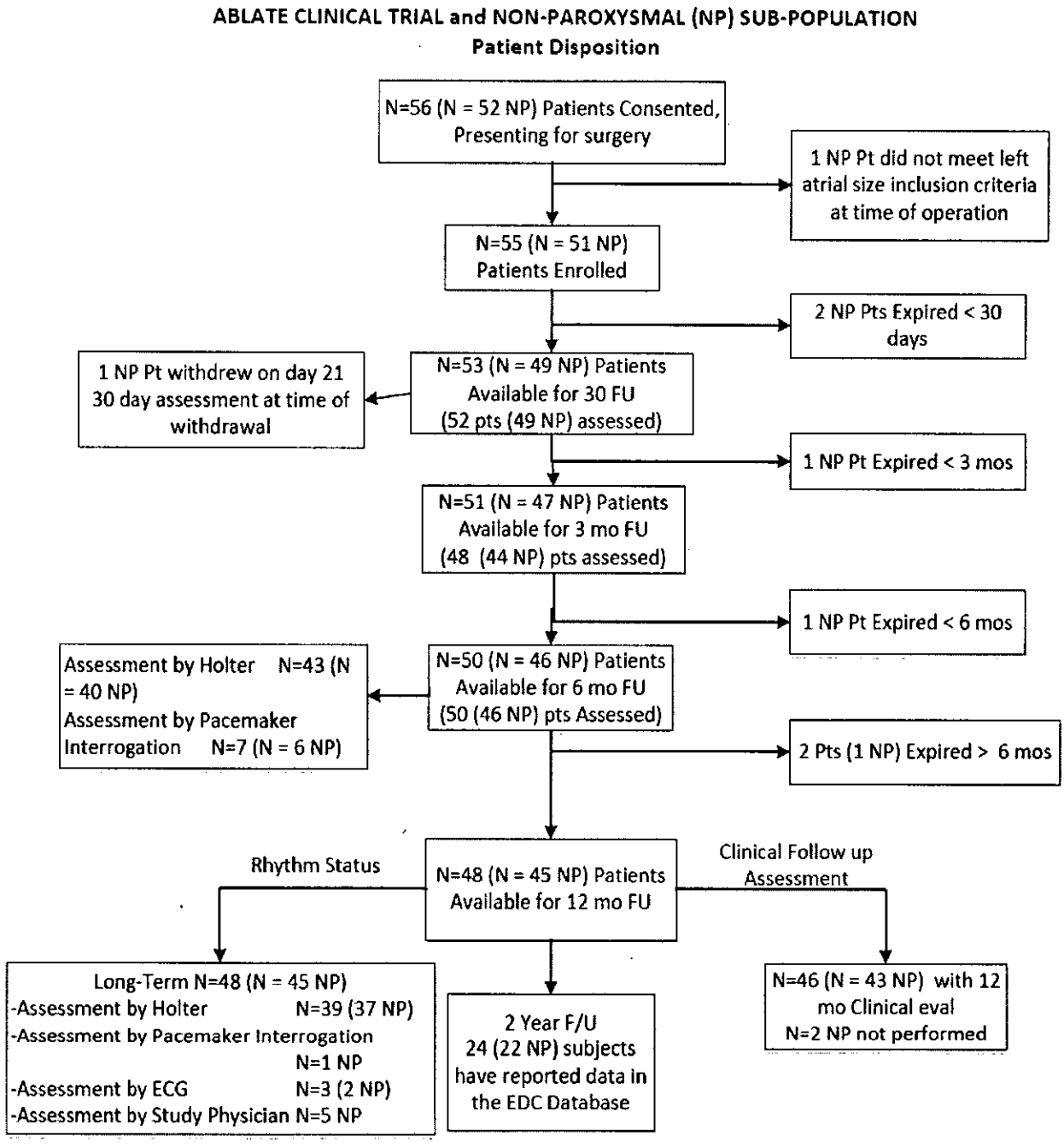

Figure 4: ABLATE Subject Accountability

C. Study Population Demographics and Baseline Parameters

The study inclusion criteria specified the target population as subjects with "permanent" AF per the 2006 ACC/AHA/ESC guidelines as shown below. As the definition for "permanent AF" has changed with the publication of the 2007 HRS Consensus Statement, subjects were reclassified during FDA review of the PMA by

two expert independent reviewers according to current AF classification definitions, which are given here.

Table 6: AF Classification per 2006 ACC/AHA/ESC Guidelines and 2007 HRS Statement

AF Classification	2006 ACC/AHA/ESC Guidelines	2007 HRS Statement
Paroxysmal	AF is self-terminating within 7 days of recognized onset	Recurrent AF (>2 episodes) that terminates spontaneously within 7 days
Persistent	AF is not self-terminating within 7 days, or is terminated electrically or pharmacologically	AF which is sustained beyond 7 days, or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion
Longstanding Persistent		Continuous AF of greater than one-year duration
Permanent	AF in which cardioversion (electrical and/or pharmacologic) has failed or has not been attempted	Patients where a decision has been made not to pursue restoration of sinus rhythm by any means

Upon reclassification, the subjects were categorized as having paroxysmal AF, persistent AF or longstanding persistent AF with the following distribution.

Table 7: Number of Subjects in ABLATE by AF Classification

AF Classification	Number of Subjects Enrolled
Paroxysmal	4
Persistent	22
Longstanding persistent	29

During review of the PMA data, FDA and the applicant agreed that the target population for the PMA should only be patients with persistent or longstanding persistent AF. For completeness, results are presented for all treated subjects as well as for non-paroxysmal (persistent and longstanding persistent) AF subjects only.

The demographics of the study population are typical for patients undergoing the mix of concomitant surgeries that were performed. Table 9 provide a summary of the significant baseline comorbidities.

Table 8: Subject Demographics

Parameter	Treated Subjects N=55	Non-Paroxysmal Subjects N=51
Age [years]		
Mean +/- SD (N)	70.5 +/- 9.3 (55)	70.8 +/- 9.6 (51)
Median	72.0	73.0

Parameter	Treated Subjects N=55	Non-Paroxysmal Subjects N=51
Min, Max	45.0, 88.0	45.0, 88.0
Gender [% (n/N)]		
Male	58.2% (32/55)	60.8% (31/51)
Female	41.8% (23/55)	39.2% (20/51)
Ethnic Group [% (n/N)]		
Caucasian	90.9% (50/55)	90.2% (46/51)
Black	3.6% (2/55)	3.9% (2/51)
Asian	1.8% (1/55)	2.0% (1/51)
Hispanic	3.6% (2/55)	3.9% (2/51)
Height [in]		
Mean +/- SD (N)	68.0 +/- 5.0 (55)	68.0 +/- 5.1 (51)
Median	68.0	68.0
Min, Max	54.9, 79.0	54.9, 79.0
Weight [lbs]		
Mean +/- SD (N)	199.6 +/- 56.2 (55)	200.0 +/- 55.2 (51)
Median	185.0	185.0
Min, Max	113.0, 349.8	113.0, 349.8
BMI		
Mean +/- SD (N)	30.1 +/- 6.9 (55)	30.1 +/- 6.6 (51)
Median	28.5	28.6
Min, Max	20.4, 47.4	20.4, 47.4

