AtriCure Synergy Ablation System

Panel Pack Executive Summary

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EXECUTIVE SUMMARY

1. OVERVIEW

The subject of this PMA is the AtriCure Synergy Ablation System. The product consists of a Synergy Ablation Clamp, the Ablation and Sensing Unit (ASU), and the Isolator Switch Matrix (ASB) as described in Chapter 3 of this Panel Pack. The product is currently marketed under K063630. The system was originally cleared in 2001 with the following indication:

> "The AtriCure Ablation System is intended to ablate soft tissues during general surgery using radiofrequency energy."

This indication statement was updated in 2007 to reflect the use of the system as a tool for ablating cardiac tissue to make lesions in the heart during a cardiac surgery procedure. The current indication for the product is:

> "The AtriCure Synergy Ablation System is intended for the ablation of cardiac tissue during surgery. "

In practice, the device is used as a tool in the Maze IV surgical procedure to create cardiac lesions. The Maze IV procedure is a widely accepted treatment option for patients that are undergoing a primary surgical procedure to correct structural or coronary heart disease and also have atrial fibrillation. The goal of the procedure is to achieve rhythm control.

Since the labeling does not identify the clinical indication of atrial fibrillation (AF), the Sponsor, AtriCure Inc., is prohibited from training physicians on the specific use of the device to treat AF or discuss AF in any manner. This type of clearance is referred to as a "tools claim." It is the goal of this PMA application to provide the necessary safety and efficacy data to support refinement of this labeling to reflect the actual use of the device; surgical ablation of AF in a concomitant open heart surgical setting as highlighted below.

> "The AtriCure Synergy Ablation System is intended to ablate cardiac tissue for the treatment of persistent or longstanding persistent atrial fibrillation in patients who are undergoing open concomitant coronary artery bypass grafting and/or valve replacement or repair."

This revised labeling will enable the Sponsor to freely discuss atrial fibrillation with physicians and conduct training on the use of the system in the treatment of AF. Education and training will focus on instructing:

- cardiac surgeons on the use of the products and the Maze IV procedure,

- electrophysiologists and other referring physicians on the risks of AF, the benefits of treating the AF in an open heart concomitant surgical setting, and on methods for patient management post treatment and
- patients that are undergoing a primary cardiac surgical procedure who also have AF regarding the risks and benefits of treating their AF with the Maze IV procedure

AtriCure has been faced with some difficulty in developing the data to refine the labeling. Attempts were originally made to conduct a randomized clinical trial enrolling subjects who have AF and are in need of a primary surgical procedure for either a valve operation or CABG to receive either the primary surgery with a Maze IV add-on or the primary surgery alone. This would be the most definitive design; however, surgeons had already accepted the Maze IV procedure for their patients and felt it unethical to participate in a randomized trial in which the patients underwent a surgical procedure with no attempt to treat the atrial fibrillation. Therefore, AtriCure reverted to an alternative design (the RESTORE SR trial) for safety comparison that utilized case matched controls in subjects meeting the same inclusion/exclusion criteria, except that they would be free of atrial fibrillation at the time of surgery. Case matched subjects were to have surgery within 3 months of treatment group subjects and be matched on gender, age (±5 years), baseline EF (±10%), and the exact primary surgical procedure. Efficacy was to be evaluated in the treatment group relative to a reference rate of . Unfortunately, the sites were unable to identify subjects without AF undergoing the same primary surgical procedure that matched based on each of the pre-specified criteria. This study was therefore abandoned and AtriCure worked closely with FDA to identify an alternative design. A presentation of the RESTORE SR study is provided in **Appendix A** of this Panel Pack for completeness.

At the time the RESTORE SR study was concluded, there were a number of literature references available on the Maze IV procedure and many of these references cited the use of the AtriCure system. However, there was considerable variability in the results and patient populations, as well as the methods used to assess efficacy. AtriCure and FDA recognized the limitations of the literature but also recognized that the product and procedure were standard of care, making clinical trials difficult to design and execute. The FDA suggested at the time that AtriCure consider a Bayesian adaptive design approach to optimize sample size and provide the needed data to support the label change. AtriCure then worked with their consulting statisticians and physicians to design the ABLATE clinical trial which is the main study of this PMA.

The study was launched in 2006 and utilized inclusion and success criteria that were accepted at that time. The ABLATE study enrolled subjects with “permanent” AF as

highlighted in the accepted guidelines at that time (ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation). In accordance with the pre-specified Bayesian adaptive design plan, enrollment in the trial stopped at 55 subjects due to the positive safety and efficacy results shown up to this point. The results of ABLATE demonstrated that 74% of subjects were AF Free and off AADs at six months (the time point that was deemed appropriate to assess efficacy in 2006). The study also demonstrated a composite safety rate of 9.1%. This rate included a composite of Death, Stroke, MI, TIA and Reoperation for bleeding within 30 days of the index procedure or hospital discharge, whichever occurred later. A complete summary of the ABLATE study is provided in Chapter 5 of this Panel Pack. The ABLATE study achieved the pre-specified goals for both safety and efficacy endpoints.

During pre-PMA meetings with FDA, several limitations of the ABLATE trial were discussed, including adherence to the medical community's more recent redefining of AF classification, changes to the recommended efficacy evaluation endpoint, and the small sample size.

Since the time of the ABLATE study design, terminology on AF classification as well as the time point for evaluation of procedure success and the definition of AF Free were all modified. To ensure that the refinement to the label is reflecting the most current medical thinking, AtriCure agreed to the suggestion by FDA to collect long term (beyond one year) AF rhythm status on ABLATE subjects, using a 48 hour Holter monitor assessment. Long term efficacy assessments (median of 21.6 months) were able to be obtained in all 48 ABLATE subjects who had not exited the trial by 12 months, with 83% of the assessments conducted via 48 hour Holter or pacemaker interrogation.

Further, the term permanent is currently obsolete and refers only to subjects who are no longer candidates for any form of treatment. Therefore, it was necessary for the AF classification of the subjects enrolled in ABLATE to be translated into current terminology; either paroxysmal, persistent or longstanding persistent AF. This reclassification effort was performed by two independent physicians who were instrumental in the development of the classification system and were masked to the subject outcome. The physicians reviewed all available source documentation leading up to the index procedure to ascertain the most appropriate AF classification of each enrolled subject. The interactions with FDA have resulted in an agreement that the target indication will include only patients with a non-paroxysmal form of AF – either persistent or long standing persistent AF. Therefore, an analysis is provided in this panel pack that summarizes results for subjects with non-paroxysmal AF. For ease of review, this document will refer to the target population as "non-paroxysmal," however the indication statement will be specific to highlight that non-paroxysmal refers to either

persistent or longstanding persistent forms of AF. A summary of this analysis is provided in Chapter 6, Proposed Indication Population Analysis.

AtriCure also offered to embark on a clinical registry, based on the principle components of the ABLATE trial, to augment the sample size. This registry, entitled ABLATE AF, was launched in 2010 while the PMA review cycle was under way. ABLATE AF is enrolling non-paroxysmal subjects and is assessing success with 48 hour Holter monitoring at both six months and one-year post index procedure. The non-paroxysmal ABLATE AF subjects are included along with the non-paroxysmal ABLATE patients in the presentation in Chapter 6, Proposed Indication Population Analysis. The outcomes in non-paroxysmal subjects from the ABLATE series (ABLATE and ABLATE AF) are the basis for the proposed labeling.

Also at the request of FDA, AtriCure undertook a further effort to identify and present additional valid sources of data to confirm the outcomes from the ABLATE trial. Presented in **Appendix L** is a supplemental sensitivity analysis which incorporates data from the

A Bayesian hierarchical model, analogous to a random-effects meta-analysis, was utilized in an effort to corroborate the ABLATE series results and to further refine the estimates for study endpoints in the intended non-paroxysmal population

An overall risk to benefit analysis is presented in Chapter 7. This highlights the outcomes in terms of the literature available for this procedure, now established as the standard of care and recommended by the medical societies. The totality of the data provided herein is believed to be sufficient to support the label revision to enable appropriate training. A summary of the proposed post approval study, provided in Chapter 8 of this Panel Pack,

.

2. INTRODUCTION

2.1. Clinical Problem

Atrial fibrillation (AF) is the most common sustained tachyarrhythmia seen in clinical practice. The Heart Rhythm Society (HRS) defines atrial fibrillation as a supraventricular arrhythmia that is characterized by chaotic and uncoordinated contraction of the atria. It is understood by electrophysiologists that AF consists of 1) a "trigger" and 2) an anatomic substrate that is capable of both initiation and perpetuation of AF. [Miyasaka 2006] AF affects more than five million Americans today and is anticipated to have a prevalence of approximately twelve to sixteen million by the year 2050. [Miyasaka 2006] AF is more prevalent in men and the elderly. The condition affects fewer than 1-2% of people under age 60, with nearly 4-6% of people 60 years and older, and 9% of people 80 years and older having been diagnosed with AF. [Go 2001; Feinberg 1995] It has been predicted that about one in every four adults over the age of 40 years of age will have a risk of developing AF in their lifetime [Lloyd- Jones 2004; Miyasaka 2006; Fuster 2006]. In the United States alone, it is estimated that AF accounts for 1.4 million outpatient visits and over 227,000 hospitalizations per year. [Fuster 2006]

Because AF causes ineffective atrial contractions, areas of blood stasis occur in the atria (particularly in the appendages) and the stasis predisposes clot formation that can lead to thromboembolic events such as transient ischemic attacks and strokes. The presence of AF has been linked to a five-fold increase in the risk of stroke in all Americans. The underlying diagnosis of AF is a major cause of stroke, with greater than 20% of strokes in elderly being attributed to the disease. [Fuster 2006; Dulli 2003]

The increased stroke risk is coupled with the, sometimes severe, life style limitations that can coincide with the presence of AF. Patients who are symptomatic suffer from fatigue, dizziness and shortness of breath. AF has been shown to correlate with a reduction in all of the subscales of the SF-36, a validated quality of life tool, suggesting a deleterious impact of this arrhythmia. [Ware 1992; Dorian 2000]

There is also a link between AF and heart failure. Atrial fibrillation can contribute to dilatation of the ventricles and result in a diminution in ventricular function. In 85-95% of cases, the AF is associated with the presence of some form of heart disease, left atrial enlargement, or abnormal atrial electrophysiology. Hypertension is one of the major risk factors for atrial fibrillation by contributing to several of these mechanisms. Again with increasing age, the combination of hypertension and AF is more prevalent; as much as 10% of the hypertensive population may have atrial fibrillation. [Morillas 2010] The presence of heart failure with AF results in an exacerbation of the symptoms of each of these ailments.

Patients with underlying coronary or valvular heart disease represent the target population for the proposed product indication. In this group of patients who are undergoing cardiac surgery, the prevalence of atrial fibrillation is even higher. A retrospective analysis of 587,479 patients undergoing bypass and/or valve surgery revealed that 11.47% of these patients had underlying AF with only 38% of them receiving any surgical treatment to attempt to correct this rhythm disturbance. [Gammie 2009]

2.2. Classification of AF

Atrial fibrillation is recognized as a progressive disease that often begins as an intermittent rhythm disturbance that can initiate and terminate spontaneously. Many patients progress to a continuous form over time; with many requiring electrical or pharmacological cardioversion to revert to sinus rhythm. The more cumulative time a patient is in atrial fibrillation, the more structural and electrical remodeling that occurs in the atria. This remodeling makes it more difficult to restore and maintain sinus rhythm. In an effort to better characterize a patient's AF status, medical societies have developed classification terminology based upon the extent of the rhythm disorder.

The terminology utilized by the medical community to classify AF has evolved over time and unfortunately there is subjectivity that is introduced when utilizing this terminology. The ABLATE study was initiated just at the time when the ACC, AHA, and other professional societies had convened a writing group to develop a consensus document to classify atrial fibrillation. This consensus document was published in 2006 and describes the patient population as follows:

> "The clinician should distinguish a first-detected episode of AF, whether or not it is symptomatic or self-limited, recognizing that there may be uncertainty about the duration of the episode and about previous undetected episodes. When a patient has had 2 or more episodes, AF is considered recurrent. If the arrhythmia terminates spontaneously, recurrent AF is designated paroxysmal; when sustained beyond 7 d, AF is designated persistent. Termination with pharmacological therapy or direct-current cardioversion does not change the designation. First-detected AF may be either paroxysmal or persistent AF. The category of persistent AF also includes cases of long-standing AF (e.g., greater than 1 y), usually leading to permanent AF, in which cardioversion has failed or has not been attempted.
>
> These categories are not mutually exclusive in a particular patient, who may have several episodes of paroxysmal AF and occasional persistent AF,

> or the reverse. Regarding paroxysmal and persistent AF, it is practical to categorize a given patient by the most frequent presentation. The definition of permanent AF is often arbitrary. The duration of AF refers both to individual episodes and to how long the patient has been affected by the arrhythmia. Thus, a patient with paroxysmal AF may have episodes that last seconds to hours occurring repeatedly for years." [Fuster 2006]

The 2006 guidelines resulted in the following general definitions to classify AF:

> ***Paroxysmal:*** AF is self-terminating within 7 days of recognized onset.
> ***Persistent:*** AF is not self-terminating within 7 days, or is terminated electrically or pharmacologically
> ***Permanent:*** AF in which cardioversion (electrical and/or pharmacologic) has failed or has not been attempted. [Fuster 2006]

Accordingly, the ABLATE study utilized these definitions and the inclusion criteria reflected inclusion of subjects with Permanent AF as defined above.

As with any area of medicine, definitions oftentimes undergo further refinement after they have been in use for a period of time. This has been the case for atrial fibrillation. While the ABLATE PROTOCOL was finalized and patient enrollment was initiated, the Heart Rhythm Society together with the European Heart Rhythm Association (EHRA) and the European Cardiac Arrhythmia Society (ECAS) developed a consensus document that was aimed primarily at discussing the optimal treatment strategy for AF, particularly in light of the expanded utilization of catheter-based technology [Calkins 2007]. This 2007 document also provided refined terminology for describing AF.

In this 2007 document, the AF definitions above were slightly refined to the following:

> ***Paroxysmal:*** recurrent AF (>2 episodes) that terminates spontaneously within seven days
> ***Persistent:*** AF which is sustained beyond seven days, or lasting less than seven days but necessitating pharmacologic or electrical cardioversion
> ***Longstanding Persistent:*** continuous AF of greater than one-year duration
> ***Permanent:*** patients where a decision has been made not to pursue restoration of sinus rhythm by any means. [Calkins 2007]

Although very similar to the definitions proposed by the 2006 ACC/AHA/ESC guidelines, the 2007 HRS/EHRA/ECAS expert consensus statement provide additional clarification on the classification of AF type. The most important adjustment to the terminology is with respect to the term "Permanent". Whereas the guidelines that had been in place in the 2006 guideline referred to Permanent AF as being reflective of any patient that had failed a treatment or were not considered to be viable candidates for any treatment, the

2007 HRS/EHRA/ECAS expert consensus statement modified the definition of Permanent AF to include only those individuals in which an attempt at restoration of sinus rhythm had been abandoned, thus no treatment option was felt to be an option.

It is useful to consider this terminology in the context of the ABLATE clinical study, which is the primary study of this PMA Application. The intent of ABLATE was to enroll patients that had either failed a cardioversion or in whom a cardioversion had not been attempted, presumably because of associated comorbidities. The specific history and duration of AF are not directly delineated in the consideration of identifying a patient as Permanent, and it is considered to be an "arbitrary" assignment of clinical status of the patient as highlighted in the 2006 guidance.

> "The definition of permanent AF is often arbitrary. The duration of AF refers both to individual episodes and to how long the patient has been affected by the arrhythmia. Thus, a patient with paroxysmal AF may have episodes that last seconds to hours occurring repeatedly for years." [Fuster 2006]

Based on this definition, it was possible for a patient that was either Paroxysmal or Persistent to additionally be considered Permanent. Influences on the decision to classify a patient as Permanent included the cumulative duration of AF at time of assessment, together with factors such as their LA dimension and age which are known predictors for successful outcomes in the treatment of AF. [Cox 2010; Damiano 20003; Gaynor 2005] The term permanent was frequently used by medical professionals and was pervasive in the literature when describing patients, especially those in the concomitant surgical arena. The implementation of the 2007 HRS/EHRA/ECAS expert consensus statement with refined definitions has led to the term Permanent becoming less prevalent and instead being replaced with terms that delineate a patient based solely on their AF duration without a link to their treatment potential to have a treatment.