Table 9: Significant Baseline Comorbidities

	Treated Subjects N=55	Non-Paroxysmal Subjects N=51
Parameter	**% (n/N)**	**% (n/N)**
Cardiomyopathy	9.1% (5/55)	7.8% (4/51)
Congestive Heart Failure	34.5% (19/55)	37.3% (19/51)
Coronary Artery Disease	54.5% (30/55)	56.9% (29/51)
Chronic Obstructive Pulmonary Disease (COPD)	14.5% (8/55)	15.7% (8/51)
Diabetes	20.0% (11/55)	21.6% (11/51)
Hyperlipidemia	65.5% (36/55)	68.6% (35/51)
Hypertension	70.9% (39/55)	76.5% (39/51)
Myocardial Infarction	7.3% (4/55)	7.8% (4/51)
Obesity	23.6% (13/55)	23.5% (12/51)

	Treated Subjects N=55	Non-Paroxysmal Subjects N=51
Parameter	**% (n/N)**	**% (n/N)**
Smoking	5.5% (3/55)	3.9% (2/51)
Cerebral Vascular Accident (CVA)/Stroke	5.5% (3/55)	3.9% (2/51)
Transient Ischemic Attack (TIA)	7.3% (4/55)	7.8% (4/51)
Valvular Heart Disease	85.5% (47/55)	84.3% (43/51)
EF (%)		
Mean +/-SD (n)	50.0 +/- 10.3 (54)	49.6 +/- 10.6 (50)
Median (Min, Max)	50.0 (20.0, 70.0)	50.0 (20.0, 70.0)
LA Size (cm)		
Mean +/-SD (n)	5.9 +/- 1.0 (50)	6.0 +/- 1.0 (46)
Median (Min, Max)	6.0 (3.9, 7.7)	6.0 (3.9, 7.7)
NYHA Classification [%(n/N)]		
I	16.4% (9/55)	17.6% (9/51)
II	41.8% (23/55)	41.2% (21/51)
III	40.0% (22/55)	39.2% (20/51)
IV	1.8% (1/55)	2.0% (1/51)
Missing	0% (0/55)	0% (0/51)

Concomitant procedures were performed on all 55 subjects who were treated with the device. As detailed in the table below, valve surgery was performed in the majority of subjects, either alone (56.4%) or in combination with coronary artery bypass grafting (25.5%). Isolated coronary bypass made up an appreciable minority of procedures (18.2%). Mitral surgery in any form was undertaken in 54.5% of subjects.

Table 10: Concomitant Procedures Performed

Concomitant Procedure Performed	Treated Subjects (N=55) Percentage	Non-Paroxysmal Subjects (N=51) Percentage
CABG only	18.2%	19.6%
Valve Surgery	40.0%	37.2%
Mitral	18.2%	17.6%
Aortic	21.8%	19.6%
Double Valve Surgery	16.4%	17.6%
Aortic & Mitral	7.3%	7.8%
Mitral & Tricuspid	9.1%	9.8%
CABG and Valve Surgery	16.4%	15.7%
CABG + Mitral	10.9%	9.8%
CABG + Aortic	5.5%	5.9%
CABG + Double Valve Surgery	9.1%	9.8%
Aortic & Mitral	5.5%	5.9%
Mitral & Tricuspid	3.6%	3.9%

D. Safety and Effectiveness Results

1. Control of Type I Error Rate

The type I error rate may be inflated in a statistical design that incorporates interim monitoring. For the ABLATE study, the Applicant calculated the type I error rate jointly for the primary safety endpoint and the primary effectiveness endpoint. However, FDA currently believes that the type I error rate should be controlled independently at a desired level for the primary safety endpoint (5% for this study) and for the effectiveness endpoint (2.5% for this study). Therefore FDA conducted its own simulations to calculate the type I error rate for each primary endpoint (safety and effectiveness) independent of the other primary endpoint. The results showed that the type I error rate for the primary safety endpoint was inflated from 5% to 6.1% and the type I error for the primary effectiveness endpoint was inflated from 2.5% to 2.6%. Given the current design scheme, if the type I error rate for the primary endpoints were controlled at 5% and 2.5% for safety and effectiveness, respectively, the corresponding posterior probability criteria for the primary endpoints at the final analysis would be increased. However, this result would not change the study conclusions.

2. Safety Results

The analysis of safety was based on the cohort of 55 patients treated with the AtriCure Synergy Ablation System available for the 30-day evaluation. The key safety outcomes for this study are presented below in Tables 10 to 12. Adverse effects are reported in Tables 14 to 16.

The primary safety endpoint was evaluated for all 55 subjects enrolled and treated. There were five safety failures: two deaths, two excessive bleeds and one stroke. Only one of the 5 MAEs, a death, was attributed to the Maze procedure by

the independent physician adjudicator. None of the MAEs was found to be device related. The safety results are detailed in the table below, along with the one-sided 95% Bayesian credible intervals (BCI) for the composite.

Table 11: Primary Safety Endpoint Results for Treated and Non-Paroxysmal Subjects

Primary Safety Endpoint	**Treated**	**Non-Paroxysmal**
	% (n/N)	**% (n/N)**
Composite MAE within 30 days	**9.1% (5/55) BCI (0.00, 0.179)**	**9.8% (5/51) BCI (0.00, 0.192)**
Death	3.6% (2/55)	3.9% (2/51)
<=30 days	3.6% (2/55)	3.9% (2/51)
>30 days, procedure related	0.0% (0/55)	0.0% (0/51)
Stroke/TIA	1.8% (1/55)	2.0% (1/51)
Stroke (with significant permanent disability)	1.8% (1/55)	2.0% (1/51)
TIA	0.0% (0/55)	0.0% (0/51)
MI	0.0% (0/55)	0.0% (0/51)
Excessive Bleeding (>2 units blood and surgical intervention)	3.6% (2/55)	3.9% (2/51)
Posterior probability that the safety rate is less than 0.1895 $\Pr(q_T < 0.1895 \mid \text{Trial Results})$	**0.967**	**0.946**

Based on the results presented in the table above, the primary safety endpoint is met for the Treated population, but not for the Non-Paroxysmal subgroup.

The secondary safety endpoints of composite 6-month major adverse event rate and overall 6-month adverse event rate are given in the following table for the Treated and Non-Paroxysmal populations.

Table 12: Secondary Safety Endpoints for Treated and Non-Paroxysmal Subjects

Secondary Safety Endpoints	Treated % (n/N)	Non-Paroxysmal % (n/N)
MAE through 6 months	10.9% (6/55)	11.8% (6/51)
Death	7.3% (4/55)	7.8% (4/51)
Stroke (with significant permanent disability)	1.8% (1/55)	2.0% (1/51)
TIA	0.0% (0/55)	0.0% (0/51)
MI	0.0% (0/55)	0.0% (0/51)
Excessive Bleeding (>2 units blood and surgical intervention)	3.6% (2/55)	3.9% (2/51)
Any Adverse Event through 6 months	90.9% (50/55)	94.1% (48/51)
Any Serious Event	74.5% (41/55)	76.5% (39/51)
Any Device Related Event	0.0% (0/55)	0.0% (0/51)
Any AF-Procedure Related Event	14.5% (8/55)	15.6% (8/51)
Any Serious Device Related Event	0.0% (0/55)	0.0% (0/51)
Any Serious AF-Procedure Related Event	12.7% (7/55)	13.7% (7/51)

Permanent Pacemaker Implantation

Ablation may have an effect on the cardiac conduction system. Damage to the sinoatrial and/or atrioventricular nodes may result in pacemaker implantation after treatment. Seven of the 55 subjects who presented for treatment already had pacemakers implanted. In the remaining 48 subjects, 12 pacemakers were implanted within 30-days after ablation (25%): 4 for A-V nodal dysfunction, and 8 for sinus node dysfunction. Four more pacemakers were implanted later, bringing the cumulative total to 33%. All of the later implants were for sinus node dysfunction, and all occurred between 30-days and 6-months. This is detailed in the table below.

Table 13: Rates of Pacemaker Implantation

	In Hospital % [n/N]	Cumulative to 30 days % [n/N]	Cumulative to 6 months % [n/N]	Cumulative to 12 months % [n/N]
Permanent Pacemaker Implantation	25.0% (12/48)	25.0% (12/48)	33.3% (16/48)	33.3% (16/48)
AV node dysfunction	8.3% (4/48)	8.3% (4/48)	8.3% (4/48)	8.3% (4/48)
Sinus node dysfunction	16.7% (8/48)	16.7% (8/48)	25.0% (12/48)	25.0% (12/48)

Adverse effects that occurred in the PMA clinical study:

A summary of the adjudicated clinical events based on attribution is provided in Table 14.

Table 14: Summary of Adverse Events Through 6 Months

	ABLATE Cumulative to 30 Days N=55		ABLATE Cumulative to 6 Months N=55		ABLATE Non-paroxysmal Cumulative to 30 Days N=51		ABLATE Non-paroxysmal Cumulative to 6 Months N=51	
Parameter [1][2]	**# of Evts**	**% (n/N) of Pts with Event**	**# of Evts**	**% (n/N) of Pts with Event**	**# of Evts**	**% (n/N) of Pts with Event**	**# of Evts**	**% (n/N) of Pts with Event**
Any Adverse Event	166	89.1% (49/55)	198	90.9% (50/55)	160	92.2% (47/51)	188	94.1% (48/51)
Investigational Device	0	0.0% (0/55)	0	0.0% (0/55)	0	0.0% (0/51)	0	0.0% (0/51)
AF Procedure	8	14.5% (8/55)	8	14.5% (8/55)	8	15.7% (8/51)	8	15.7% (8/51)
Ancillary Device	1	1.8% (1/55)	1	1.8% (1/55)	1	2.0% (1/51)	1	2.0% (1/51)
General Surgical Procedure	140	87.3% (48/55)	144	87.3% (48/55)	134	90.2% (46/51)	138	90.2% (46/51)
Other Relationship	17	20.0% (11/55)	45	41.8% (23/55)	17	21.6% (11/51)	41	43.1% (22/51)
Serious Adverse Event	84	63.6% (35/55)	106	74.5% (41/55)	80	64.7% (33/51)	99	76.5% (39/51)
Investigational Device	0	0.0% (0/55)	0	0.0% (0/55)	0	0.0% (0/51)	0	0.0% (0/51)
AF Procedure	7	12.7% (7/55)	7	12.7% (7/55)	7	13.7% (7/51)	7	13.7% (7/51)
Ancillary Device	1	1.8% (1/55)	1	1.8% (1/55)	1	2.0% (1/51)	1	2.0% (1/51)
General Surgical Procedure	67	60.0% (33/55)	70	61.8% (34/55)	63	60.8% (31/51)	66	62.7% (32/51)
Other Relationship	9	14.5% (8/55)	28	32.7% (18/55)	9	15.7% (8/51)	25	33.3% (17/51)

[1] As Adjudicated or site reported if not yet adjudicated.
[2] Relationship presented hierarchally as listed in table.

Device- and Ablation-Procedure Related Adverse Events

The following table presents rates for adverse events related to the device and AF ablation procedure. All of these events occurred prior to discharge for the index procedure. There were no adverse events adjudicated as related to the device. Of the 8 adverse events related to the AF procedure, 7 were serious. In addition to those listed in the table, one serious adverse event (ischemia requiring coronary bypass) was attributed to the ancillary AtriCure pen used to complete the lesion to the tricuspid annulus.

Table 15: Rates of Adjudicated Device- and AF Procedure-Related Adverse Events

	Treated		Non-Paroxysmal	
Parameter	**# of Events**	**% (n/N) of Pts with Event**	**# of Evts**	**% (n/N) of Pts with Event**
Device Related Adverse Event	0	0.0% (0/55)	0	0.0% (0/51)
AF Procedure Related Adverse Event	8	14.5% (8/55)	8	15.7% (8/51)
Cardiac disorders	6	10.9% (6/55)	6	11.8% (6/51)
Atrial rupture	1	1.8% (1/55)	1	2.0% (1/51)
Atrioventricular block	1	1.8% (1/55)	1	2.0% (1/51)
Atrioventricular block first degree	1	1.8% (1/55)	1	2.0% (1/51)
Atrioventricular block second degree	1	1.8% (1/55)	1	2.0% (1/51)
Bradycardia	2	3.6% (2/55)	2	3.9% (2/51)
Injury, poisoning and procedural complications	2	3.6% (2/55)	2	3.9% (2/51)
Vena cava injury	1	1.8% (1/55)	1	2.0% (1/51)
Venous injury	1	1.8% (1/55)	1	2.0% (1/51)

A summary of the adjudicated clinical events specifically associated with the AF ablation procedure is provided in Table 16. Of the nine events associated with the AF ablation procedure, one event met the criteria of a primary safety event. These events are described further below.

Table 16: Adverse Events Adjudicated as Associated to the AF Ablation Procedure or Ancillary Device Use

Subject	Event Name	Adjudication	Relationship	Treatment	Primary Safety Endpoint
11-04-GKE	Atrioventricular Block First Degree	Non-Serious AE	AF Ablation Procedure	Recovery	NO
05-03-LRG	A-V Node Dysfunction	Serious AE	AF Ablation Procedure	PPM	NO
11-10-ECW	A-V Node Dysfunction	Serious AE	AF Ablation Procedure	PPM	NO
13-06-JDH	A-V Node Dysfunction	Serious AE	AF Ablation Procedure	PPM	NO
19-01-EEE	A-V Node Dysfunction	Serious AE	AF Ablation Procedure	PPM	NO

Subject	Event Name	Adjudication	Relationship	Treatment	Primary Safety Endpoint
11-08-NTW	Cardiac Akinesis	Serious AE	Ancillary Device Related	CAB x2	NO
11-01-HPH	Pulmonary Vein Tear (LPV)	Serious AE	AF Ablation Procedure	Suture	NO
13-02-JCM	Torn IVC Cannulation Site	Serious AE	AF Ablation Procedure	Patch	NO
13-04-PJP	Left Atrial Tear	Serious AE	AF Ablation Procedure	Suture	DEATH

As previously stated, a death occurred in subject 13-04 who had a significant bleeding event caused during dissection of the pulmonary veins prior to placing the clamp in position. This was attributed to the Maze IV procedure.

The other six serious adverse events (SAEs) that were attributed to the ablation procedure included four cases of AV nodal dysfunction that required placement of a permanent pacemaker, one pulmonary vein tear after the left pulmonary vein was retracted, and one tear at the IVC cannulation site for cardiopulmonary bypass.

There was one episode of AV block that was deemed non-serious because the subject was treated with medication and no permanent pacemaker was implanted.