These improved definitions for AF classification have important implications when considering the most appropriate labeling for the AtriCure Synergy Ablation System. As stated earlier, the ABLATE clinical study was designed and initiated prior to the implementation of the current consensus statement and utilized the term Permanent as the primary eligibility criteria. The study was intended to enroll patients that were undergoing a primary surgical procedure for their underlying coronary or valvular heart disease and who also had a history of AF that was not amenable to other non-surgical treatment options. Since the institution of the refined definitions however, the term permanent has fallen out of favor and it is therefore appropriate to adjust the product labeling to be reflective of current terminology as used in medical practice. All subjects enrolled in ABLATE met the criteria for Permanent AF based on the 2006

ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation. All subjects' baseline factors have been reviewed by an independent set of physicians who are experts in the field of AF, and each subject was mapped to the appropriate AF classification based on the current 2007 HRS/EHRA/ECAS expert consensus statement. The vast majority of subjects fell into the category of either persistent AF or longstanding persistent AF and therefore the proposed labeling for the product has been adjusted to include these classes of non-paroxysmal patients.

2.3. Treatment of AF

The awareness of the clinical issues associated with atrial fibrillation has increased over the past several years and there is increased focus on the diagnosis and treatment of this disease. In fact, the United States Senate unanimously passed a resolution on July 29, 2011 (Senate resolution S. Res, 243) directed at atrial fibrillation. The Resolution called for "Promoting increased awareness, diagnosis, and treatment of atrial fibrillation to address the high morbidity and mortality rates and to prevent avoidable hospitalizations associated with the disease". The Senate indicated that the Secretary of the U.S. Department of Health and Human Services should work with leaders in the medical community to explore ways to improve medical research, screening and prevention methods, and surveillance efforts in order to prevent and appropriately manage atrial fibrillation, including "improving access to appropriate medical care for patients suffering from atrial fibrillation by encouraging education programs that promote collaboration among the Federal health agencies and that increase public and clinician awareness of atrial fibrillation, including risk assessment, screening, treatment, and appropriate clinical management." The proposed updated labeling requested in this application will enable AtriCure to address this recognized public health problem.

The current treatment options for patients with atrial fibrillation consist of antiarrhythmic medications, catheter ablation or surgical ablation. A brief overview of each treatment is provided below.

2.3.1. Pharmacologic Therapies

Although pharmacologic treatment is always considered the first line of therapy for an AF patient, the side effects of these drugs are not benign. The medications include both rate control agents such as digoxin, diltiazem, verapamil and metoprolol as well as rhythm control medications including sotalol, flecanide, amiodarone and propafenone. [Musco 2008; Conway 2009; Camm 2006; Fuster 2006] Unfortunately, all of these drugs have been shown to have significant toxic effects and many practitioners are less prone to offer them to an elderly patient who may have other comorbidities or the potential for drug-drug interactions that make them poorer candidates for therapy. [Camm 2006] In addition, the effectiveness of these medications is suboptimal.

Success rates for antiarrhythmic drug treatments for AF often range from 9 to 23% after one year of treatment for patients with paroxysmal or persistent AF. [Wilber 2010] In most drug trials AF recurrence rate approaches 50% within 6 to 12 months. [Wilber 2010] Since the results are not favorable, many of these patients who have an extended chronicity of AF are not considered for medical therapy with its attendant risks. This is the situation for the target population of this PMA. Patients who have underlying coronary or valvular heart disease necessitating a complex open cardiac surgery operation have significant comorbid conditions. These factors have often led physicians to classify these patients as not appropriate for pharmacological conversion therapy to address their AF.

Anticoagulants such as warfarin are a cornerstone of therapy for patients with atrial fibrillation as a means to reduce the frequency of thromboembolic events such as stroke, but do not address the underlying AF. [Lewis 2009] Anticoagulation therapy is frequently underutilized in these patients, particularly by primary care physicians. [Loo 2009; Mostaza 2009; Mazzaglia 2010; Nieuwlaat 2008] Further, anticoagulant therapy is also associated with significant bleeding risks, although these have been reduced with improvements in monitoring strategies. [Tomek 2010] Newer anticoagulant agents such as direct thrombin and factor Xa inhibitors also show promising initial results, but even with these drugs the underlying AF with its debilitating symptoms is not addressed and do not include patients with valvular heart disease. [Granger 2011; Connolly 2009]

2.3.2. Catheter Ablation

Catheter ablation is aimed at correcting the AF through thermal destruction of myocardial cells that initiate or can perpetuate atrial fibrillation. Recent advances in technology and reduction in complications has resulted in an increased use of catheter ablation as primary or secondary therapy for atrial fibrillation. This is particularly true for patients with paroxysmal atrial fibrillation. There appears to be a consensus that this therapy is associated with better outcomes than medical therapy in appropriately selected patients, such as paroxysmal AF (PAF). [Wilber 2010; Packer 2010-1; Packer 2010-2] It is not without complications, however, and therefore is reserved for those patients that can receive the most benefit with the lowest attendant risks. [Siegel 2010; Voroshilovsky 2010; Weachter 2010; Zellerhoff 2010] Even in this population, it may be necessary to perform the procedure multiple times to achieve the best outcome. [Calkins 2009]

Catheter ablation in subjects with non-paroxysmal forms of AF however, has not had the anticipated level of efficacy and is still considered an evolving treatment. [Calkins 2009; Cappato 2010; Spragg 2008] Rates of success have been highly variable ranging from 25% to 70% and the results are significantly dependent upon predictive factors such as chronicity of AF, cycle length and left atrial size. [Balk 2010] Those subjects with an

extended history of AF or left atrial size greater than 5 cm have experienced a low rate of success at most centers with catheter ablation, even after multiple attempts.

2.3.3. Surgical Ablation

The Cox-Maze procedure was the fundamental surgical procedure that was developed by Dr. James Cox in the late 1980's to treat AF (**Figure 1**). The procedure was aimed at obliterating electrical reentry pathways by creating a series of surgical incisions. This procedure had reported efficacy rates in the 80-95% range but was associated with technical challenges for many surgeons and required extensive time to complete with extended time on bypass.[Kosakai 1994; Damiano 2003; Stulak 2007] This resulted in the procedure only being performed effectively by a limited number of surgeons at select centers..

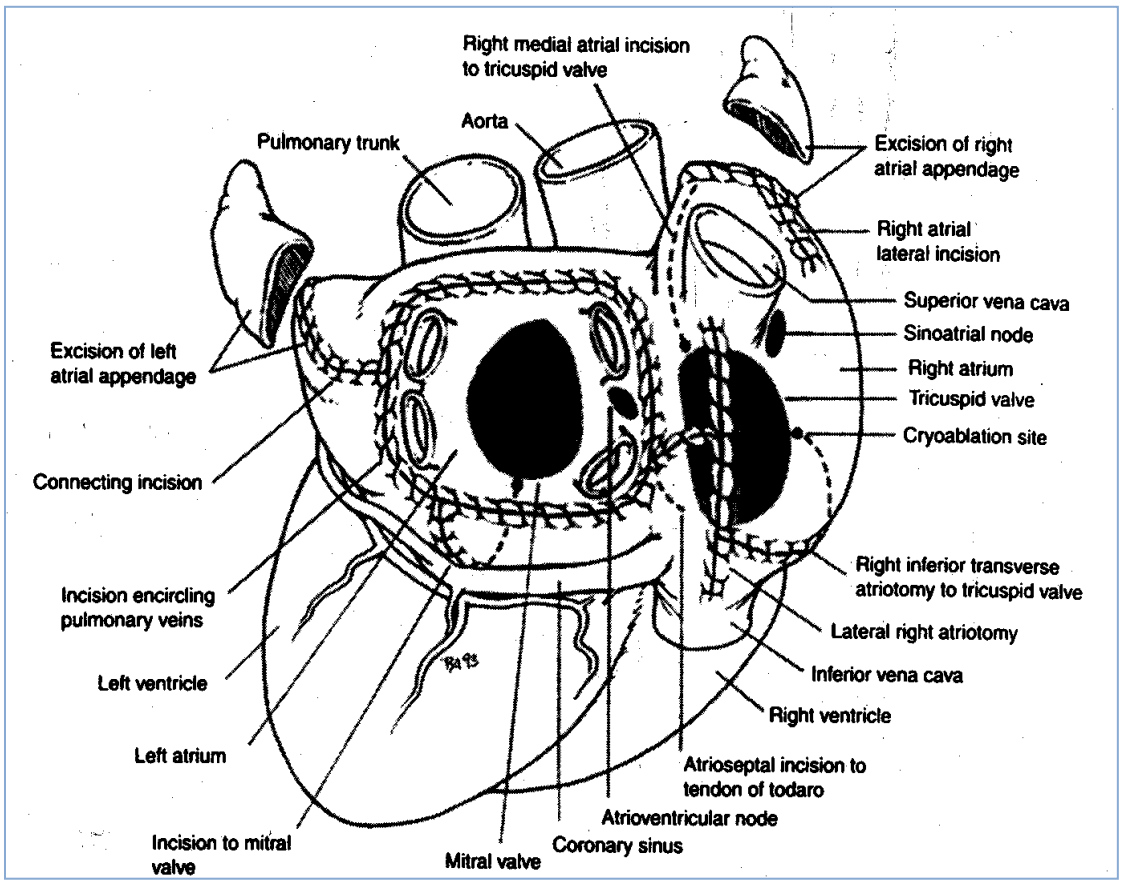


Figure 1: Cox-Maze Procedure

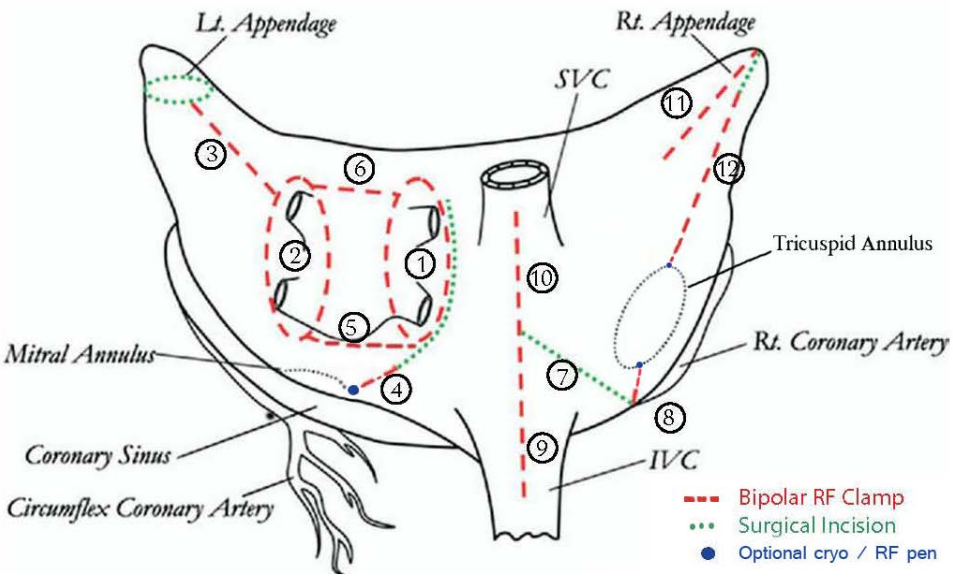
taken from Sundt TM 3rd, et al. Cardiol Clin. 1997;15(4):739-748

In the late 1990's, to alleviate some of the technical challenges of the original Cox-Maze procedure, surgeons began using other methods to replicate the Cox-Maze surgical incision lines. The modified procedure, termed the Maze IV, has become the benchmark procedure used today to treat AF to achieve rate control. The procedure consists of a series of ablation lesions together with the excision/exclusion of the left atrial appendage

that intend to reproduce the cut and sew lesions of the original Cox-Maze procedure. The operation consists of the following elements (Figure 2):

A) Pulmonary vein isolation (PVI)
   a. Left Antral PV Isolation
   b. Right Antral PV Isolation
B) Left atrium
   a. Superior connecting line (left PVI to right PVI) "ROOF Line"
   b. Inferior connecting line (left PVI to right PVI) – "FLOOR Line"
   c. Connecting lesion for right PVI to mitral valve annus
   d. Connecting lesion for left atrial appendage to the left PVI through stump or purse string incision)
C) Right atrium
   a. Complete atriotomy to tricuspid valve annulus. If atriotomy not completed to tricuspid valve, create lesion onto annulus of tricuspid valve.
   b. SVC to IVC lesion
   c. Right atrial appendage lesion (along right atrial freewall)
   d. Right atrial appendage to tricuspid annulus lesion
D) Left atrial appendage excision/exclusion

Figure 2: Maze IV Procedure



The ablation procedure has now been adopted by a large majority of cardiac surgeons, but there is some variability in the way surgeons perform the procedure. Sometimes surgeons will not complete the full set of biatrial lesions and this results in variability in

the efficacy outcomes. Several clinical investigations have been performed to compare the outcomes of surgical procedures in patients that have the Maze procedure with either a full set of lesions to those that have a more limited set, such as pulmonary vein isolation alone. These research efforts support the conclusion that, to maximize the efficacy outcome for patients, the full lesion set should be performed. [Melby 2006]

Further, there are multiple energy sources that have been used to create the ablation lesions. They include microwave, high frequency ultrasound (HIFU), cryoablation or radiofrequency (RF) ablation. Today, the most prevalent modalities in use are RF ablation (38%) followed by cryoablation (12.4%) [Gammie 2008]. The surgical instruments currently in use by surgeons have been reviewed by FDA and are commercially available through the 510(k) clearance process. All of these products have a basic "tools claim" indication that does not specifically claim to treat AF.[i]

Currently, surgeons learn this Maze IV procedure through the usual mentorship and proctorship training mechanisms from their peers and training program faculty. This has resulted in the high level of variability in the performance of the procedure and consequently, outcomes. It is the goal of this PMA Application to have an updated product label specifically for treatment of atrial fibrillation. This new indication would enable AtriCure to conduct training programs to ensure surgeons learn the optimal surgical technique with the AtriCure Synergy Ablation System to maximize the efficacy outcomes for their patients while ensuring safety.

Despite the variability that may exist in the medical community, the Maze IV procedure is endorsed and accepted as the standard of care for the treatment of AF in the setting of a concomitant surgical procedure. Numerous medical societies including the AHA, ACC, HRS, ECS, STS, EHRA, ISMICS, and ECAS, have all documented their endorsement of the Maze IV to be performed as an add on procedure in patients with AF who are undergoing a primary surgical operation to correct their underlying coronary or valvular heart disease. [Fuster 2006-1; Calkins 2007; Ad 2010]

The strongest recommendation is found in the HRS/EHRA/ECAS Consensus Statement. [Calkins 2007] These groups of experts strongly support this approach when the add-on surgical therapy of AF can be performed at low risk. Although this is not a guideline statement and therefore does not utilize the standard classification and level of evidence grading systems, this recommendation is based on review RCTs, Registries, and Meta-analyses and is stated in terms that would be consistent with Class I or II and level of evidence A or B.

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[i]Radiofrequency: K013873, K022008, Microwave: K003978, K041340, High-Intensity Focused Ultrasound: K022894

2.3.3.1. Risks and Benefits of the Maze IV Procedure

It is important to consider the overall risks and benefits of performing the Maze IV procedure in a concomitant setting, since this procedure is directly related to the proposed clinical indication for the PMA product. The procedure has been extensively studied in a variety of clinical trials and these studies have formed the basis for establishment of the procedure as the standard of care. Research studies conducted at the Mayo Clinic and the Cleveland Clinic reviewed the risks of subjects that had baseline AF in comparison to those subjects that were AF free at the time of their primary operation, specifically coronary artery bypass grafting (CABG), aortic valve, or mitral valve surgery. These were all surgeries performed without the inclusion of a Maze. These data illustrate the risks for patients with coronary or valvular heart disease with underlying AF that is left untreated. Table 1 provides a summary of the number of subjects and the cross clamp and bypass time for each series of patients.