There was one serious adverse event attributed to an ancillary device. After an RF ablation pen was used to complete the lesion line to the tricuspid annulus, the lateral and inferior wall of the left ventricle became akinetic. This was successfully treated by placing bypass grafts on the circumflex and distal right coronary arteries.

3. Effectiveness Results

The analysis of effectiveness was based on the *50* evaluable subjects at the *6*-month time point. Key effectiveness outcomes are presented in Tables 17 to 20. The primary effectiveness endpoint was evaluated for 50 evaluable subjects out of 55 treated subjects. This excludes 4 deaths and 1 withdrawal. The following table presents the primary effectiveness results along with the one-sided 97.5% Bayesian credible intervals (BCIs).

Table 17: Primary Effectiveness Endpoint Results for Treated and Non-Paroxysmal Subjects

	Treated N=50	Non-Paroxysmal N=46
Primary Effectiveness Endpoint	**% (n/N)**	**% (n/N)**
Primary Success at 6 months[12]	74.0% (37/50) BCI (0.604, 1.00)	73.9% (34/46) BCI (0.597, 1.00)
Failure by AAD	10.0% (5/50)	8.7% (4/46)
Failure by Rhythm	16.0% (8/50)	17.4% (8/46)
Posterior probability that the effectiveness rate is greater than 60% **Pr(p_T > 0.60 | Trial Results)**	0.978	0.972

The primary effectiveness endpoint is met for the Treated population but not met for the Non-Paroxysmal subpopulation.

Freedom from AF, whether on or off AADs, is shown in the table below. The table also shows the AF burden in a 24-hour period measured either with a 24-hour Holter (44 Treated, 40 Non-Paroxysmal) or pacemaker interrogation (6 Treated, 6 Non-Paroxysmal).

Table 18: Secondary Effectiveness Endpoints for Treated and Non-Paroxysmal Subjects

Secondary Effectiveness Endpoint	All Treated N=50	Non-Paroxysmal N=46
	% (n/N)	**% (n/N)**
Free of AF, Regardless of AADs[13]	84.0% (42/50)	82.6% (38/46)
AF Burden		
= 0 min	82.0% (41/50)	82.6% (38/46)
<= 5 min	2.0% (1/50)	0% (0/46)
> 5 min - 1 hr	2.0% (1/50)	0% (1/46)
> 1 hr	14.0% (7/50)	15.2% (7/46)

Acute Pulmonary Vein Isolation

Exit block was assessed by pacing from the pulmonary veins after ablation. This was technically possible in 23 subjects. Complete block was demonstrated in all of them.

12 One subject was weaned from AADs after the 3-month period dictated by the study protocol. A Holter monitor was performed *after the drug washout period* and used retrospectively for assessment of the primary effectiveness endpoint.

13 Using the definition of the 2006 Guidelines: "AF free" = no episodes > 5 minutes

Table 19: Pulmonary Vein Isolation

Secondary Effectiveness Endpoint	% (n/N)
Both Right & Left Pulmonary Vein Isolation	
Isolation Confirmed (Of 23 evaluable subjects)	100.0% (23/23)

Freedom from AF at 12 or More Months

Late follow-up was obtained for subjects at least one year after treatment in order to assess effectiveness over time. The additional endpoints to be studied were: (1) Freedom from AF, off AADs; (2) Freedom from AF, regardless of AADs; and (3) AF burden. This data collection was not prospectively specified was data collection for this effort began after many subjects had already completed one year of follow-up. The median follow-up was 658 days (range 365 - 952 days). The data shown below are divided according to the populations of interest; the exact number of subjects varies because of the retrospective collection without all subjects being available.

Table 20: Additional Effectiveness Endpoints for Treated and Non-Paroxysmal Subjects

	All Treated	Non-Paroxysmal
Additional Effectiveness Endpoints	**% (n/N)**	**% (n/N)**
Effectiveness Evaluable at 12 month Follow-up or greater	N=48	N=45
Free of AF[14] at 12+ months	75.0% (36/48)	73.3% (33/45)
Free of AF and off AAD at 12+ months	62.5% (30/48)	62.2% (28/45)
Time to Evaluation (days)		
Mean +/- SD (N)	640.9 +/- 147.3	641.7 +/- 151.7
Min, Max	365.0, 952.0	365.0, 952.0
Method of Evaluation		
Holter	81.3% (39/48)	82.2% (37/45)
Pacemaker Interrogation (PMI)	2.1% (1/48)	2.2% (1/45)
ECG	6.3% (3/48)	4.4% (2/45)
Other/Telephone Assessment	10.4% (5/48)	11.1% (5/45)
AF Burden (initial 24 hrs or >24 - 48 hrs) at 12+ months		
= 0 min	77.5% (31/40)	76.3% (29/38)
<= 5 min	0.0% (0/40)	0.0% (0/38)
> 5 min - 1 hr	0.0% (0/40)	0.0% (0/38)
> 1 hr	22.5% (9/40)	23.7% (9/38)

4. Additional Analyses

Lesion Set Deviations

According to the study protocol, 6 of 9 of the ablative lesions were to be created only with the Synergy Ablation Clamp. Several deviations from the lesion set protocol were observed in the ABLATE study. Although only 4% of all lesions

14 Using the definition of the 2006 Guidelines: "AF free" = no episodes > 5 minutes

(24/550 lesions in 55 subjects) were performed with device(s) or techniques other than the Synergy Ablation Clamp or not performed at all, this occurred in about 25% of subjects (14/55 treated subjects and 13/51 non-paroxysmal subjects). An accounting of these deviations is shown in the tables below on a per-lesion and per-patient basis, respectively. These results demonstrate the extent to which the AtriCure Synergy Ablation System was used in achieving the reported effectiveness results.

Table 21: Lesion Set Deviations Presented by Lesion

Lesion	Deviations	Alternative Method Used	Lesion not Performed
Pulmonary veins	0	0	0
Box lesion - Floor	8	Cut & Sew (6) RF Pen (1)	1
Box lesion – Roof	2	RF Pen (1)	1
Mitral valve annulus*	2	Cryoablation alone used (1)	1
LA appendage	3	Cryoablation (2)	1
Tricuspid valve**	1	0	1
SVC-to-IVC line	1	0	1
Free wall	5	0	5
RA appendage**	2	0	2
*lesion must be initiated with the clamp but can be completed by another modality **lesion can be performed by any method			

Table 22: Lesion Set Deviations Per Patient

Number of deviations per patient	Number of patients	Note
Patients with only 1 deviation	12	9 subjects had a lesion performed with an alternative method 3 subjects had a lesion omitted
Patients with > 1 deviation		
4 deviations	1	In this patient 2 lesions (Roof and Floor) were performed with an alternative method (RF pen) and 2 were omitted (Free wall and RA appendage)
8 deviations	1	This subject was classified has having paroxysmal AF. Only pulmonary vein isolation was performed on this patient.

Additional per-lesion detail is outlined in the following tables.