Table 1: Case Matched Series of Patients with AF versus without AF at Baseline

Indication	Citation	Number of Subjects	Cross Clamp Time (mean ± SD)		CPB Time (mean ± SD)	
			AF present	AF absent	AF present	AF absent
CABG	Quader et al Annals of Thorac Surgery, 2004	46,984	71 ± 23	71 ± 27	98 ± 36	100 ± 31
Aortic Valve	Ngaage et al Annals of Thorac Surgery, 2006	381	50 ± 16	50 ± 18	NR	NR
Mitral Valve	Ngaage et al Annals of Thorac Surgery, 2007	370*	40 ± 18	39 ± 18	NR	NR
CABG	Ngaage et al Journal of Thorac and Cardiovasc Surgery, 2007	526	50 ± 18	50 ± 18	91 ± 33	92 ± 32

**Excluded any cut & sew Cox-Maze operations;* NR =not reported

The outcomes of patients that had baseline AF at the time of their cardiac surgery operation were compared to those that did not have baseline AF (Table 2). Each of these studies demonstrated a significant increase in mortality in the AF group. In addition, the studies suggest an increased risk of post-operative morbidity including stroke. Furthermore, Ngaage et al also identified patients with aortic valve surgery and atrial fibrillation classified as “permanent” having a poorer outcome than those patients with a shorter history. These studies support the premise that correction of underlying coronary or valvular heart disease alone does not ameliorate the risks of AF. Further, it highlights the need to treat the atrial fibrillation to minimize long-term risks.

Table 2: Summary of Outcomes – AF Treated vs Non Treated Studies

Indication	Citation	Survival*		Stroke	
		AF present	AF absent	AF present	AF absent
CABG	Quader et al Annals of Thorac Surgery, 2004	42% (10 years)	66% (10 years)	3.1% in hospital	1.6% p=0.1
CABG	Ngaage et al Journal of Thorac and Cardiovasc Surgery, 2007	41% (10 years)	58% (10 years)	14% (6.7 years)	10% p=0.27
Aortic Valve	Ngaage et al Annals of Thorac Surgery, 2006	50% (7 years)	61% (7 years)	16% (4.5 years)	5% p=0.005
Mitral Valve	Ngaage et al Annals of Thorac Surgery, 2007	70% (10 years)	88% (10 years)	12% (5 years)	5% p= 0.03

* $p < 0.05$

In addition, five randomized clinical trials (RCTs) have been performed in patients that received surgical treatment for a mitral valve procedure with or without a concomitant Maze IV procedure.[Deneke 2002; Abreu Filho 2005; Doukas 2005; Chevalier 2009; Von Oppell 2009] Each study demonstrated a significant improvement in rhythm status, and this improvement was maintained through 12 months with a p value that was less than 0.05 (Table 3). The importance of the observed outcomes is enhanced by the additional significant improvements noted in LV function parameters (Table 4). These benefits were demonstrated to be significant even in these studies that were of limited size.

Table 3: Randomized Trials of Maze IV Procedure- Sinus Rhythm Achieved

Author, Year	Sample Size	Lesion Set	Device	Control 12 Month NSR	Treated 12 Month NSR	P value	Method of Assessment
Deneke, 2002	30 (15 tx, 15 ctl)	Biatrial Maze	Unipolar, cooled tip RF	26.7%	80%	(p=0.005)	Holter
Abreu Filho, 2005	70 (42 tx, 28 ctl)	Biatrial Maze	Unipolar, cooled tip RF	26.9%	79.4%	(p=0.001)	24hr ECG
Doukas, 2005	97 (49 tx, 48 ctl)	PVI and Left Atrial	Unipolar RF	4.5%	44.4%	(p<0.001)	ECG (Holter if sx)
Chevalier, 2009	43 (21 tx, 22 ctl)	PVI and Left Atrial	Unipolar RF	4%	57%	(p=0.004)	Holter
Von Oppell 2010	49 (24 tx, 25 ctl)	Biatrial Maze	Both Unipolar and Bipolar RF	39%	75%	(p=0.030)	ECG

Table 4: Randomized Trials of Maze IV Procedure-Other Clinical Outcomes

Outcome Parameter	Trials, Year	Control	Treated	P value
BNP (fmol/mL) Δ base to 12 mo	Doukas, 2005	30±71	76±125	P=0.02
Max Work Load (Stress Test)	Deneke, 2002	43±16	73±29	P=0.008
Shuttle Walk Distance (m) - 12 mo	Doukas, 2005	304±120	359 ±140	P=0.02
LVESD (cm) - 6 mo - 12 mo	Doukas, 2005	4.33±0.7 4.26±0.6	3.96±0.7 3.93±0.7	P=0.02 P=0.03
Survival at 12 mo	Deneke, 2002	73%	93%	P=0.131
Atrial Contraction	Von Oppell 2009	36 ±14%	43 ±18%	NS

These studies provide relevant information to assess the Maze IV procedure's overall clinical benefit. Because these studies were performed in the early phase of the Maze IV procedure's inception, the products used were rudimentary. They were all systems that preceded the development and release of the AtriCure system to the marketplace. Unfortunately, there have been no other randomized trials performed with RF ablation technology since the procedure is now widely accepted as the standard of care. Two other trials have been published with the use of other energy sources (cryoablation and microwave) but these studies were not included in the summary of outcomes since the modality of energy is not consistent with the product of this PMA Application. [Blomstrom-Lundqvist 2007; Schuetz 2003] Results with these other energy sources are generally consistent with those reports for RF ablation; reporting with AF Free ratesat 73.3% for cryoablation and 80% for microwave energy at one-year post procedure.

A recent meta analysis examining both RCT and non RCT studies concluded that, when examined over an extended period of time beyond one year, restoration of sinus rhythm was associated with reduction in stroke or thromboembolic events. [Cheng 2010]

The medical community has accepted the Maze IV procedure as an option for achieving rhythm control in the AF population undergoing a primary operation for coronary or valvular heart disease. The acceptance of this procedure and technology is further evidenced by the established CPT codes established by The Centers for Medicare and

Medicaid Services (CMS).[ii] Thus RCTs are no longer felt to be medically necessary or appropriate since equipoise no longer exists.

2.3.3.2. Risks of the Maze IV procedure

It is necessary to summarize the potential risks of the concomitant Maze IV in order to appreciate the risk to benefit ratio. The same RCTs describing the efficacy of the procedure have also provided insight into the potential added risk that a patient may be exposed to with this add-on procedure. Despite a reported longer bypass and cross clamp time for the additional Maze IV component of the surgery, none of the papers reported a higher rate of complications in this group compared to the surgery alone group (Table 5).

Table 5: Randomized Trials of Maze IV Procedure- Procedure Times

Author, Year	Cardiopulmonary Bypass Time (mean ± SD) (min)		P value	Cross Clamp Time (mean ± SD) (min)		P value
	Control	Treated		Control	Treated	
Deneke, 2002	127	188	NR	85	103	NR
Abreu Filho, 2005	78.2 ± 24.4	107.2 ± 21.1	p <0.001	47.1 ± 15.8	67.5 ± 13.5	p <0.001
Doukas, 2005	99 ± 37	106 ± 34	NR	64 ± 28	70 ± 26	NR
Chevalier, 2009	NR	NR	NR	74 ± 19	93 ± 32	p= 0.4

NR =not reported

These studies represent a limited experience but the results are corroborated by an extensive review of the Maze IV procedure reported in the Society of Thoracic Surgeons (STS) National Cardiac Database, a voluntary cardiac surgery database that was established in 1989 to support national quality improvement efforts. It contains detailed perioperative data on more than three million cardiothoracic surgical procedures. [Gammie 2008]

Gammie, et al (2008) extracted data on patients included in the database from January 2004 through December 2006. The analysis included the cases of mitral valve surgery alone or in combination with coronary artery bypass grafting. A comparison of patients with baseline AF that were treated with the Maze procedure was made to those patients with baseline AF that did not have a Maze procedure. A total of 11,475 patients who underwent mitral valve surgery with a diagnosis of preoperative AF were available for analysis. Of this group, 6,231 had received a Maze procedure as an add-on to their mitral

[ii] Three CPT codes established for open heart concomitant procedures, CPTs 33257-33259

valve procedure. The primary modality used to perform the Maze was bipolar RF ablation (38.1%). The other modalities included the cut and sew Maze (21.4%), cryothermy (12.4%), unipolar radiofrequency (6.1%), microwave energy (7.6%), and a combination of energy sources (9.9%).

The analysis demonstrated an increase in both median cross clamp time (nine minute difference) and bypass time (nine minute difference) in the group receiving the Maze procedure. Despite this increase, the unadjusted mortality was lower in the AF correction group (4.5% versus 6.6%, p< 0.0001). Further, the majority of postoperative complications were also lower in those patients receiving the concomitant Maze (Figure 3).

Figure 3: Operative Characteristics – STS Database

Table 3. Operative Characteristics of Patients Having Mitral Valve Surgery With or Without Concomitant Surgical Treatment of Atrial Fibrillation

Variable	AF Correction Surgery (n = 6,231)	No AF Correction Surgery (n = 5,244)	*p* Value
Median CPB time (min)	138 (108, 176)	129 (99, 169)	<0.0001
Median cross-clamp time (min)	102 (77, 131)	93 (70, 124)	<0.0001
Concomitant CABG (%)	34.1	38.5	<0.0001
Reoperation for bleeding	4.7	5.8	0.0008
DSWI	0.51	0.42	0.2207
Stroke	1.46	2.44	0.0020
Prolonged ventilation	14.8	20.5	<0.0001
Renal failure[a]	6.5	8.1	0.0004
Permanent pacemaker[b]	6.8	6.3	0.0878
Operative mortality	4.5	6.6	<0.0001
LOS (median, days)	7 (6, 10)	8 (6, 12)	<0.0001

[a] Excluded patients with preoperative renal failure. [b] Excluded patients with preoperative pacemaker.

AF = atrial fibrillation; CABG = coronary artery bypass grafting; CPB = cardiopulmonary bypass; DSWI = diastolic stroke work index; LOS = length of stay.

Taken from Gammie, et al (Ann Thorac Surg 2008;85:909-15)

After an adjustment for baseline characteristics was performed, no statistical differences between the two groups mortality or major morbidity were identified. The only statistical difference was in the need for pacemaker implantation that demonstrated a statistically higher rate in the AF correction cohort (Figure 4) with an odds ratio of 1.26.

Figure 4: Risk-Adjusted Mortality & Morbidities – STS Database

Table 4. Risk-Adjusted Mortality and Morbidities for Patients Having Mitral Valve Surgery With (Versus Without) Concomitant Surgical Treatment of Atrial Fibrillation, Adjusting for Participant Clustering and Other Potential Variables[a]

Outcome	Total N	Adjusted OR	Lower (95% CI for Adjusted OR)	Upper (95% CI for Adjusted OR)	Adjusted *p* Value
Mortality					
Death	11,475	1.00	0.83	1.20	0.975
Complications					
Any reoperation	11,475	0.98	0.87	1.12	0.802
Renal failure/dialysis[b]	10,820	1.03	0.88	1.21	0.689
Prolonged ventilation	11,475	0.98	0.88	1.09	0.715
Need for permanent pacemaker[c]	10,475	1.26	1.07	1.49	0.007
Hospital stay					
Postprocedure LOS > 14 days	11,475	1.00	0.88	1.13	0.949

Taken from Gammie, et al (Ann Thorac Surg 2008;85:909-15)

2.3.3.3. Summary of Risk to Benefit for the Maze IV Procedure

It is clearly recognized that the Maze IV procedure is a well-accepted procedure by the surgical community. Careful randomized clinical trials have demonstrated the ability of the Maze IV procedure to provide an option for rhythm control in patients with pre-existing AF a the time of their surgery. While limited in scope, these randomized studies have found significant markers of potential long-term clinical benefit. The most important finding is that this potential benefit is achieved while incurring low added risk to the procedure. The variability in the procedure that has been reported in other non-randomized trials underscores the need for standardized, formal clinical training programs to be established for the operating surgeon. Although the concomitant procedure has been studied in many non-randomized trials, it is necessary to provide a validation of these published findings that established the procedure's acceptance with the AtriCure product to support the proposed labeling. This was the aim of the IDE Clinical Trials that are summarized herein.

In summary, these factors support the need for a refined label for the AtriCure Synergy Ablation System and the establishment of formal training programs in conjunction with a post approval study.

3. DEVICE DESCRIPTION

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

- AtriCure Synergy Ablation Clamps - Product Codes: OLL2, OSL2
- Ablation and Sensing Unit – ASU – RF Generator
- Isolator Switch Matrix– ASB – allows user to connect multiple AtriCure devices to ASU

3.1. 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 those of the OLL2 to provide surgeons with different options for accessing patient anatomy.

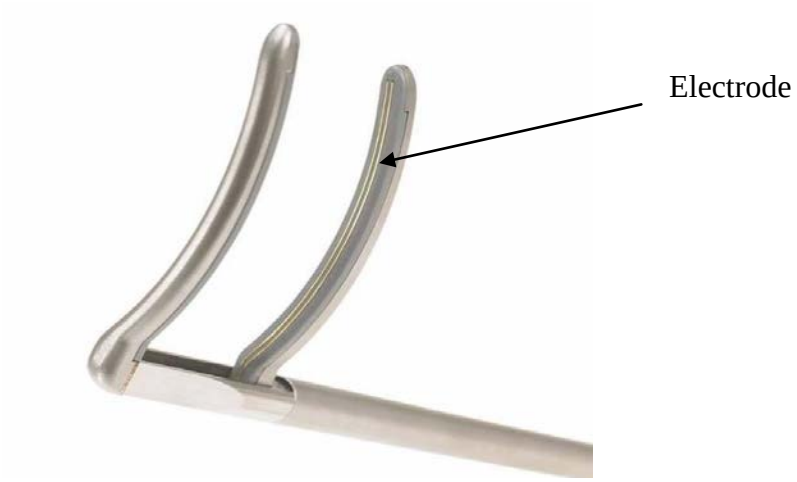
3.1.1. Synergy Ablation Clamp

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 5**).**

The Clamp device handle is connected by a cylindrical shaft affixed 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 6). 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 (ASU) and the Isolator Switch Matrix (ASB).

Figure 5: AtriCure Synergy Ablation Clamp (OLL2)

Figure 6: AtriCure Synergy Ablation Clamp End Effector



3.1.2. Ablation Sensing Unit

The Ablation and Sensing Unit (ASU) is a radiofrequency (RF) generator used to power AtriCure Handpieces (Figure 7). 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 7: RF Generator- AtriCure Model ASU/ASB

3.1.3. Isolator Switch Matrix

The ASU is used in conjunction with the Isolator Switch Matrix (ASB). The Isolator Switch Matrix (ASB) is an accessory interface module allowing various AtriCure ablative devices to connect to the RF generator (ASU) (Figure 7). The ASB also provides the RF switching mechanism for the two electrode pairs in the AtriCure Synergy Ablation Clamps. The ASU and ASB are connected via a short cable. These units (ASU/ASB) are always outside of the sterile field and function to provide the RF energy (ASU) and to direct the energy delivery to the Handpieces.

The ASB 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 ASB. The operator is able to mechanically select and switch between ablation handpieces connected to the ASU RF generator.