Table 23: Biatrial Lesion Details - Right Atrial Lesions

	ABLATE N=55	ABLATE Non-paroxysmal N=51
Parameter	**% (n/N)**	**% (n/N)**
Left Sided Lesions [1]		
I. Mitral Valve Connecting Lesion [2]	100.0% (54/54)	100.0% (51/51)
AtriCure Clamp	33.3% (18/54)	29.4% (15/51)
Cryothermy	1.9% (1/54)	2.0% (1/51)
AtriCure Clamp and AtriCure Pen	27.8% (15/54)	29.4% (15/51)
AtriCure Clamp and Cryothermy	29.6% (16/54)	31.4% (16/51)
AtriCure Clamp and Surgical (cut and sew)	7.4% (4/54)	7.8% (4/51)
II. Floor Line Lesion	100.0% (54/54)	100.0% (51/51)
AtriCure Clamp	87.0% (47/54)	86.3% (44/51)
AtriCure Pen	1.9% (1/54)	2.0% (1/51)
Surgical (cut and sew)	11.1% (6/54)	11.8% (6/51)
III. Roof Line Lesion	100.0% (54/54)	100.0% (51/51)
AtriCure Clamp	98.1% (53/54)	98.0% (50/51)
AtriCure Pen	1.9% (1/54)	2.0% (1/51)
IV. LAA Appendage to Pulmonary Vein	100.0% (54/54)	100.0% (51/51)
AtriCure Clamp	96.3% (52/54)	96.1% (49/51)
Cryothermy	3.7% (2/54)	3.9% (2/51)

[1] One subject did not undergo the Maze 4 procedure.

[2] Mitral valve connecting lesion includes the full complement of the mitral valve annular lesion (lesion taken from the atriotomy to the mitral valve annulus and lesion completed on the posterior mitral valve annulus).

Table 24: Biatrial Lesion Details - Right Atrial Lesions

	ABLATE N=55	ABLATE Non-paroxysmal N=51
Parameter		**% (n/N)**
Right Sided Lesions [1]		
I. Tricuspid Valve Annulus lesion	100.0% (54/54)	100.0% (51/51)
AtriCure Clamp	46.3% (25/54)	43.1% (22/51)
AtriCure Pen	14.8% (8/54)	15.7% (8/51)
Surgical (cut and sew)	1.9% (1/54)	2.0% (1/51)
Cryothermy	14.8% (8/54)	15.7% (8/51)
AtriCure Clamp and AtriCure Pen	9.3% (5/54)	9.8% (5/51)
AtriCure Clamp and Cryothermy	11.1% (6/54)	11.8% (6/51)
AtriCure Clamp and Surgical (cut and sew)	1.9% (1/54)	2.0% (1/51)
II. Ablation of SVC / IVC	100.0% (54/54)	100.0% (51/51)
AtriCure Clamp	100.0% (54/54)	100.0% (51/51)
III. Free wall Appendage Lesion	92.6% (50/54)	92.2% (47/51)
AtriCure Clamp	100.0% (50/50)	100.0% (47/47)
IV. Right Atrial Appendage Lesion	98.1% (53/54)	98.0% (50/51)
AtriCure Clamp	54.7% (29/53)	52.0% (26/50)
AtriCure Pen	9.4% (5/53)	10.0% (5/50)
Cryothermy	18.9% (10/53)	20.0% (10/50)
AtriCure Clamp and AtriCure Pen	7.5% (4/53)	8.0% (4/50)
AtriCure Clamp and Cryothermy	5.7% (3/53)	6.0% (3/50)
AtriCure Clamp and Surgical (cut and sew)	1.9% (1/53)	2.0% (1/50)
Surgical (cut and sew) and Cryothermy	1.9% (1/53)	2.0% (1/50)
[1] One subject did not undergo the Maze 4 procedure.		

Modified Effectiveness Analysis

In addition to the information presented above, FDA believes the effectiveness results should be presented considering contemporary definitions for AF treatment success. In the ABLATE study, freedom from AF was defined as freedom from episodes < 5 minutes in duration and no more than 1 hour total AF

duration in 24 hours. Current guidelines consider recurrence of AF to include any episode of AF, atrial flutter, or atrial tachycardia lasting longer than 30 seconds. Ideally, rhythm status is measured with a 24-48 hour Holter monitor. In the ABLATE study, the 6 month evaluation was primarily performed with a 24 hour Holter recording. The 12 month (or greater) evaluation was primarily performed with a 48 hour Holter recording. The results in the table below include 2 cases of atrial flutter greater than 5 minutes (non-paroxysmal subjects) and 1 case of AF between 30 seconds and 5 minutes (paroxysmal subject) at the 6 month evaluation. At 12+ months, the results in the table include one additional case of atrial flutter and one additional case of atrial tachycardia (counting these cases as failures), compared to results using the original ABLATE definitions.

Current guidelines also consider cardioversion performed after a 3 month blanking period to be effectiveness failures. According to the study protocol, DC cardioversions were permitted at any time during the follow-up period, up to the 6-month assessment. In the ABLATE study, 12 subjects underwent cardioversion during their 6 month follow-up period. Of these, four (4) were cardioverted after 3 months. All four were classified as having longstanding persistent AF prior to treatment. In the primary effectiveness analysis, one was considered a primary effectiveness success, one a secondary effectiveness success, and two were effectiveness failures. In addition, one subject underwent cardioversion between 6 and 12 months after treatment that resulted in the patient's classification as a success at the long-term assessment. That subject had longstanding persistent AF and was a primary effectiveness endpoint failure (in AF at 6 months) but a secondary effectiveness success (in a paced rhythm and off AADs at 12 months). The table below considers subjects who have been cardioverted more than 3 months after treatment to be effectiveness failures.

Table 25 presents the effectiveness results using an alternative definition for treatment success, where any episode of AF, atrial flutter, or atrial tachycardia > 30 seconds, or any cardioversion after a 3 month blanking period is treated as a failure.

Table 25: Effectiveness Results for ABLATE using an Alternative Definition for Treatment Success

	Treated	**Non-Paroxysmal**
Effectiveness Endpoint	**% (n/N) [97.5% BCI]**	**% (n/N) [97.5% BCI]**
Effectiveness Evaluable at 6-Month Follow-up	**N=50**	**N=46**
Free of AF, AFL, and AT and off AADs[1]	**66% (33/50)[2] [0.521, 1.00]**	**67.4% (31/46)[2] [0.529, 1.00]**
Failure by rhythm AF Atrial flutter	11 (9) (2)	10 (8) (2)
Failure by AAD[3]	6	5
Failure by CV after 3 months	4	4

	Treated	Non-Paroxysmal
Effectiveness Endpoint	**% (n/N) [97.5% BCI]**	**% (n/N) [97.5% BCI]**
Free of AF, AFL, and AT	**74.0%% (37/50)**	**73.9% (34/46)**
Failure by rhythm	11	10
AF	(9)	(8)
Atrial flutter	(2)	(2)
Failure by CV after 3 months	4	4
Effectiveness Evaluable at 12+-Month Follow-up	**N=48**	**N=45**
Free of AF, AFL, and AT and off AADs	**54.2% (26/48)[2]**	**53.3% (24/45)[2]**
Failure by rhythm	14	14
AF	(12)	(12)
Atrial flutter	(1)	(1)
Atrial Tachycardia	(1)	(1)
Failure by AAD	7	6
Failure by CV after 3 months	6	6
Free of AF, AFL, and AT	**64.6% (31/48)**	**62.2% (28/45)**
Failure by rhythm	14	14
AF	(12)	(12)
Atrial flutter	(1)	(1)
Atrial Tachycardia	(1)	(1)
Failure by CV after 3 months	**6**	**6**

[1] Treatment success is defined as no episode of AF, atrial flutter, or atrial tachycardia > 30 seconds, or any cardioversion after a 3 month blanking period.