3.2. Principles of Operation

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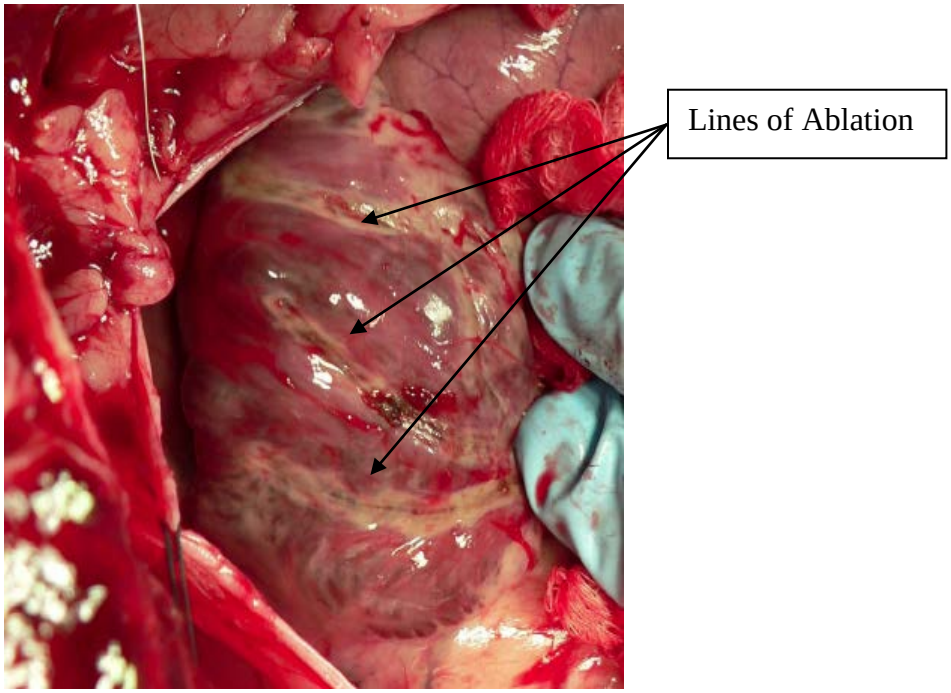
3.3. Regulatory History

The AtriCure RF technology was initially cleared in 2001 (K011722) for the indication of ablating and coagulating soft tissue during General, ENT, Thoracic, Gynecology, and Urology surgical procedures. This product established one of the initial systems that surgeons used to develop and refine the current Maze IV procedure as it is performed today. The technology utilized a bipolar RF ablation single-electrode clamp consisting of a handle connected to a pair of grasping jaws with an electrode on each jaw arm. The clamp was designed to grasp tissue between the electrodes, and when energy applied, the tissue touching the electrodes is ablated. The Clamps were used in conjunction with the AtriCure Bipolar Electrosurgical Generator to create the ablative lesions.

Enhancements were made to the system that led to the current bipolar technology that is utilized in the AtriCure Synergy Ablation System that is the subject of this PMA Application. This system received initial clearance from FDA in 2007 (K063630).

The dual electrode bipolar technology offers an option for surgeons to perform the procedure with consistent results and transmural lesions.

Figure 8: Heart ablated with the Maze IV technique



The indication statement for the initial clearance of the bipolar system (K063630) was:

> "The AtriCure Ablation System is intended to ablate soft tissues during general surgery using radiofrequency energy."

This labeling was expanded later in 2007 to more accurately highlight the type of tissue that was being ablated, namely cardiac tissue. This expanded label was cleared through K043579 and K101174. The labeling stated: The AtriCure Synergy Ablation System is intended for the ablation of cardiac tissue during surgery. To support this label claim, the 510(k) submission included the clinical data from 64 AF ablation cases performed by surgeons. All of the support data came from information provided by surgeons that were performing the Maze IV procedure at their institution. The clinical data gave the confirmation regarding the product safety and technical capability for the device to support the new labeling. Since the only reason to ablate cardiac tissue is to perform the Maze IV procedure, it is important to shift the current "tools claim" discussed in Chapter 1 to a claim that will support the clinical indication of AF treatment so effective training programs may be established.

AtriCure has been working with FDA since 2003 to develop the clinical support data to refine the labeling to reflect the treatment of AF. The RESTORE-SR trial was designed in collaboration with the Agency as a matched controlled trial for AF treatment in a concomitant open cardiac surgical procedure. The Maze IV procedure was intended to be performed at the time of a primary procedure to address some form of coronary or valvular heart disease in patients with baseline AF. Since the Maze IV procedure was already believed to be the standard of care in the concomitant setting, surgeons were reticent to conduct a randomized clinical trial. Hence, a matched control design was established to determine the safety risks of the procedure in comparison to subjects that were receiving a "matched" procedure in patients that did not have preexisting AF. Criteria for matching included gender, age within ±5 years, type of primary surgical procedure (ie: mitral valve replace/repair, aortic valve replace/repair, etc), and baseline ejection fraction within ±10 percentage points (but in no case less than 30%). The control subjects were required to be within 3 months of the matched treatment patient at the same institution. This control was aimed at providing contemporary comparison information to evaluate the overall safety of the product. The primary efficacy endpoint comparison was made to a performance goal established from literature available on the Maze procedure at the time of study design. The primary efficacy endpoint was defined as the proportion of treated patients AF Free without the need for anti-arrhythmic agents at the six-month follow-up visit based on a 12-lead electrocardiogram (ECG). The rate of efficacy at six months was compared to the target of 60% with a ten percent margin resulting in a tolerance for the lower confidence interval bound (based on 95% CI) of 50%.

It was discovered after the clinical trial was underway that the case matched controls were very difficult to identify. After 32 months of enrollment, only five matched controls were identified out of the 39 treatment subjects enrolled. AtriCure worked with their physician advisors and the FDA to modify the study and realized that instead, a new clinical trial design should be utilized. The results for the RESTORE-SR study are still relevant and provide corroborative evidence to support the primary study that evolved from this process, ABLATE. A copy of the RESTORE-SR clinical study report is provided in **Appendix A** for review.

4. SUMMARY OF PRECLINICAL STUDIES

In vitro and *in* vivo testing was performed to demonstrate the safety and effectiveness of the AtriCure Synergy Ablation System in bench and animal models. As demonstrated in the data below, the results support the safety and effectiveness of the AtriCure Synergy Ablation System.

4.1. *In Vitro* Bench Testing

In vitro bench testing to support the AtriCure Synergy Ablation System was developed based on design specification and applicable standards. The tests summarized in Table 6 were conducted to demonstrate the safety and effectiveness of the AtriCure Synergy Ablation System in an *in vitro* setting. As illustrated in Table 6**,** all results support the safety and effectiveness of the AtriCure Synergy Ablation System.

Table 6: Summary of *In Vitro* Testing and Results

In Vitro Test	Overall Purpose and Description	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.	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.	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.
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.	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.	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.	Pass. The OLL2 and OSL2 met electrical safety requirements specified in the product specification and IEC 60601-2-2 and AAMI HF-18.
Surface Temperature	To verify the OLL2 and OSL2 meets the External Surface Temperature Requirements per EN 60601-1 Section 42.	The OLL2 and OSL2 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	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.	Pass. The OLL2 and OSL2 (2x EtO Sterilization) meets the Closing Force requirements.
Closure Latch	To verify the OLL2 and OSL2 meet the Closure Latch unlatching requirement after exposure to 2x EtO sterilization.	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.	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.	Pass. The OLL2 and OSL2 met shaft stiffness specifications.
Force Testing	To verify that the OLL2 and OSL2 meet jaw force specifications.	Pass. The OLL2 device met jaw force specifications.

4.2. *In Vivo* Animal Studies

The AtriCure Synergy Ablation System was tested in multiple acute and chronic animal studies. The *in vivo* studies were performed to verify ablation performance in live tissue. In all studies, device efficacy was assessed by gross examination of tissue after staining with 2,3,5,-triphenyl-tetrazolium chloride (TTC). The ablation performance was determined by assessing transmurality; the ablation was successful if the ablation was transmural (full thickness). All lesions were also examined for any signs of adverse tissue effects such as tissue charring, tissue perforation, and lateral thermal spread. When possible, the lesions were also assessed for effectiveness by pacing and/or histology.
In all cardiac tissue ablations, all lesions were 100% transmural. In addition to effectiveness, safety was evaluated by examining the lesions grossly for adverse tissue effects such as charring or perforation, and chronically by examining the health of the animal over the duration of the study. In both acute and chronic studies, the animals demonstrated no adverse effects specifically associated with ablation energy delivery. Although not a formal assessment in the acute studies, there were no instances of thrombosis observed in any animal. In the chronic study, animals survived to the terminal surgery with no complications attributed to the ablation protocol. Results from these studies demonstrate that the AtriCure Synergy Ablation Clamps are able to effectively ablate cardiac tissue with a reasonable safety profile. A summary of all animal studies is provided below in Table 7.

Table 7: Summary of *In Vivo* Animal Testing and Results

Document Title	Chronic or Acute, # of Animals	Purpose and Description	Key Assessment Criteria	Key Outcomes
Evaluation of the AtriCure Synergy Ablation Technology in the Porcine	Chronic – n= 9 pigs	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).	• Endpoints used to evaluate the safety of the devices were gross pathology of heart, brain, liver, lung, kidneys, bowel, and spleen; 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 maintained at 1-month follow-up. • The OLL2 ablations did not cause pulmonary vein stenosis, regurgitation at mitral/ tricuspid valves, no decrease in LV ejection fraction, nor thrombus. • Histopathology of the ablation lesions showed 100% transmurality at 1-month follow-up. • No clinical observations or events attributed to ablation energy delivery.
Performance Evaluation of the Dual Electrode System for Cardiac Ablation in a Chronic Porcine Model	Chronic – n=6 pigs	To verify the performance of the AtriCure Synergy Ablation Clamp (model OLL2) for ablation of cardiac tissue in the chronic porcine model (n=6 pigs). The study also compared the AtriCure Synergy Ablation Clamp (OLL2) to previous generation Handpieces for the following variables: RF time, energy delivered, lesion width.	• Ablation line gross exam and assessment: visual examination of lesions for transmurality, width (lateral thermal spread), presence or absence of thrombus, charring, and pulmonary vein stenosis. • Histological exams to confirm visual assessment of transmurality. • Engineering analysis of energy delivery: total energy delivery, duration of application.	• The OLL2 device isolates cardiac tissue in one application. • The OLL2 device creates ablations that are discreet and visible to the naked eye without damaging adjacent structures. • The OLL2 ablations do not cause charring, thrombus, or pulmonary vein stenosis. • Gross Exam and Histology of the lesions, showed 100% transmurality at 28 days survival.

Document Title	Chronic or Acute, # of Animals	Purpose and Description	Key Assessment Criteria	Key Outcomes
OLL2 Acute Animal Lab	Acute – n=2 pigs	To verify that the AtriCure Synergy Ablation Clamp (OLL2) functions as required in live tissue. The following were assessed: device must be atraumatic to tissue (i.e. free of pinch surfaces, sharp edges, snags) in order to prevent unintended damage during tissue interface, device must be able to be operated 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 OLL2 device to previous AtriCure Handpieces was also performed to verify performance.	• Ablation line gross exam and assessment: visual examination of lesions for transmurality, width (lateral thermal spread), presence or absence of thrombus, or charring. • Intraoperative device use was observed to determine whether the device was atraumatic to tissues.	• The OLL2 devices created 100% transmural lesions as evidenced by gross examination and measurement. Lesions did not exhibit thrombus or charring. • The OLL2 devices were atraumatic to tissue and did not cause any damage during tissue interface. The surgeon was able to operate the device with one hand. • The OLL2 device functioned as well as previous generation AtriCure Handpieces.
OLL2 Animal Lab	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. Ablation performance of the OLL2 was assessed on various tissues and compared to previous generation AtriCure Handpieces.	• Ablation line gross exam and assessment: visual examination of lesions for transmurality, width (lateral thermal spread), presence or absence of thrombus, or charring. • Tissue temperatures were captured to obtain data on the maximum tissue temperature. • Energy delivered per unit volume of tissue being 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 previous generation AtriCure Handpieces. • The OLL2 devices created 100% transmural lesions as evidenced by gross examination and measurement. Lesions did not exhibit thrombus or charring. No tissue damage beyond that intended by the ablation process occurred. • The average maximum temperature outside of the jaw was less than 50°C on all tissue types.

Document Title	Chronic or Acute, # of Animals	Purpose and Description	Key Assessment Criteria	Key Outcomes
OSL2 Animal Lab	Acute – n=2 pigs	To verify the ablation performance of the OSL2 Handpiece on cardiac tissue in an in vivo porcine model. The following were assessed: device must be atraumatic to tissue (i.e. free of pinch surfaces, sharp edges, snags) in order to prevent unintended damage during tissue interface. The study also compared the Handpiece to previous generation Handpieces for the following variables: RF time, energy delivered, lesion width.	• Ablation line gross exam and assessment: visual examination of lesions for transmurality, width (lateral thermal spread), presence or absence of thrombus, or charring. • Energy delivered per unit volume of tissue being ablated and time to transmurality was also evaluated. • Intraoperative device use was observed to determine whether the device was atraumatic to tissues.	• The OSL2 device creates ablations that are discreet and visible to the naked eye without damaging adjacent structures. • The OSL2 ablations do not cause charring or thrombus. • Gross Exam of the lesions showed 100% transmurality. • The OSL2 devices were atruamatic to tissue and did not cause any damage during tissue interface.

4.3. 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 8**.**

Table 8. 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

4.4. 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 Matrix 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. A sub-lethal study (fractional cycle) may also be performed to gather information about the load and the cycle.

4.5. 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.

The results of the *in* vitro and *in vivo* testing demonstrate the safety and effectiveness of the AtriCure Synergy Ablation System.

5. ABLATE CLINICAL TRIAL

5.1. ABLATE Clinical Protocol Highlights

The ABLATE clinical trial was conducted under an Investigational Device Exemption) initiated in June of 2007. The first patient was enrolled on February 8, 2008. A summary of the modifications that were made in the clinical study during the execution phase are provided in **Appendix B** (ABLATE Regulatory History). ABLATE AF is the ongoing registry study serves as a continuation of ABLATE and a precursor to the Post Approval Study. A copy of the final clinical protocol utilized in ABLATE and the current revision of the ABLATE AF protocol are provided in **Appendix C** and **Appendix D,** respectively.

5.1.1. Study Purpose

The aim of the ABLATE study was to demonstrate the safety and efficacy of the AtriCure Synergy Ablation System in the treatment of subjects with permanent atrial fibrillation that are undergoing a cardiac surgery procedure primarily for significant structural and/or coronary heart disease indications.

5.1.2. Primary Endpoints

The ABLATE trial has primary endpoints for both safety and efficacy. The clinical protocol outlines the following endpoints:

PRIMARY SAFETY:

The primary safety endpoint for the study was defined as the rate of Major Adverse Events occurring within the initial 30 days post procedure or discharge (whichever was later). Major Adverse Events consist of: Death, Excessive Bleeding (defined as > 2 units of RBCs with reoperation), Stroke, TIA or MI). A clinic visit was performed at 30 days to fully assess the patient for adverse events. It should be noted that this composite of events includes events regardless of attribution, and is not specific to events attributed to the investigational device or even the Maze IV component of the operation. In all cases, a determination of the causality of each endpoint event was made based on adjudication by an independent cardiac surgeon.

PRIMARY EFFICACY:

The primary efficacy endpoint was defined as 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 via 24-hour Holter monitor assessment (or permanent pacemaker interrogation in the case of those subjects that have a pacemaker implanted).

5.1.3. Secondary Endpoints

Several secondary endpoints are included for both safety and efficacy. Through discussions with FDA at the completion of study enrollment, there was a request for additional long-term assessments for efficacy. As such, additional post hoc efficacy endpoints were added to the study to assess subject rhythm status at 12 months or thereafter utilizing a 48-hour Holter (rather than 24-hour Holter as was the case in the primary endpoint). Below a list of all endpoints for the trial, both preplanned and post hoc.

5.1.3.1. Secondary Safety

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

5.1.3.2. Secondary Efficacy

The proposed preplanned secondary efficacy endpoints were:

- 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 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 and
- Reduction of overall atrial fibrillation burden on 24-hour Holter at 6 months.

The following additional unplanned secondary efficacy endpoints have been identified since the original writing of the protocol:

- 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) independent of the need for anti-arrhythmic drugs (Class I and Class III) as assessed 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 a 48-hour Holter recording performed at a minimum of 12 months post procedure.
- Reduction of overall atrial fibrillation burden on 48-hour Holter at 12 months or after.

In addition, the rate of pacemaker implantation was highlighted in the protocol as an important outcome and is summarized in this report.

The protocol also described left atrial transport function (LATF) and the relationship of LATF to ablation of AF and the potential of improving atrial function as a consequence of obliterating the atrial fibrillation. This was an optional assessment in the protocol. Only one center attempted to perform this assessment but unfortunately subjects were not willing to consent for the follow-up TEE required to evaluate the LATF. Therefore, this assessment is not available for analysis.

5.1.4. Study Design

ABLATE was a multi-center, prospective, non-randomized study based on a Bayesian adaptive design that provides high probability of demonstrating non-inferiority of the AtriCure Synergy Ablation System for the treatment of permanent atrial fibrillation. The safety and efficacy of the device was compared to current standards (historical controls).

Subjects were to undergo pulmonary vein isolation and ablation to create atrial connecting lesions with the AtriCure Synergy Ablation System along with left atrial appendage exclusion/excision (as appropriate) concomitant with elective open-heart cardiac procedures requiring cardiopulmonary bypass. The study was considered successful if permanent atrial fibrillation was eliminated based on a 24 hour Holter at six months past procedure and the need for Class I or III antiarrhythmic drugs was eliminated.

The study utilized a Bayesian adaptive clinical design that incorporated interim analyses of the data to determine the point of completion of trial enrollment. Enrollment was targeted to be between

5.1.5. Efficacy Success Criterion

Table 9:

5.1.6. Safety Success Criterion

ABLATE was designed to demonstrate safety of the AtriCure Synergy Ablation System by establishing non-inferiority to a performance goal for the Primary Safety Endpoint rate, which included a composite of select major adverse events. These events include: death, stroke, transient ischemic attack, myocardial infarction and reoperation for bleeding. The study intent was to ensure that the safety was within the bounds established by from the base procedure originally established by Dr. Cox, referred to as the classic cut-and-sew Maze.

5.1.7. Study Eligibility Criteria

The following inclusion and exclusion criteria were utilized in the ABLATE study.

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 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 or cardiac catheterization performed within 60 days of enrollment as documented in patient medical history).*
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.

**EF can be assessed intra-operatively*

EXCLUSION CRITERIA
Stand alone AF without indication(s) for concomitant CABG and/or valve surgery
Previous cardiac ablation including catheter 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

5.1.8. Study Procedures

Subjects were screened for enrollment and consented based on the eligibility criteria outlined above. Subjects were consented prior to being brought to the operating room with the potential that they may not be eligible based on some criteria that were evaluated in the operating room (i.e. left atrial size assessed by TEE). In fact, one subject was found to have a LA Size that was greater than 8 cm by TEE and therefore was excluded from the trial in the operating room and was therefore not enrolled. All subjects were required to undergo a primary cardiac surgical procedure to address a form of underlying coronary or valvular heart disease as part of the study eligibility. The requirement also was made that the procedure be performed as an open chest operation on bypass.

Investigators were required to perform the Maze IV procedure using the investigational system. This procedure has been well described and is performed routinely by surgeons worldwide. [Damiano 2007] It includes both right and left pulmonary vein isolation as well as a series of ablation lines to create “the box lesion” in addition to valvular lesions. Confirmation of exit block was to be performed as appropriate to ensure that the pulmonary vein isolation was effective. The detailed summary of the surgical steps of the procedure is provided in an appendix of the ABLATE protocol.

Subjects were followed through discharge, at 30 days, 3 months, 6 months, 12 months, 18 months, 2 years and annually for five years thereafter (Table 13).

The clinical assessments included a targeted history and physical exam as well as an assessment of medication and ECG. At two months an optional clinical assessment was encouraged as a means of evaluating the subject’s AF status while on antiarrhythmics. All subjects were required to have a clinical visit at three and six months. The three-month visit was intended to be the point at which subjects were required to discontinue antiarrhythmic medications, if possible. This enabled the AADs to be washed out by the time the six-month visit, when the primary efficacy evaluation was performed. The protocol for managing the AADs and cardioversions is shown in Table 14.

Upon completion of the primary efficacy endpoint evaluation at six months post procedure, subjects were entered into a long-term surveillance phase to assess long-term results. The study originally outlined a surveillance plan that consisted of a phone call assessment of subjects at twelve months and then annually thereafter for a total of five years. During interactions with the FDA however, an assessment of rhythm status at 12 months or greater was added to provide more insights on the durability of the procedure. Therefore, a protocol amendment was added to obtain a 48-hour Holter in as many subjects as possible at a time point at or beyond twelve months.

Table 13: Overall Schedule of Events

Assessment	Baseline	Procedure	Pre-Discharge	30 days	2 months[iii]	3 months	Interim Visit[iv]	6 months	12 & 18 mo	Years 2 - 5

Table 14: AAD/Cardioversion Protocol

Time Period	Rhythm Status	Action
Pre-Discharge	NSR (or other non-fibrillatory rhythm)	Initiate AADs for the first 3 months
	Atrial fibrillation or flutter	Initiate AADs for the first 3 months and attempt cardioversion if tolerated (pacing wires may also be used)
30 day Visit	NSR (or other non-fibrillatory rhythm)	Continue AADs
	Atrial fibrillation or flutter	Continue AADs and attempt cardioversion if tolerated
2 month Visit (optional)	NSR (or other non-fibrillatory rhythm)	Start to wean off AADs
	Atrial fibrillation or flutter	Continue AADs and attempt cardioversion if tolerated
3 month Visit	NSR (or other non-fibrillatory rhythm)	Discontinue AADs
	Atrial fibrillation or flutter	Attempt cardioversion If unsuccessful, continue AADs If successful, discontinue AADs
Interim Visit (See Section V.4.)	NSR (or other non-fibrillatory rhythm)	Discontinue AADs
	Atrial fibrillation or flutter	Attempt cardioversion if tolerated Alter or discontinue AADs as medically appropriate
6 month Visit	AF Free, amiodarone discontinued for at least 12 weeks, all other AADs discontinued for at least 4 weeks	Primary Treatment Success
	AF Free regardless of AAD Status	Secondary Treatment Success
	Atrial fibrillation	Treatment Failed
12 month or later Holter monitoring	AF Free, amiodarone discontinued for at least 12 weeks, all other AADs discontinued for at least 4 weeks	Secondary Treatment Success

5.1.9. Study Independence/Committees

The ABLATE trial utilized several methods to assure data integrity. A Data and Safety Monitoring Board ensured that patient safety was maintained. The committee was comprised of two cardiac surgeons, an electrophysiologist and a biostatistician. All members of the committee were independent of the ABLATE study and the Sponsor. The group established safety stopping rules and met to review the adjudicated safety data periodically in reference to these stopping criteria. The study never exceeded these safety bounds and the committee never communicated any concerns regarding patient safety to the Sponsor.

5.1.9.1. Study Endpoint Data

Efficacy data are presented based on the review performed by an independent core laboratory. All Holter and ECG results were reviewed by this core laboratory. In the cases in which a permanent pacemaker interrogation was performed, the summary reports from the interrogations were reviewed by the core lab for a determination of efficacy success. The safety endpoint data are reported based on the adjudication performed by a cardiac surgeon that was independent of the study. He reviewed all relevant patient source documentation and determined event level of seriousness and attribution. All events in the trial were adjudicated and all safety data are presented based on this independent adjudication.

5.1.10. Training of Study Personnel

All sites received training prior to the start of the study. The clinical monitor/AtriCure representative reviewed the product with the site and ensured that the Investigators understood the investigational protocol requirements and their obligations to conduct the investigation by following Good Clinical Practice. Instructions for use of the device were provided to the Investigators and copies of the instructions accompanied each packaged device.

5.1.11. Data Management

The data were collected using an electronic case report forms system AtriCure developed the electronic case report form system to reflect all aspects of the clinical protocol.

Data management was performed by BBA was not involved with the development of the study database but was utilized for query generation and data cleaning. The database has been locked through the primary endpoint for the purposes of the generation of this report. The final database lock for the analysis supplied in the original clinical study report (PMA P100046 . Since that data lock, outlined in Table 15 and are reflected in the data presented in this panel pack.

Table 15:

		)

5.1.12. Statistical Methods

The ABLATE study incorporated a Bayesian Adaptive Study Design that assessed the outcomes at periodic points of enrollment to make a decision regarding cessation of enrollment based on pre-specified stopping thresholds for success and futility.

The detailed description of planned statistical analysis methods can be found in **Appendix E,** ABLATE Statistical Analysis Plan.

5.1.12.1. Statistical Study Design

5.1.12.2. Study Populations

Safety was evaluated in all subjects enrolled and treated with the device. This treated population included a total of 55 subjects.

The analysis population for the primary efficacy endpoint was defined as the completer population to be consistent with

. The completer population for ABLATE excluded the five subjects that were not available at 6 months. The five cases included two post operative deaths (considered safety endpoint events), two deaths beyond three months but less than six months and one subject that withdrew from the study at the 30 day visit. Evaluation of the primary study effectiveness analysis population using the completer population was pre-specified in the Statistical Analysis Plan reviewed with FDA

This analysis population is reasonable for evaluation of efficacy since the enrolled subjects were undergoing high risk and complex cardiac surgery for their underlying valve and coronary artery disease and in some cases may not survive to the intended six-month assessment point. The subjects that expired prior to the 6-month follow-up time point expired due to reasons related to their comorbid condition and not associated with their AF disease. The subject that withdrew (pt) had a similar profile to enrolled subjects on average with respect to baseline characteristics (LA size 5.2 cm, ejection fraction 40%, duration of atrial fibrillation 66 months). Further, all of the subjects were undergoing a primary surgical procedure for their cardiovascular disease, not primary surgical therapy for their atrial fibrillation.

5.1.12.3. Overview of Statistical Methods

Data from this study are tabulated using descriptive statistics. Continuous variables are summarized using means, standard deviations, medians and ranges. For categorical variables, relative frequencies are provided.

Statistical evaluations of the primary outcome measures were performed using Bayesian methods. In the final analysis, the posterior distribution of Primary Safety and Primary Efficacy endpoints were summarized graphically and one-sided Bayesian Credible Intervals (BCIs) are computed. The posterior probabilities were calculated and compared against the a priori thresholds established for study success.

Statistical analyses were conducted using SAS Version 9.1.3. Statistical evaluations were performed using a two-sided significance level of 0.05 unless otherwise specified. Bayesian analyses of the primary study endpoints were conducted with the R: A Language and Environment for Statistical Computing Version 2.12.

5.1.12.4. Interim Analysis for Adaptive Sample Size Determination

5.2. ABLATE Study Results

5.2.1. Subject Disposition

A total of 57 subjects were screened and consented for enrollment in the ABLATE study. There was one subject that was consented but expired before the date of procedure. This subject does not appear in any data tables as the subject did not have a baseline case report form entered into the EDC system. A total of 56 subjects presented for surgery and 55 subjects were treated (Figure 9 and Table 16). One subject who presented for surgery was noted by intraoperative TEE to have a left atrial size that did not meet the eligibility criteria (observed LA size > 8 cm diameter) and therefore was not treated with the investigational system. All other subjects that were consented received treatment with the AtriCure Synergy Ablation System.

A total of 53 of the 55 subjects treated were discharged and followed through 30 days post operatively. Two subjects expired in the early postoperative phase

At three months post procedure, a total of 48 subjects out of the 53 potential evaluable subjects had an assessment performed. One subject had withdrawn from the trial after their 30-day assessment was performed indicating that he no longer wanted to participate in the follow-up assessments. It was not appreciated at the time of consent that this subject would not comply with the follow-up regimen. There was one additional subject that had expired due to co-morbid conditions prior to the three-month assessment). A complete summary of all subject deaths is provided with all other significant patient event narratives in **Appendix G**. The remaining three subjects that do not have a three-month post procedure assessment ( ) had missed their visit and were documented as protocol deviations.

At six months post procedure, 50 of the subjects were available for assessment. One additional subject expired after the 3-month visit and prior to the 6-month assessment due to co-morbid conditions . All 50 of the remaining subjects had the 6-month visit performed with either a Holter assessment or Pacemaker interrogation conducted resulting in an excellent compliance rate for the critical Primary Efficacy Endpoint assessment.

The 12-month phone call assessment (original protocol) was obtained in 46 subjects out of the 48 subjects that were available at this point in time. The two subjects that did not have this follow up assessment performed each had multiple unsuccessful attempts at a phone contact; one also had a certified letter sent. Despite the fact that they were not available for the 12-month phone assessment, they were able to be assessed at 18 months via phone call as well as for the long term rhythm status assessment.

An additional rhythm assessment was requested by FDA to assess long term AF status. A rhythm and AAD status assessment at one year or greater was obtained in all available subjects, n = 48. The aim was to have this assessment performed via 48-hour Holter/PPM interrogation. This was achieved in the vast majority subjects (n = 40). The balance of subjects had their rhythm reported to the Sponsor through ECGs or referring physician notes that referenced an ECG, or documented interim recurrence of arrhythmia, or symptoms. The compliance on this added protocol assessment was very high with over 80% of the potential subjects having obtained a 48-hour Holter/PPM assessment and 100% of potential subjects providing supportive information on rhythm status and AAD usage.

At the time of the database closure, a total of 29 subjects were eligible and potentially assessable for an evaluation at two years. Of this group, 28 had an assessment performed at this interval but only 24 of the subjects had data entered into the database at the time of PMA filing. Longer-term follow-up beyond two years is not yet available.

The follow-up compliance for the trial is 90% for every follow-up interval through 6 months, with 100% of available subjects having assessments at the primary endpoint follow-up points (30 days and 6 months).

Figure 9: Subject Disposition

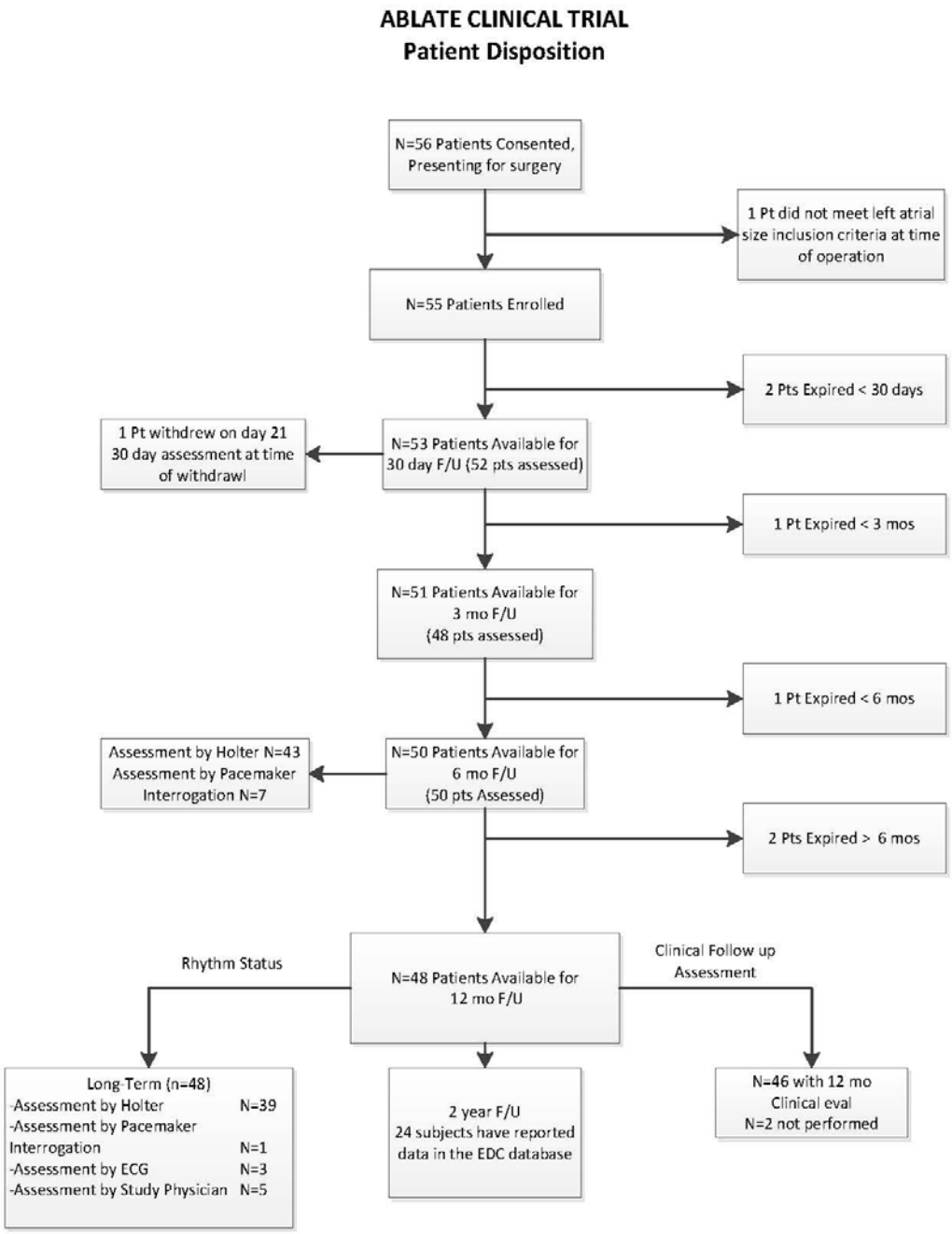


Table 16: Patient Accountability

Patient Status	Total
Patients Consented [1]	56
LA Size > 8 cm	1
Patients Enrolled [n] [2]	55
Procedure and Follow-up visit data available [% (n/N)]	N=55
Procedure	100.0% (55/55)
Discharge	96.4% (53/55)
30 Day [3]	96.4% (53/55)
3 Month	87.3% (48/55)
6 Month	90.9% (50/55)
12 Month	83.6% (46/55)
18 Month	80.0% (44/55)
Year 2 [6]	43.6% (24/55)
Follow-up Time in Study (Days) [4]	
Mean +/- SD (N)	555.6 +/- 208.1 (55)
Median	554.0
Min, Max	4.0, 743.0
Patients Exited Study [% (n/N)]	12.7% (7/55)
<30 days	28.6% (2/7)
Patient Deceased	28.6% (2/7)
>= 30 days, < 6 month Follow-up [5]	42.9% (3/7)
Patient Refused Additional Follow-up	14.3% (1/7)
Patient Deceased	28.6% (2/7)
>= 6 month, < 12 month Follow-up	28.6% (2/7)
Patient Deceased	28.6% (2/7)
>= 12 month Follow-up	0.0% (0/55)
Time to Study Exit (Days)	
Mean +/- SD (N)	106.9 +/- 102.4 (7)
Median	60.0
Min, Max	4.0, 226.0

[1] Patient excluded by TEE during surgery. One additional patient consented and expired prior to surgery.
[2] All patients treated with Ablation procedure.
[3] Patient discharged at 35 days. Assessment performed on that day included in both discharge and 30 days summaries.
[4] Study entry to last scheduled follow-up assessment or study exit.
[5] Includes patients who exited without a 6 month follow-up visit.
[6] Four (4) additional patients have had the 2 year visit performed but entry of data into the database for these subjects was pending at the time of this report writing.