[2] Overall rate can not be computed by simple summation of counts for individual failure modes as several subjects failed by more than one mode. At 6 months: Late CV and AAD (1); Rhythm (AFL) and AAD (1); Late CV and Rhythm (AF) (2). At 12+ months: Rhythm (AF), AAD and Late CV (1); Rhythm (AF) and Late CV (2); AAD and Late CV(1).

[3] In this analysis, subjects that had not completed AAD washout at 6 months are considered failures. There was one such subject that was originally considered an effectiveness success based on later Holter recordings.

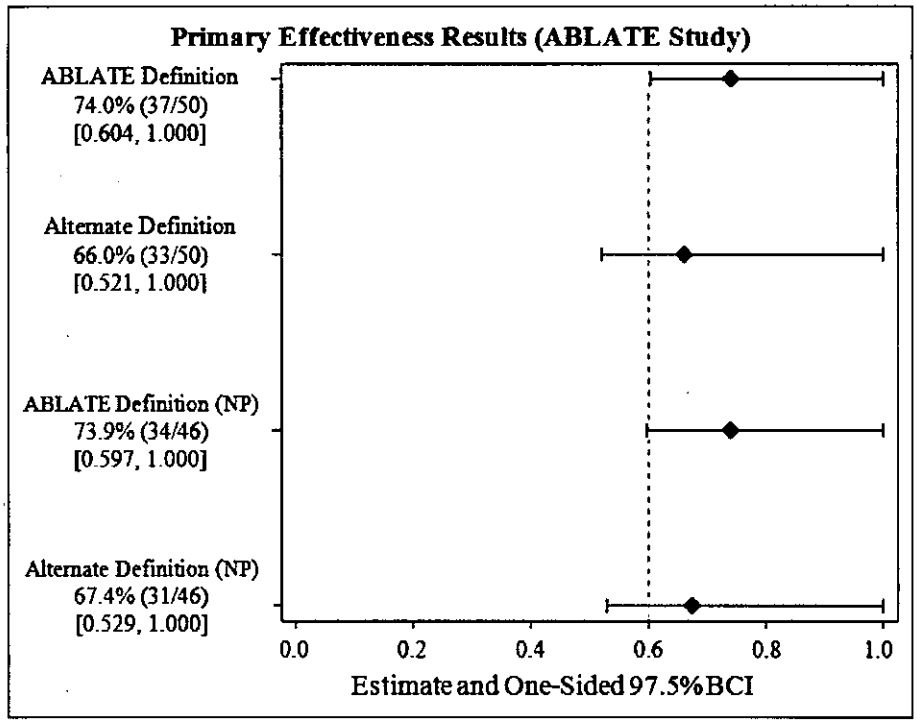

Figure 5: Effectiveness Results using ABLATE and Alternative Definitions for Treatment Success. Alternative definition for treatment success: no episode of AF, atrial flutter, or atrial tachycardia > 30 seconds, or any cardioversion after a 3 month blanking period. "NP" is "non-paroxysmal".

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

The Applicant conducted its ABLATE clinical study according to the pre-specified protocol. After enrollment in the ABALTE study was completed, the applicant initiated a registry study called ABLATE AF, which is very similar to the ABLATE study. In addition, the applicant obtained data from two institutional databases and their previously abandoned RESTORE IDE to support the PMA. Brief descriptions of each of these data sources and results are provided below.

A. ABLATE AF

Description

ABLATE AF is an ongoing clinical registry enrolling subjects with non-paroxysmal AF who are undergoing ablation with the test device along with a concomitant cardiac surgical procedure. The inclusion and exclusion criteria are identical to those in ABLATE, with the exception that the inclusion criteria specify non-paroxysmal AF rather than permanent AF. In addition, the protocol specifies that a 48-hour rather than 24-hour Holter recording be performed at both 6 and 12 months. As of October 26, 2011, there were 15 centers actively enrolling; 12 centers have enrolled subjects. The safety data have been monitored and adjudicated through 30-day follow-up for a subset of patients. A core lab assessed 6-month rhythm results and source documentation was used for assessment of AAD status.

Subject Accountability

As of August 31, 2011, 32 subjects have been enrolled in the ABLATE AF registry with 14 subjects enrolled at 3 centers monitored and adjudicated through 30 days. Twelve (12) of these 14 subjects have undergone follow-up for evaluation of the primary effectiveness endpoint at 6 months or later and have been monitored through 6 months. One was found to have paroxysmal AF through an independent AF classification assessment described above. The thirteen (13) non-paroxysmal subjects have been followed through 30 days. Eleven (11) have Holter recordings at 6 months. The table below summarizes the available data for the ABLATE AF registry at this time. Additional information on subject accounting can be found in the Applicant's executive summary. Note that results presented in this section focus on the non-paroxysmal subjects.

Results

The primary safety and effectiveness endpoints are the same as ABLATE, except that the 6-month and 12-month rhythms assessments are performed with a 48-hour Holter recording, rather than a 24-hour recording. No ABLATE AF subjects have reached the 12-month evaluation time point. The results are presented in the following tables.

Table 26: Primary Safety Results (ABLATE AF) for Non-Paroxysmal Subjects

	ABLATE N=51	**ABLATE AF N=13**	**ABLATE + ABLATE AF N=64**
Primary Safety Endpoint	**% (n/N)**	**% (n/N)**	**% (n/N)**
Composite MAE within 30 days	9.8% (5/51)	0% (0/13)	7.8% (5/64)
Death	3.9% (2/51)	0% (0/13)	3.1% (2/64)
<=30 days	3.9% (2/51)	0% (0/13)	3.1% (2/64)
>30 days, procedure related	0.0% (0/51)	0% (0/13)	0.0% (0/64)
Stroke/TIA	2.0% (1/51)	0% (0/13)	1.6% (1/64)
Stroke (with significant permanent disability)	2.0% (1/51)	0% (0/13)	1.6% (1/64)
TIA	0.0% (0/51)	0% (0/13)	0.0% (0/64)
MI	0.0% (0/51)	0% (0/13)	0.0% (0/64)
Excessive Bleeding (>2 units blood and surgical intervention)	3.9% (2/51)	0% (0/13)	3.1% (2/64)

Table 27: Primary Effectiveness Results (ABLATE AF) for Non-Paroxysmal Subjects

Primary Effectiveness Endpoint	ABLATE % (n/N) N=46	ABLATE AF % (n/N) N=11	ABLATE + ABLATE AF % (n/N) N=57
Primary Success at 6 months	73.9% (34/46)	81.8% (9/11)	75.4% (43/57)
Failure by AAD	8.7% (4/46)	9.1% (1/11)	8.8% (5/57)
Failure by Rhythm	17.4% (8/46)	9.1% (1/11)	15.8% (9/57)

Table 28: Secondary Safety Endpoints (ABLATE AF) for Non-Paroxysmal Subjects

Secondary Endpoints	ABLATE % (n/N) (N=51)	ABLATE AF [1] % (n/N) (N=13)	ABLATE AF [1] + ABLATE % (n/N) (N=64)
MAE through 6 months	11.8% (6/51)	7.7% (1/13)	10.9% (7/64)
Death	7.8% (4/51)	0.0% (0/13)	6.3% (4/64)
Stroke (with significant permanent disability)	2.0% (1/51)	7.7% (1/13)	3.1% (2/64)
TIA	0.0% (0/51)	0.0% (0/13)	0.0% (0/64)
MI	0.0% (0/51)	0.0% (0/13)	0.0% (0/64)
Excessive Bleeding (>2 units blood and surgical intervention)	3.9% (2/51)	0.0% (0/13)	3.1% (2/64)
Any Adverse Event through 6 months	94.1% (48/51)	84.6% (11/13)	92.2% (59/64)
Any Serious Event	76.5% (39/51)	69.2% (9/13)	75.0% (48/64)
Any Device Related Event	0.0% (0/51)	0.0% (0/13)	0.0% (0/64)
Any Procedure Related Event	15.7% (8/51)	0.0% (0/13)	12.5% (8/64)
Any Serious Device Related Event	0.0% (0/51)	0.0% (0/13)	0.0% (0/64)
Any Serious Procedure Related Event	13.7% (7/51)	0.0% (0/13)	10.9% (7/64)

[1] For ABLATE AF, events > 30 days post index procedure are included based on site reported classification if not yet adjudicated.