Twenty-three (23) sites were screened as potential candidates for participation in the ABLATE clinical trial. Twenty of the 23 sites were selected to participate. Twelve (12) of the sites submitted an IRB application at their institution and IRB approval was obtained at all sites. Eleven (11) of the sites with IRB approval were initiated by AtriCure but only 9 sites enrolled patients in the trial. Two (2) of the 11 sites with IRB approval initiated by AtriCure were closed due to lack of enrollment. One additional site received IRB approval but was never initiated since the study was closed due to enrollment cessation. Thus, there were 9 active sites in the ABLATE trial. These 9 sites enrolled all 55 patients (Table 17). Enrollment was distributed across the 9 enrolling sites as shown in Table 17.

Table 17: Patient Enrollment by Site

Site No.	Site Name	# Patients Enrolled	Percent of Total N=55 % (n/N)	First Subject Enrolled
		3	5.5% (3/55)	1/22/2009
		9	16.4% (9/55)	6/4/2008
		7	12.7% (7/55)	2/19/2008
		10	18.2% (10/55)	6/11/2008
		4	7.3% (4/55)	2/8/2008
		4	7.3% (4/55)	3/31/2008
		10	18.2% (10/55)	9/3/2008
		7	12.7% (7/55)	7/11/2008
		1	1.8% (1/55)	5/22/2009

5.2.2. Protocol Deviations

A summary of all protocol deviations is presented in Table 18 by major categories. Although not desirable, it is recognized that protocol deviations occur in all clinical studies and a review of the type and frequency of the deviations is necessary to understand whether the deviations affect the scientific integrity and clinical conclusions drawn from the study.

Table 19 highlights the deviations based on follow-up interval. It should be highlighted that there were NO deviations associated with informed consent process and only 3% of the deviations observed were related to eligibility criteria. Each of these eligibility criteria deviations has been reviewed in detail and is not believed to threaten the validity of the study outcomes.

Six subjects (eight deviations) had documented deviations related to the eligibility criteria. There was one enrollment deviation that was in a patient treated after having thoracic radiation (. This was a specific exclusion in the study but the physician documented that he believed it was in the best interest of the subject to have the procedure and therefore enrolled the individual. Two additional subjects were enrolled with eligibility criteria based on their baseline clinical status. One patient (08-04) had several eligibility deviations including LVEF <30%, NYHA Class IV, and a pre-op need for an intra-aortic balloon pump/intravenous inotropes. This patient died 5 days post procedure as the result of multi-organ failure. The subject was enrolled based on the physician belief that the procedure should be performed in the best interest of the patient. A third eligibility criterion deviation was noted in subject , who had a documented MI within 6 weeks prior to the procedure. This fact was not fully appreciated at the time of subject enrollment by the center so was documented as a deviation. This patient withdrew just after 30-day follow-up.

The remaining three individuals that had documented deviations regarding inclusion criteria were cases in which the site noted the subjects having paroxysmal AF . Subjects were required to have *permanent* atrial fibrillation which required them to have AF in which cardioversion had failed or had not been attempted (in accordance with the AHA/ACC guidelines. [Fuster 2006] At the time of enrollment, all three patients were believed to be paroxysmal based on their medical records; but their histories were also consistent with the categorization of permanent AF (cardioversion had failed or had been abandoned as an option for the patient). Each of the subjects had a long history of AF (33 mos, 26 mos and 16 mos, respectively) with documentation of enlarged left atrial dimension, one of which was significantly enlarged (3.9 cm, 4.2 cm and 7.7 cm, respectively). These are factors that are consistent with the status of a more intractable or “chronic” form of AF. Upon further scrutiny of the medical records through adjudication of their AF classification based on current HRS 2007 consensus statement terminology, it was discovered that two of the subjects would most

appropriately be categorized as persistent. These facts were discussed with the site however since these deviations had already been reported to the IRB, the site was reluctant to modify the deviation but the AF classification fields were updated to reflect persistent on the baseline CRFs.

The most common deviation type observed in the ABLATE study was a missed follow up visit or specific protocol assessments being performed outside of the protocol specified window. The protocol had very strict time windows (+ 7 days for 30 day follow-up, + 14 days for 3 and 6 month follow-up, and +/- 14 days for all later term follow-up) that were often difficult for patients as well as sites to adhere to based on personal scheduling challenges. Despite the fact that a visit was performed late, the data is still available so a protocol endpoint assessment can still be performed in the final outcome analysis. In fact there were only six incidences in which a visit was not performed at all; three at the three-month follow-up, one at the six-month follow-up and two at the twelve month follow up. Notably, the three-month follow up visit did not have an associated endpoint evaluation so this missed visit did not compromise the assessment of the study outcomes. All patients that missed the visit were available for the six-month visit and all of them received a Holter assessment for the primary endpoint evaluation at that time. The one subject that missed the six-month visit was hospitalized at another facility for a Klebsiella Urinary Tract Infection so was not able to be seen for the study. This event, coupled with an exacerbation of her CHF and recurrent pneumonia, contributed to a deconditioning that resulted in her subsequent death. This subject therefore never had a six-month assessment since she was hospitalized at that time interval. She expired during that hospitalization and her AF rhythm status was not noted. She was therefore considered to be unevaluable for the primary endpoint assessment. Finally, the two subjects that missed their one-year assessment were evaluated at the two-year time point and both had subsequent 48-hour Holter assessments performed for long-term rhythm assessment (day 836 and day 692). Therefore, except for the one subject that had expired and was not evaluable for their efficacy endpoint, all other subjects that “missed” a visit were able to have their rhythm status evaluated and have been included in the final endpoint assessment.

The concern regarding a strict follow-up time window was identified and addressed in the future clinical work. A broadened window of assessments is now included in the ABLATE AF registry study. The wider window of visits and the close surveillance of the patients by the Sponsor were efforts put in place to reduce the level of visits outside of the target window.

The second most common deviation noted in the ABLATE study was for assessments that were not performed. The most common assessments not performed were clinical pathology labs (i.e. blood work), components of the physical exam (BP) or an evaluation

of the NYHA class during a follow up visit. The physical exam components and the NYHA classification are not routinely performed during follow up unless there is some clinical adverse event that is correlated with a decline in clinical status. Training for all investigative sites has now emphasized the importance of evaluating and documenting each subject per protocol during each follow up interval for the ABLATE AF study. It should be noted that these assessments are NOT part of either a primary or secondary endpoint so these deviations do not affect study conclusions. It does supply further information on the subject overall status, however, so will continue to be emphasized as important assessments for any future clinical studies. There were also lab values that were inadvertently not performed (primarily INR) and the reason given was again associated with the fact that the labs are not routine standard of care in subjects that did not have any clinical issues. All future studies will enforce the labs to be obtained to provide further descriptions on all subject follow up status.

There were four cases in which deviations were documented as the procedure not being performed in accordance with the protocol criteria. In one case, the physician only performed the pulmonary vein isolation portion of the procedure and indicated that he did not feel that the patient required the full Maze procedure. In the remaining three cases, the physician noted that one of the required lesions was not able to be performed or completed (lesion to the mitral valve annulus was not completed in two cases, and both the right atrial appendage to the tricuspid annulus lesion and right atrial free wall appendage lesion were not completed in the other case). All subjects did undergo pulmonary vein isolation, however. Despite the fact that these four subjects had documented deviations, all of the subject data was included in the final endpoint analysis as a conservative approach

In summary, the deviations that have been noted in the ABLATE clinical study have been reviewed and are not believed to pose a risk to the study conclusions. Inclusion of all of the patients with deviations will provide the most conservative outcome evaluation for the study.

Table 18: Protocol Deviation Types

Type of Deviation	Number of Deviations	Percentage of Total Deviations
Eligibility Criteria	8	3.3
Procedure not in Compliance	4	1.7
Assessment Not Performed	63	26.4
Assessment Incomplete or not Per Protocol [1]	73	30.5
Visit outside of window	85	35.6
Visit not performed	6	2.5
Total Deviations	239	.
[1] Includes assessments performed out of time window.		

Table 19: Protocol Deviation Details

	Total N=55	
Protocol Deviations	**# of Deviations**	**% (n/N) of Pts with Deviations**
Pre-Procedure	11	14.5% (8/55)
Labs not done	1	1.8% (1/55)
Subject did not meet Inclusion/Exclusion criteria [1]	8	10.9% (6/55)
Class IV NYHA	1	1.8% (1/55)
LVEF < 30 %	1	1.8% (1/55)
MI <= 6wks prior	1	1.8% (1/55)
Need IABP or inotropes	1	1.8% (1/55)
No hx perm AF	3	5.5% (3/55)
Treated w/thoracic radiation	1	1.8% (1/55)
Other	2	3.6% (2/55)
TTE INCOMPLETE	1	1.8% (1/55)
TTE or TEE NOT DONE	1	1.8% (1/55)
Procedure	8	14.5% (8/55)
Procedural [2]	4	7.3% (4/55)
Other	4	7.3% (4/55)
DURING THE PRE-OP TEE, A LAA CLOT COULD NOT BE RULED OUT SO PRECAUTIONS WERE TAKEN. THE PATIENT WAS PLACED ON BYPASS BEFORE PERFORMING THE MAZE PROCEDURE.	1	1.8% (1/55)
NON-STUDY CLAMP UTILIZED	1	1.8% (1/55)
TEE INCOMPLETE	1	1.8% (1/55)
TEE NOT DONE	1	1.8% (1/55)
Discharge	19	29.1% (16/55)
Labs not done	2	3.6% (2/55)
ECG not done	1	1.8% (1/55)
ECG done out of time window	2	3.6% (2/55)
Other	14	25.5% (14/55)
AMIODARONE NOT STARTED IN THE HOSPITAL	1	1.8% (1/55)
AMIODARONE STOPPED EARLY	1	1.8% (1/55)
PATIENT NOT DISCHARGED ON AADS	12	21.8% (12/55)
30 Days	45	56.4% (31/55)
Visit outside of follow-up window	18	32.7% (18/55)
Labs not done	6	10.9% (6/55)
Labs done out of time window	8	14.5% (8/55)
NYHA not done	5	9.1% (5/55)
Other	8	12.7% (7/55)
AADS DISCONTINUED EARLY	2	3.6% (2/55)
BLOOD PRESSURE NOT DONE	2	3.6% (2/55)
CARDIOLOGIST D/C'ED THE AMIODARONE PRIOR TO 3 MONTHS	1	1.8% (1/55)

	Total N=55	
Protocol Deviations	**# of Deviations**	**% (n/N) of Pts with Deviations**
ECG DONE BUT NOT SENT TO CORE LAB	1	1.8% (1/55)
NO PHYSICAL EXAM	1	1.8% (1/55)
TELEPHONE CONTACT	1	1.8% (1/55)
3 Month	64	76.4% (42/55)
Missed Visit	3	5.5% (3/55)
Visit outside of follow-up window	27	49.1% (27/55)
Labs not done	12	21.8% (12/55)
ECG not done	2	3.6% (2/55)
Labs done out of time window	4	7.3% (4/55)
NYHA not done	3	5.5% (3/55)
Other	13	20.0% (11/55)
AADS NOT DISCONTINUED	8	14.5% (8/55)
B/P NOT DONE	1	1.8% (1/55)
BP OR HEART RATE NOT DONE	3	5.5% (3/55)
EKG DONE AT MD OFFICE, NOT VIA CORE LAB HOLTER	1	1.8% (1/55)
6 Month	47	61.8% (34/55)
Missed Visit	1	1.8% (1/55)
Visit outside of follow-up window	17	30.9% (17/55)
Labs not done	9	16.4% (9/55)
Labs done out of time window	3	5.5% (3/55)
ECG done out of time window	1	1.8% (1/55)
NYHA not done	2	3.6% (2/55)
Other	14	21.8% (12/55)
BLOOD PRESSURE NOT DONE	1	1.8% (1/55)
HOLTER COMPLETED WHILE ON AADS [3]	5	9.1% (5/55)
HOLTER MONITOR DONE OUT OF WINDOW	1	1.8% (1/55)
HOLTER WORN LESS THAN 24 HOURS [4]	4	7.3% (4/55)
NO PHYSICAL EXAM	1	1.8% (1/55)
PACEMAKER INTERROGATION OUT OF WINDOW	2	3.6% (2/55)
12 Month	12	21.8% (12/55)
Missed Visit	2	3.6% (2/55)
Visit outside of follow-up window	10	18.2% (10/55)
18 Month	9	16.4% (9/55)
Visit outside of follow-up window	9	16.4% (9/55)
2 Year	4	7.3% (4/55)
Visit outside of follow-up window	4	7.3% (4/55)
Long Term Follow-up Holter Monitoring deviations	20	36.4% (20/55)
Holter Monitor Not Done	9	16.4% (9/55)
Other	11	20.0% (11/55)

	Total N=55	
Protocol Deviations	**# of Deviations**	**% (n/N) of Pts with Deviations**
HOLTER WORN LESS THAN 48 HOURS [5]	11	20.0% (11/55)

[1] As documented on Inclusion/Exclusion form and/or Protocol Deviation form.
[2] Lesion set not performed per protocol.
[3] 4 patients are efficacy endpoint failures; one patient weaned from AADs late by referring cardiologist had a later Holter used to confirm primary endpoint success.
[4] Holter assessment was successful in 3 of 4 cases. Holter times were 19hrs 15 min, 23 hrs 25 min and 23hrs 35 min for these 3 patients. No episodes of AF documented for the available Holter duration.
[5] Holter was 24-36 hours in 6 cases, and >36 hours in the remaining 5 cases.

5.2.3. Baseline Information

5.2.3.1. Demographics

The subjects enrolled in the ABLATE study ranged in age from 45 to 88 with a mean age of 70.5 ±9.3 years (Table 20). The gender distribution of subjects treated in the trial is consistent with expectations regarding the population of patients with AF undergoing concomitant cardiac surgery. [Feinberg 1995] Females were adequately represented in the trial (42% 23/55).

To ensure that the primary study outcomes were not different between male and female subjects, a gender analysis was performed. The results of the gender analysis do not identify any differences in the primary safety and efficacy endpoints related to gender. Caucasians represented the majority of subjects treated in this trial (90% 50/55). This is consistent with the demographics in the communities of the enrolling sites and is a typical population undergoing cardiac surgical procedures that also have atrial fibrillation. [Yaariv 2004; Cox 1997]

Table 20: Patient Demographics

Parameter	Total N=55
Age [years]	
Mean +/- SD (N)	70.5 +/- 9.3 (55)
Median	72.0
Min, Max	45.0, 88.0
Gender [% (n/N)]	
Male	58.2% (32/55)
Female	41.8% (23/55)
Ethnic Group [% (n/N)]	
Caucasian	90.9% (50/55)
Black	3.6% (2/55)
Asian	1.8% (1/55)
Hispanic	3.6% (2/55)
Height [in]	
Mean +/- SD (N)	68.0 +/- 5.0 (55)
Median	68.0
Min, Max	54.9, 79.0
Weight [lbs]	
Mean +/- SD (N)	199.6 +/- 56.2 (55)
Median	185.0
Min, Max	113.0, 349.8
BMI	
Mean +/- SD (N)	30.1 +/- 6.9 (55)
Median	28.5
Min, Max	20.4, 47.4

5.2.3.2. AF History/Classification

Subjects in the ABLATE trial were included if they had permanent AF in accordance with the ACC/AHA guidelines published in 2006 [Gersh 2007]. This guidance describes the patient population as:

Permanent: AF in which cardioversion (electrical and/or pharmacologic) has failed or has not been attempted

As highlighted in the introduction of this Executive Summary, there is sufficient ambiguity regarding the definition of permanent AF and in fact this term is now considered obsolete in describing any subject other than those who will not have ANY further attempt, surgical, interventional or medical to regain sinus rhythm. AtriCure also recognizes that this has resulted in some significant confusion in terms of reviewing and interpreting the ABLATE study results. All subjects enrolled in the ABLATE trial were considered to be permanent by the investigator and documented as such on the eligibility Case Report Forms. Further, the Performance Goal

established for the efficacy endpoint in ABLATE utilized the surgical literature from the recognized experts in the field of AF ablation and some of these papers were utilizing the AtriCure technology.

An independent review of all subjects was performed by two recognized physician thought leaders in the area of AF; Dr. Albert Waldo of Case Western Reserve and Dr. Hugh Calkins of Johns Hopkins University. Dr. Calkins is the lead author of the 2007 HRS Consensus Statement and present chair of the committee currently revising this consensus statement. These physicians reviewed all available medical record information on all subjects and classified the subjects while being blinded to patient outcome using the currently accepted terminology outlined in the 2007 HRS Consensus Statement. A prospectively designed protocol was utilized for this review process and all results were documented on individual case report forms. A copy of the procedure and case report form is provided as well as a listing of the adjudicated AF classification in comparisons to that identified by the site is provided in **Appendix H**.

Table 21 provides a summary of the ABLATE baseline AF characteristics. The AF classification was based on the adjudication.

Table 21: Atrial Fibrillation History

Parameter	**Total N=55**
Type of AF [% (n/N)] [1]	
Paroxysmal	7.3% (4/55)
Persistent (7 days continuous)	40.0% (22/55)
Longstanding Persistent (1 year continuous)	52.7% (29/55)
History of AF > 12 months	85.5% (47/55)
Time since AF onset (months)	
Mean +/- SD (N)	61.2 +/- 49.5 (55)
Median	48.6
Percentile: 25th, 75th	20.1, 96.1
Min, Max	1.78, 188.39

[1] Based on adjudication utilizing definitions provided in Calkins, H., et al., HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation, Europace, 2007. 9(6): p. 335-7 .

There were only four cases in which the AF could be designated as paroxysmal (PAF) using the updated HRS terminology. As previously discussed, all of the subjects in ABLATE were considered permanent as outlined in the inclusion criteria for the trial. Table 22 is a summary of the justification for the categorization of permanent for the four cases of paroxysmal patients:

Table 22:Summary of Paroxysmal Patients

PAF Patient ID	Justification for Permanent	History of AF	LA Size	Site AF Class
	Subject initial diagnosis six years prior to surgery with permanent AF; placed on sotalol which has controlled the AF and then led to situation of PAF prior to surgery	Six years	5.4cm	
	Subject diagnosed with PAF four years prior to surgery; prescribed sotalol two years prior to surgery but subject having breakthrough episodes of AF that last three days	Four years	5.4cm	
	Subject diagnosed with AF many years prior to surgery; AF controlled with flecinaide	Many years prior	4.2cm	PAF
	Subject initially diagnosed with AF six years prior to surgery with no attempts at cardioversion	Six years	6.0cm	

It should be noted that although one site had identified three of their subjects as being paroxysmal and also designated them as protocol deviations (subjects the independent review of these cases determined that only one of these cases was actually paroxysmal) and the other two were more appropriately classified as persistent As highlighted previously, they remain described as deviations for the purposes of this report but are included in any non-paroxysmal subset analyses.

5.2.3.3. Medical History

The subjects enrolled in the ABLATE trial all had underlying coronary or valvular disease requiring some type of cardiac surgery procedure. Most subjects had some type of valvular heart disease (85.5%, 47/55) with most of the subjects having mitral valve disease (70.9%, 39/55) (**Table 23**). Other comorbidities reported in this population include common cardiovascular risk factors such as hyperlipidemia (65.5%, 36/55) and hypertension (70.9%, 39/55) which are also significant risks for stroke.

Table 23: Medical History and Risk Factors

	Total N=55
Parameter	**% (n/N)**
Alcohol Use	23.6% (13/55)
Other Arrhythmia	9.1% (5/55)
SICK SINUS SYNDROME	7.3% (4/55)
SVT	1.8% (1/55)
AV Node Dysfunction	1.8% (1/55)
Cardiomyopathy	9.1% (5/55)
Cancer	20.0% (11/55)
Congestive Heart Failure	34.5% (19/55)
Coronary Artery Disease	54.5% (30/55)
COPD	14.5% (8/55)
Diabetes	20.0% (11/55)
Insulin dependent	7.3% (4/55)
Endocarditis	1.8% (1/55)
Hyperlipidemia	65.5% (36/55)
Hypertension	70.9% (39/55)
Ischemic Heart Disease	14.5% (8/55)
Myocardial Infarction	7.3% (4/55)
Within last 6 weeks	1.8% (1/55)
Obesity	23.6% (13/55)
Peripheral Arterial Occlusive Disease	1.8% (1/55)
Pacemaker	12.7% (7/55)
ICD	1.8% (1/55)
Rheumatic Heart Disease	16.4% (9/55)
Smoking	5.5% (3/55)
CVA/Stroke	5.5% (3/55)
TIA	7.3% (4/55)
Valvular Heart Disease	85.5% (47/55)
Aortic Valve	45.5% (25/55)
Stenosis	38.2% (21/55)
Regurgitation/Insufficiency	14.5% (8/55)
Mitral Valve	70.9% (39/55)
Stenosis	12.7% (7/55)
Regurgitation/Insufficiency	63.6% (35/55)
Prolapse	5.5% (3/55)
Other Valve Disease (Specify)	32.7% (18/55)
PULMONARY REGURGITATION	3.6% (2/55)
TRICUSPID REGURGITATION	32.7% (18/55)
Other Cardiac History [1]	20.0% (11/55)
Patent Foramen Ovale	1.8% (1/55)

	Total N=55
Parameter	**% (n/N)**
Left Atrial Thrombus	1.8% (1/55)
Left Ventricular Hypertrophy	5.5% (3/55)
Pulmonary Hypertension	10.9% (6/55)
Other Non-Cardiac History	36.4% (20/55)

5.2.3.4. Baseline Assessments

Subjects had a standard history and physical examination as part of their baseline visit. The findings of this physical are summarized in Table 24. The NYHA classification for the subjects was indicative of what would be anticipated for this patient population with most subjects (82%) presenting with an NYHA class of either II or III. The subjects all had a stable heart rate and blood pressure on baseline exam.

Table 24: Baseline Clinical Assessment

Parameter	Total N=55
Resting HR [bpm]	
Mean +/- SD (N)	76.4 +/- 13.3 (55)
Median	76.0
Min, Max	44, 123
Systolic Resting BP [mmHg]	
Mean +/- SD (N)	133.0 +/- 19.9 (55)
Median	134.0
Min, Max	79, 190
Diastolic Resting BP [mmHg]	
Mean +/- SD (N)	73.7 +/- 11.7 (55)
Median	74.0
Min, Max	47, 101
NYHA Classification [% (n/N)]	
I	16.4% (9/55)
II	41.8% (23/55)
III	40.0% (22/55)
IV	1.8% (1/55)
[xiv]CHADs Score Risk Category	
Low Risk (score=0)	18.2% (10/55)
Medium Risk (score=1)	27.3% (15/55)
High Risk (score>=2)	54.5% (30/55)

As summarized in Table 25, all but one subject had an assessment for EF and LA thrombus performed at the time of the procedure and 50 of the 55 subjects had the LA size determined at the time of procedure. In addition, nearly half of the population (49%, 27/55) had a TTE performed prior to the surgical intervention. This exam was utilized to assess ejection fraction and left atrial size. The ejection fraction was confirmed to be within the inclusion criteria (>= 30%) with this baseline assessment. At the time of the procedure there was one subject that had an ejection fraction of 20% by TEE that was a decline from their baseline value of 30% by TTE. This subject was therefore excluded from the trial in the operating room prior to the initiation of the procedure. Since the

[xiv] **CHADS Score** is a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF);

$CHADS_2$ Score		
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age >/=75 years	1
D	Diabetes Melitus	1
S_2	Prior Stroke or TIA	2

patient was withdrawn, no follow up information on rhythm status is available on this subject. The left atrial size met the inclusion criterion (< 8 cm) both at baseline and at the time of the procedure in all 55 enrolled subjects (Note: as previously described in Table 16: Patient Accountability, one subject without a Baseline TTE who was consented for the trial was found to have an LA size > 8mm at time of procedure based on the intra operative TEE and was therefore not enrolled into the trial). It should be noted that the majority of subjects had a documented left atrial size that was greater than 5 cm, a known predictor of a poorer outcome for the treatment of AF. [Grubitzsch 2008; Gaynor 2005]

In one subject), left atrial thrombus was noted to be present at the time of the procedure. The physician believed that the patient should continue with the treatment. The investigator did however take extra precautions by putting the patient on bypass before performing any ablations.

Table 25: TTE/TEE assessment

Parameter	**Baseline TTE [1] N=55**	**Intra-procedure TEE N=55**
Assessment available [% (n/N)]	49.1% (27/55)	100.0% (55/55)
EF (%)		
Mean +/- SD (N)	57.9 +/- 10.2 (27)	50.0 +/- 10.3 (54)
Median	60.0	50.0
Min, Max	30.0, 77.0	20.0, 70.0
Left Atrial Size (cm)		
Mean +/- SD (N)	5.5 +/- 1.1 (21)	5.9 +/- 1.0 (50)
Median	5.3	6.0
Min, Max	3.8, 7.5	3.9, 7.7
>= 5 cm	61.9% (13/21)	86.0% (43/50)
Left Atrial Thrombus [% (n/N)]	0.0% (0/27)	1.8% (1/55)
[1] within 60 days of procedure		

A summary of the medications that the subjects were taking at the baseline assessment is provided in Table 26. Approximately 22% of the subjects were on some type of Class I/III AAD. In addition, a large majority of subjects were on either a beta blocker or calcium channel blocker (or both) to assist in control of their AF.

To try to protect the subjects from the risk of stroke, a large majority of subjects were receiving an anticoagulant (80%). In addition, nearly half of the subjects were taking an antiplatelet agent (41.8%, 23/55).

Table 26: Medication Summary at Baseline

Medication	Baseline N=55
Current Class I/III AADs	21.8% (12/55)
Class I A	0.0% (0/55)
Class I B	0.0% (0/55)
Class I C	5.5% (3/55)
FLECAINIDE	1.8% (1/55)
PROPAFENONE	3.6% (2/55)
Class III	16.4% (9/55)
AMIODARONE	9.1% (5/55)
SOTALOL	7.3% (4/55)
Current or Previous Cardiovascular Medications	
Anticoagulants	80.0% (44/55)
Antiplatelets	41.8% (23/55)

Baseline ECGs were performed on all subjects as part of the baseline requirements outlined in the ABLATE protocol. The ECGs were evaluated by a central core lab for consistency. The presence of atrial fibrillation at baseline was confirmed in 87.3% of the subjects.

5.2.4. Procedural Assessments

A summary of the primary surgical procedures performed is provided in Table 27. The subjects included in the ABLATE study had complex surgical procedures highlighting their significant underlying heart disease. More than 40% of the population had primary cardiac surgical procedures including a double valve, CABG and valve or CABG and double valve. An additional 40% had an isolated single valve procedure performed with their AF treatment. These subjects obviously had critical coronary or valvular heart disease and the treatment of their AF was warranted to avoid the risk mortality and stroke events.

Table 27: Summary of Surgical Procedure

	Total N=55
Parameter	**% (n/N)**
Surgical Procedure Type(s)	
CABG only	18.2% (10/55)
Valve Surgery	40.0% (22/55)
Mitral Valve Repair/Replacement	18.2% (10/55)
Aortic Valve Repair/Replacement	21.8% (12/55)
Double Valve Surgery	16.4% (9/55)
Aortic & Mitral	7.3% (4/55)
Mitral & Tricuspid	9.1% (5/55)
CABG and Valve Surgery	16.4% (9/55)
CABG + Mitral Valve Repair/Replacement	10.9% (6/55)
CABG + Aortic Valve Repair/Replacement	5.5% (3/55)
CABG + Double Valve Surgery	9.1% (5/55)
Aortic & Mitral	5.5% (3/55)
Mitral & Tricuspid	3.6% (2/55)
Any Mitral Valve Surgery	54.5% (30/55)

Despite the complex surgical procedures, the cross clamp time was acceptable with a mean value of 124.4 ± 56.4 min and a total bypass time of 172.0 ± 63.1 min (Table 28).

Table 28: Surgical Procedure Times

	Total N=55
Parameter	**% (n/N)**
Bypass Procedure	
Total Time on Cardiopulmonary Bypass (min)	
Mean +/- SD (N)	172.0 +/- 63.1 (55)
Median	164.0
Min, Max	88.0, 427.0
Total Aortic Cross Clamp Time (min)	
Mean +/- SD (N)	124.4 +/- 56.4 (55)
Median	112.0
Min, Max	42.0, 330.0

5.2.4.1. Ablation Procedure

As discussed in the background section of this Panel Pack, the MAZE IV lesion set is based upon the classic cut and sew Cox-MAZE procedure originally established by Jim Cox in the late 1980s. [Cox 2000; Cox 1996] The cut and sew surgical procedure proved to be technically challenging for cardiac surgeons and was associated with significantly longer procedure and cardiopulmonary bypass times and potentially more clinical complications as a result. In the 1990s, this procedure was modified from using a scalpel to create the "lines" to using devices that have an energy source such as radiofrequency. The goal of these other modalities was always to produce a set of lesions that mirror the set of lines in the classic cut and sew method.

The ABLATE protocol utilized the procedure described by Damiano and his colleagues as the Maze IV lesion set [Damiano 2004]. This procedure outlines the RF energy clamps being used to isolate the pulmonary veins and then being used to make a series of lesions in the left atrium and the right atrium. There are two valvular lesions (mitral valve and tricuspid valve annular lesions) that can be completed with another spot ablation modality using either cryoablation or RF energy with a system such as the AtriCure Bipolar Pen.

Physician judgment enters into the specific technique required for each lesion based on the characteristics presented to them for each specific subject. The ABLATE protocol was written with recommended surgical steps outlined but with the recognition that modifications to a specific lesion may be necessary to accommodate a particular patient anatomy or surgical constraint. This requirement is also highlighted in the FDA guidance document on surgical ablation[xv]. A summary of the Maze IV procedure is provided below, as well as specific details on each lesion performed with specifics on all subject lesions with deviations to the protocol recommended lesion set.