Table 29: Secondary Effectiveness Endpoints (ABLATE AF) for Non-Paroxysmal Subjects

	ABLATE N=46	ABLATE AF N=11	ABLATE + ABLATE AF N=57
Secondary Effectiveness Endpoint	**% (n/N)**	**% (n/N)**	
Free of AF, Regardless of AADs15	82.6% (38/46)	90.9% (10/11)	84.2% (48/57)
AF Burden			
= 0 min	82.6% (38/46)	90.9% (10/11)	84.2% (48/57)
<= 5 min	0% (0/46)	0.0% (0/11)	0.0% (0/57)
> 5 min - 1 hr	2.2% (1/46)	0.0% (0/11)	1.8% (1/57)
> 1 hr	15.2% (7/46)	9.1% (1/11)	14.0% (8/57)

B. Additional Data Sources

RESTORE

RESTORE, conducted under IDE G020237, was a multi-center, prospective, non-randomized study with case-matched controls to assess the safety and effectiveness of the AtriCure Bipolar System in the treatment of subjects with continuous atrial fibrillation. The ablation system components were identical except for the clamps, which were determined to be substantially equivalent for indications of "ablation of cardiac tissue" by K101174.

The RESTORE and ABLATE endpoints were quite similar, with 30-day primary safety and 6-month primary effectiveness endpoints. However there were differences in the eligibility criteria, the specific definition of the composite primary safety endpoint, and that rhythm status was primarily measured with ECG. The problem that led to RESTORE's abandonment was the use of a matched, concurrent, control cohort to determine device safety. Enrollment was targeted at 113 subjects per group, but by the time of RESTORE's termination 39 subjects had been treated with the device, and only 5 had been enrolled in the control arm. Of these 39 subjects, 3 were determined to have paroxysmal AF. Primary safety data are available for the 36 non-paroxysmal AF subjects; primary effectiveness data at 6 months are available for 28 non-paroxysmal AF subjects.

Although not part of the original RESTORE protocol, as part of the effort to obtain supportive data for their PMA, the Applicant retrospectively obtained 12-month (or later) rhythm status data for 24 of the 36 non-paroxysmal AF subjects.

Institutional Databases

In addition to the Applicant's own IDE studies, the Applicant queried databases at the Heart Hospital of Plano (Baylor-Plano) and Washington University (Wash U). Baylor-Plano maintains a database of subjects that receive a cardiac surgical

15 Using the definition of the 2006 Guidelines: "AF free" = no episodes > 5 minutes

procedure. Wash U maintains a database that tracks all patients undergoing the Maze procedure and utilizes the STS database system with extended variables. Wash U also maintains a follow-up database that tracks AF status with Holter monitoring or pacemaker interrogation performed at 6 month intervals.

The Baylor-Plano database was queried to extract data from patients operated upon between February 2007 and September 2008. The Wash U database was queried to extract data from January 2002 through April 30, 2010. For each data source, consecutive eligible patients have been included in the analysis. Both the Isolator and Synergy Ablation Clamps were represented. The following criteria were used to query the databases:

- Patients with non-paroxysmal AF undergoing Maze IV
- AF procedure using AtriCure Bipolar System
- Concomitant cardiac surgical procedure

The queries yielded 8 subjects from the Baylor-Plano database and 56 subjects from the Wash U database.

Results from Additional Data Sources

In order to take advantage of all of the data sources presented by the Applicant, composite tables of each source's results are presented below. The data are not pooled, as poolability is not justified due to differences in subject population, differences in endpoint definitions, and heterogeneity of actual follow up times. Rather, the data are juxtaposed to provide a comparison. These tables report results for non-paroxysmal subjects only. The table below summarizes the data available from all data sources.

Table 30: Number of Non-Paroxysmal Subjects in All Data Sources

Source	Primary Safety Endpoint Data	6 Month Efficacy Data	≥ 12 month Efficacy Data
ABLATE	51	46	45
ABLATE AF	13	11	0
RESTORE	36	28	24
Baylor-Plano	8	2	3
Wash U	56	47	46
TOTAL	164	134	118

Primary Safety Endpoint

The primary safety endpoint for all five data sources is a composite of:

- Death within 30 days, or beyond 30 days if procedure-related,
- Stroke or TIA with permanent residual disability,
- Bleeding more than 2 units PRBC with re-operation, and

- Myocardial infarction

Table 31: Primary Safety Endpoint for All Data Sources (Non-Paroxysmal Subjects)

	ABLATE	ABLATE AF	RESTORE	Wash U	Baylor-Plano
Primary safety	9.8% (5/51)	0% (0/13)	8.3% (3/36)	14.3% (8/56)	25.0% (2/8)
Death	3.9% (2/51)	0% (0/13)	5.6% (2/36)	3.6% (2/56)	12.5% (1/8)
Bleeding	3.9% (2/51)	0% (0/13)	8.3% (3/36)	8.9% (5/56)	24.0% (2/8)
Stroke/TIA	2.0% (1/51)	0% (0/13)	0.0% (0/36)	1.8% (1/56)	0% (0/11)
MI	0% (0/51)	0% (0/13)	0.0% (0/36)	0% (0/56)	0% (0/11)

Primary Effectiveness Endpoint

The primary effectiveness endpoint for all studies is freedom from AF, off AADs, at 6-months.

Table 32: Primary Effectiveness Endpoint for All Data Sources (Non-Paroxysmal Subjects)

	ABLATE	ABLATE AF	RESTORE	Baylor-Plano	Wash U
AF Free, off AADs at 6 months	73.9% (34/46)	81.8% (9/11)	64.3% (18/28)	0% (0/2)	74.5% (35/47)

Secondary Endpoints

FDA requested uniformity for the several secondary endpoints:

- Freedom from AF at 6-months regardless of AADs,
- Freedom from AF at 12-months (or greater), off AADs, and
- Freedom from AF at 12-months (or greater), regardless of AADs.

Because some of these data were gathered retrospectively, after interactions between FDA and the Applicant, the 12-month-or-greater information was gathered at a median of 658 days for ABLATE and 439 days for RESTORE. (The 12-month data for Wash U was gathered at 12 months, as this was a prospective protocol at that institution.)

Table 33: Secondary Effectiveness Endpoints for all Data Sources (Non-Paroxysmal Subjects)

	ABLATE	ABLATE AF	RESTORE	Baylor Plano	Wash U
AF Free at 6 months	82.6% (38/46)	90.9% (10/11)	81.8% (27/33)	50.0% (1/2)	91.5% (43/47)
AF Free, off AADs at >= 12 months	62.2% (28/45)	--	45.8% (11/24)	0% (0/3)	84.8% (39/46)
AF Free at >=12 months	73.3% (33/45)	--	66.7% (16/24)	0% (0/3)	91.3% (42/46)

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on October 26, 2011, the Circulatory System Devices Panel, three questions were put to a vote. The outcome of the votes was as follows:

Question 1

The Panel voted 5* *yes* to 4 *no* to 1 *abstention* that the data does show that there is reasonable assurance that the AtriCure Synergy Ablation System is safe for use in patients who meet the criteria specified in the proposed indication.

*The vote was 4 *yes* to 4 *no* to 1 *abstention*; the chair broke the tie by voting *yes*.

Question 2

The Panel voted 9 *yes* to 0 *no* that there is reasonable assurance that the AtriCure Synergy Ablation System is effective for use in patients who meet the criteria specified in the proposed indication.

Question 3

The Panel voted 5 *yes* to 3 *no* to 1 *abstention* that the benefits of the AtriCure Synergy Ablation System do outweigh the risks of the AtriCure Synergy Ablation System for use in the indicated patient population.

The Panel further recommended refinements to the labeling, and that a refined Post Approval Study be submitted, as follows:

(1) Inclusion of patients with persistent and longstanding persistent AF in the indication statement in the Instructions for Use (IFU), but disclosure of results for all subjects including those with paroxysmal AF in product labeling,
(2) Addition of a warning statement regarding use of the device in the re-operative setting,
(3) Addition of a warning statement indicating that the lesion set can not be completed with the AtriCure Synergy Ablation System alone,
(4) Presentation of statistical data in a more understandable and/or familiar manner,
(5) Additional refinements to the patient label, especially in interpretation of effectiveness results, and
(6) Refinements to the Post-Approval Study protocol to
    i. Specifically include collection of data regarding survival, baseline characteristics, and subsequent therapies invoked for treatment of atrial fibrillation (e.g. repeat ablations, cardioversions, etc.) in the follow-up period,
    ii. Incorporate an imputation strategy for handling missing data,
    iii. Include use of a Clinical Events Committee to adjudicate attribution of serious adverse events, and

iv. Include collection of data on MAEs as defined in the ABLATE study, but also device- and ablation procedure-related adverse events and data on pacemaker implantation

B. FDA's Post-Panel Action

FDA worked interactively with the applicant to refine the labeling and Post-Approval Study protocols to meet all of the recommendations of the Panel and the FDA.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The ABLATE clinical study demonstrated a rate of MAEs at 30-days of 9.1% in the Treated population and 9.8% in the Non-Paroxysmal subpopulation with one-sided 95% Bayesian credible intervals of [0, 17.9%], and [0, 19.2%] respectively. The posterior probability that the MAE rate at 30 days was less than 18.95% was 0.967 for the all treated population and 0.946 for the non-paroxysmal population. The success criterion for the posterior probability was 0.95. Thus, the primary safety endpoint was met for the Treated population, but not for the Non-Paroxysmal subpopulation. Both the primary and secondary safety endpoints demonstrated that the majority of all adverse events were attributed to the concomitant surgical procedure.

Results from additional data sources were consistent with those observed in the ABLATE pivotal study.

The rate of serious device- and ablation procedure-related adverse events in the ABLATE study was 14.5% in the Treated population. The pacemaker implantation rate was 25% at 30 days and 33% at 12 months. During the advisory panel meeting, the panel expressed concern over these issues, as reflected in the vote on safety, which was 5-4-1 in favor.

In summary, FDA finds that the data presented to support this PMA provide a reasonable assurance that the AtriCure Synergy Ablation System is safe for use in patients who meet the criteria specified in the Indications for Use. The occurrence of device- and ablation procedure-related adverse events and pacemaker implantation will be followed closely in the larger, more generalized Post-Approval Study.

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above

B. Effectiveness Conclusions

The ABLATE study demonstrated a rate of freedom from AF, off AADs at 6 months of 74.0% in the Treated population and 73.9% in the Non-Paroxysmal subpopulation, with one-sided 97.5% Bayesian credible intervals of [60.4%, 100%] and [59.7%, 100%], respectively. The posterior probability that the primary effectiveness rate at 6 months

days was greater than 60% was 0.978 for the Treated population and 0.972 for the Non-Paroxysmal population. The success criterion for the posterior probability was 0.975. Thus, the primary effectiveness endpoint was met for the Treated population, but not for the Non-Paroxysmal population.

The secondary effectiveness endpoints demonstrated a rate of freedom from AF, regardless of AADs at 6 months about 10% higher than the primary endpoint, and an approximate decline in effectiveness of about 10% at longer-term follow up of greater than 1 year. When defining freedom from AF (off AADs) per current definitions, rates are 66% and 67.4% at 6-months for the Treated and Non-Paroxysmal populations, respectively.

Results from the additional data sources are consistent with those found for the ABLATE study.

FDA and the Advisory Panel find that the data presented to support this PMA provide a reasonable assurance that the AtriCure Synergy Ablation System is effective for use in patients who meet the criteria specified in the Indications for Use.

C. **Overall Conclusions**

The primary safety and effectiveness results demonstrated in the clinical study were close to the performance goals for the Treated population as well as the Non-Paroxysmal subpopulation. The clinical acceptability of the observed performance was discussed during the panel meeting. Although some safety concerns were raised, FDA and the Panel believe that the benefits of the AtriCure Synergy Ablation System for use in patients who meet the criteria specified in the proposed indication outweigh the risks. The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIV. CDRH DECISION

CDRH issued an approval order on December 15, 2011. The final conditions of approval cited in the approval order are described below.

The applicant must conduct a post-approval study to evaluate clinical outcomes through 36 months postoperatively in a newly enrolled cohort of patients treated during commercial use of the AtriCure Synergy System by physicians performing the Maze IV procedure.

The primary objectives of this study are to evaluate the proportion of patients: (1) with any serious ablation device- or procedure-related adverse events within 30 days post-procedure or hospital discharge (whichever is later) as adjudicated by a Clinical Events Committee, and (2) free from AF (i.e. no episodes lasting > 30 continuous seconds duration of either Atrial Fibrillation, Atrial Flutter or Atrial Tachycardia) while off Class I and III antiarrhythmic drugs for at least 4 weeks

(except amiodarone which must be 12 weeks prior to assessment), as determined by an independent core lab assessment of 48 hour Holter recording performed at a minimum annually through 36 months postoperatively.

An initial total sample size of 350 subjects is required to demonstrate that: (1) the 30 day serious ablation device- or procedure-related AE proportion is < 10% (the performance goal) with 80% power and 5% censoring through 30 days and (2) freedom from AF is > 47.8% at 3 years with at least 80% power when assuming background proportion of 57.8% and 21.5% censoring through 3 years.

Should a national registry be developed, which tracks RF energy lesions for non-paroxysmal forms of atrial fibrillation treatment during concomitant on-pump cardiac surgery, consideration should be given towards nesting data elements for this study (i.e. pre-procedure, peri-procedure, post-procedure, discharge, and 30-day follow-up) within the national registry.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1. Caulkins et al., 2007 Europace, 9, 335-379.

2. Fuster et al., 2006, Circulation, 114, e257-e354