[xv] *Draft Guidance for Industry and FDA Staff; Clinical Study Designs for Surgical Ablation Devices for Treatment of Atrial Fibrillation; Sept 14, 2009.*

5.2.4.2. Maze Procedure Summary

The full Maze IV was able to be completed in 87% (48/55) of the population but 98% of the cohort had an attempt at the full lesion set performed (54/55). A summary of the overall procedure (Table 29) is provided as well as each subcomponent of the operation (Table 30 through Table 33).

Table 29: Ablation Procedure Summary

	Total N=55
Parameter	**% (n/N)**
Complete MAZE Procedure	87.3% (48/55)
Lesion not Completed	
Pulmonary Vein Isolation only	1.8% (1/55)
Right Atrial Ablation Lesions	7.3% (4/55)
Right Anterior freewall appendage lesion not done	7.3% (4/55)
Lesion from right atrial appendage to tricuspid annulus not done	1.8% (1/55)
Left Atrial Ablation Lesions	3.6% (2/55)
Completion lesion to mitral valve annulus not done	3.6% (2/55)

Table 30: Left Atrial Lesions

	Total N=54 [1]
Parameter	**% (n/N)**
I. Mitral Valve Connecting Lesion [2]	100.0% (54/54)
AtriCure Clamp	33.3% (18/54)
Cryo	1.9% (1/54)
AtriCure Clamp and AtriCure Pen	27.8% (15/54)
AtriCure Clamp and Cryo	29.6% (16/54)
AtriCure Clamp and Surgical (cut and sew)	7.4% (4/54)
II. Floor Line Lesion	100.0% (54/54)
AtriCure Clamp	87.0% (47/54)
AtriCure Pen	1.9% (1/54)
Surgical (cut and sew)	11.1% (6/54)
III. Roof Line Lesion	100.0% (54/54)
AtriCure Clamp	98.1% (53/54)
AtriCure Pen	1.9% (1/54)
IV. LAA Appendage to Pulmonary Vein	100.0% (54/54)
AtriCure Clamp	96.3% (52/54)
Cryo	3.7% (2/54)

[1] Patient 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 31: Right Atrial Lesions

	Total N=54 [1]
Parameter	**% (n/N)**
I. Tricuspid Valve Annulus lesion	100.0% (54/54)
AtriCure Clamp	46.3% (25/54)
AtriCure Pen	14.8% (8/54)
Surgical (cut and sew)	1.9% (1/54)
Cryo	14.8% (8/54)
AtriCure Clamp and AtriCure Pen	9.3% (5/54)
AtriCure Clamp and Cryo	11.1% (6/54)
AtriCure Clamp and Surgical (cut and sew)	1.9% (1/54)
II. Ablation of SVC / IVC	100.0% (54/54)
AtriCure Clamp	100.0% (54/54)
III. Freewall Appendage Lesion	92.6% (50/54)
AtriCure Clamp	100.0% (50/50)
IV. Right Atrial Appendage Lesion	98.1% (53/54)
AtriCure Clamp	54.7% (29/53)
AtriCure Pen	9.4% (5/53)
Cryo	18.9% (10/53)
AtriCure Clamp and AtriCure Pen	7.5% (4/53)
AtriCure Clamp and Cryo	5.7% (3/53)
AtriCure Clamp and Surgical (cut and sew)	1.9% (1/53)
Surgical (cut and sew) and Cryo	1.9% (1/53)
[1] Patient did not undergo the Maze 4 procedure.	

Table 32: Biatrial Lesion Details - Optional Procedures

	Total N=54 [1]
Parameter	**% (n/N)**
Right atrial appendage removal	1.9% (1/54)
Surgical (cut and sew)	100.0% (1/1)
Septal lesion	20.4% (11/54)
AtriCure Clamp	63.6% (7/11)
Cryo	36.4% (4/11)
[1] Patient did not undergo the Maze 4 procedure.	

Table 33 presents the summary of the left atrial appendage exclusion procedure. The appendage was excised in the majority of cases (88.9% 48/54) with the method nearly split between suturing and stapling. Exclusion was performed in the balance of the six cases with a suturing technique.

Table 33: Left Atrial Appendage Exclusion

	Total N=54 [1]
Parameter	**% (n/N)**
Left Atrial Appendage	
Excised	88.9% (48/54)
Left Atrial Appendage	
Excluded Only	11.1% (6/54)
[1] Patient did not undergo LA exclusion/excision	

5.2.4.3. Specific Lesion Details

A description of each of the lesions is presented with the details regarding any cases in which there was a deviation required. It should be noted that in one case the physician only performed the two pulmonary vein lesions as he felt, based on his medical judgment, that this subject did not require the full lesion set. This subject has been determined to be a paroxysmal form of AF and therefore is not included in the subset analysis of non-paroxysmal AF subjects presented in this panel pack. Further, this subject was not a primary efficacy success. Accordingly, there is no further need to elaborate on this subject in the detailed section regarding each lesion below. A summary of the deviations from the recommended protocol is provided in Table 34. Additional detail, including a justification for the deviation, as well as the category of AF and the Primary Success outcome for each subject provided in **Appendix I**.

Table 34: Lesion Set Details

Lesion Name	Description of Lesion	Device to be Used	Summary of Deviations
Pulmonary Vein Lesions	The MAZE IV lesion set consists of a biatrial lesions coupled with encircling lesions on the left and right atrium of each set of pulmonary veins.	AtriCure Synergy Ablation Clamp	All subjects received pulmonary vein lesions with the AtriCure Synergy Ablation System.
Box Lesion	The left atrial lesions include four contiguous lesions which are aimed at isolating any electrical activity emanating from the left atrial substrate. The superior connecting line (commonly referred to as the ROOF line), the inferior connecting line (commonly referred to as the FLOOR line) is used to join the pulmonary vein lesions to form an isolated area, known as the posterior corridor, or BOX.	ROOF and FLOOR lines: AtriCure Synergy Ablation Clamp	In six cases it was noted that the inferior (FLOOR) line was performed using a cut and sew technique during a mitral valve procedure. To gain optimal exposure during these mitral cases, the physician utilized a full incision. He utilized this incision line as the FLOOR lesion as he believed it was a safer approach to the combined procedure, thereby limiting the number of maneuvers associated with the target anatomy.. In one additional case superior lesion (ROOF) and inferior lesion (FLOOR) were performed using the AtriCure Pen rather than the AtriCure Clamp. This subject had an implanted AICD with epicardial leads and scarring that, based on the physician's judgment, precluded safe use of the AtriCure clamp in order to ensure patient safety.
Mitral Valve Annulus Lesion	A lesion which extends to the mitral valve annulus is required by the MAZE IV lesion set.	The clamp is used to start the lesion and the AtriCure Cryoablation System or the AtriCure Bipolar Pen is used to complete the lesion at the annulus of the tricuspid and mitral valve.	There was only a single deviation noted for this lesion in the cases in which a full lesion set was attempted. In this case (, the lesion was performed using cryoablation only as the physician felt the distance between the floor and annulus was limited and it was in the best interest of the patient to use cryoablation only. Notably, all other cases in this series of ABLATE subjects utilized the clamp and completed the line with the pen or cryo.
LA Appendage Lesion	A lesion extending from the Left Atrial Appendage to the pulmonary vein is performed to complete the full left atrial lesion set.	AtriCure Synergy Ablation Clamp	Two subjects ( ) had the left atrial appendage to the pulmonary vein executed with cryoablation because the practice at the time was to oversew the appendage to exclude it, which made incising the left appendage simply for clamp placement contrary to the best patient outcome.

Lesion Name	Description of Lesion	Device to be Used	Summary of Deviations
Tricuspid Valve Lesion	Four right atrial lesions are utilized in the MAZE IV procedure. This includes a lesion that extends from an incision made in the right atrium to the tricuspid annulus,	To be performed with the modality of ablation desired by the surgeon.	All subjects received the Tricuspid Valve Lesion with the appropriate modality.
SVC to IVC Lesion	The second lesion highlighted for the right side of the heart is one which is also performed using the incision in the right atrium and extends from the Superior Vena Cava to the Inferior Vena Cava.	AtriCure Synergy Ablation Clamp	All subjects received pulmonary vein lesions with the AtriCure Synergy Ablation System.
Right Atrial Free Wall Appendage Lesion	The third lesion on the right side of the heart is on the free wall of the Right Atrial Appendage. This lesion is unique because it is the only lesion that is not connected to valve, orifice, or another ablation line.	AtriCure Synergy Ablation Clamp	Besides who only had pulmonary vein isolation intended, the four other cases represented situations in which the physician reported that the corridor was too small to complete this lesion. In the investigators opinion, the corridor was small and there was not enough "atrial turf" to warrant a lesion. In all other subjects, the lesion was created with the Synergy Ablation Clamp.
Right Atrial Appendage to Tricuspid Annulus Lesion	The final right atrial lesion is made from the Right Atrial Appendage to the Tricuspid Annulus.	The ABLATE protocol highlights that this lesion should be started with the Synergy Ablation Clamp and completed at the annulus with the AtriCure Cryoablation System or the AtriCure BiPolar Pen.	There was one subject that did not have this lesion performed due to anatomical constraints.

The MAZE IV procedure was performed as recommended in 41 out of the 55 patients; with only a small percentage of the total number of lesions performed with a different technique than originally prescribed. The procedure outlines a total of ten lesions (two PV, four left and four right atrial lesions, respectively). Out of the potential 550 lesions, 24 of them were not performed as recommended for a lesion deviation rate of approximately 4%. This is not unexpected, given slight variations encountered and expected when applying surgical technique to a broad population with a variety of primary surgical requirements. Moreover, as highlighted in the FDA Guidance Document on Surgical Ablation, it is recognized that the recommended lesion set may require modification to accommodate physician and/or patient necessity. It is

most appropriate to present the efficacy results with an intention-to-treat approach with a description of each lesion that did not comply with recommended procedure. This is also the recommendation provided in the FDA Guidance document on Surgical Ablation Studies. In the single case in which the subject clearly did not receive the procedure as intended a sensitivity analysis was deemed unnecessary since the subject was already a primary efficacy failure and also was adjudicated to be paroxysmal so is not included in any analyses devoted to examining non-paroxysmal patients only. For the final labeling it would be most appropriate to report rates of adherence to the Maze IV procedure in the ABLATE trial on a patient basis (41/55, 74.5%) as well as on a lesion basis (526/550, 96%). These resulting values would be highlighted as a measure of technical performance with the AtriCure Synergy Ablation Clamp.

5.2.4.4. Confirmation of Pulmonary Vein Isolation

The ABLATE protocol outlined a requirement to confirm exit block in subjects after pulmonary vein isolation. The effectiveness of pulmonary vein isolation in the treatment group as determined by the intraoperative pacing protocol was specified as a secondary efficacy endpoint in the study. If the pacing protocol indicated successful electrical isolation of the pulmonary veins the procedure was considered successful. Table 35 shows pulmonary vein isolation details.

It should be noted that patients who were not in normal sinus rhythm and could not be safely cardioverted into normal sinus rhythm during the procedure were not able to be tested for pulmonary vein isolation. Confirmation of right pulmonary vein block was attempted in a total of 25 of the 55 subjects. Block was confirmed in all 25 of the subjects tested (100%). Confirmation of left pulmonary vein block was attempted in a total of 23 of the 55 subjects. Block was confirmed in all 23 subjects that were tested (100%).

Table 35: Pulmonary Vein Isolation

	Total N=55
Parameter	**% (n/N)**
Right Pulmonary Vein Isolation Evaluated	45.5% (25/55)
Right Pulmonary Vein Isolation Confirmed	100.0% (25/25)
Confirmed with Pacing (exit block)	56.0% (14/25)
Confirmed with Sensing (entrance block)	44.0% (11/25)
Left Pulmonary Vein Isolation Evaluated	41.8% (23/55)
Left Pulmonary Vein Isolation Confirmed	100.0% (23/23)
Confirmed with Pacing (exit block)	56.5% (13/23)
Confirmed with Sensing (entrance block)	43.5% (10/23)
Both Right & Left Pulmonary Vein Isolation Evaluated [1]	41.8% (23/55)
Both Right & Left Pulmonary Vein Isolation Confirmed	100.0% (23/23)
Confirmed with Pacing (exit block)	56.5% (13/23)
Confirmed with Sensing (entrance block)	43.5% (10/23)
[1] Includes patients evaluable on both sides.	

5.2.5. Follow-up Phase

Subjects were evaluated during the follow-up phase at discharge, thirty days, three months and six months with an added assessment of rhythm and AAD usage that was added at twelve months or greater. A long-term surveillance phase is currently ongoing with subjects having an evaluation via phone at yearly intervals starting at one year for a total of five years.

5.2.6. Medications

A summary of the medication course for patients in the ABLATE trial is presented in Table 36. The use of Class I/III antiarrhythmics (most commonly, amiodarone) was required by protocol to be maintained for the initial one to two months post-procedure and then to be weaned in an attempt to clear the medication for the efficacy endpoint evaluation at six months. The majority of patients (73.6%, 39/53 [xvi]) were treated with a Class I/III antiarrhythmic at discharge, which reduced to 66.0% of the population by one-month follow-up and then only 18.8% (9/48) by three months. One of the nine subjects remaining on AADs at 3 months had expired prior to 6-month assessment and thus was not evaluable for the primary endpoint evaluation.

[xvi] *Medication was not documented for the two subjects who died prior to discharge*

There is discrepancy in the medical records regarding the patient's medications so it is not clear whether this patient remained on amiodarone through the time of death. There is no documented evidence of atrial fibrillation in the available source documents. Of the remaining eight subjects on antiarrhythmic agents at 3 months, four were failures at 6 months due to a requirement for continuing on AADs at that time, and the remaining four were verified to be through the AAD washout period at the time of the primary endpoint rhythm evaluation, which in some cases was conducted beyond the 6 month follow-up assessment to ensure the patient was through the washout period.

At the time of the six month assessment, only 12% of the subjects (6/50) were on a Class I or III antiarrhythmic agent. Two of these six subjects were not properly weaned by the cardiologist, and therefore were sent for a second late Holter evaluation post antiarrhythmic drug washout to confirm their study success (day 630 and day 412). One of the two subjects remained a success at this later point, and is considered a success for the primary study endpoint . The second of the two subjects ultimately was put back on AADs and is therefore considered a failure for the primary endpoint. The remaining 4 subjects that remained on AADs at 6 months are considered primary efficacy failures since the proper weaning protocol had been followed in these cases. FDA and the Sponsor are in disagreement regarding the one subject maintained as a success for the primary endpoint. FDA will be including this subject as a failure for the primary endpoint in their evaluation.

Antiplatelet and anticoagulant therapy was demonstrated to be reduced over the follow-up time course. By six months the anticoagulant usage had been reduced from 73.6% (39/53) at discharge to 56% (28/50) by the six-month follow-up. There was also a decline in the usage of antiplatelet medication over the follow-up time course. The majority of subjects (84.9%, 45/53) were taking an antiplatelet at discharge and this decreased to 66% (33/50) by the six-month follow-up, which is consistent with the reduction observed in anticoagulant therapy. Reduction/elimination of anticoagulant/antiplatelet medication was not required by protocol and was left up to the discretion of the physician based on patient status. Management of individuals like those enrolled in ABLATE with their multiple comorbidities can be complex and therefore it is not appropriate to make any claims regarding stroke prevention specific to correction of their AF.

Table 36: Medication Summary across Visits

Medication	Discharge N=53	30 Day N=53	3 Month N=48	6 Month N=50
Current Class I/III AADs	73.6% (39/53)	66.0% (35/53)	18.8% (9/48)	12.0% (6/50)
Class I A	0.0% (0/53)	0.0% (0/53)	0.0% (0/48)	0.0% (0/50)
Class I B	0.0% (0/53)	0.0% (0/53)	0.0% (0/48)	0.0% (0/50)
Class I C	1.9% (1/53)	1.9% (1/53)	2.1% (1/48)	2.0% (1/50)
FLECAINIDE	1.9% (1/53)	1.9% (1/53)	2.1% (1/48)	2.0% (1/50)
Class III	71.7% (38/53)	64.2% (34/53)	16.7% (8/48)	10.0% (5/50)
AMIODARONE	66.0% (35/53)	58.5% (31/53)	12.5% (6/48)	6.0% (3/50)
SOTALOL	5.7% (3/53)	5.7% (3/53)	4.2% (2/48)	4.0% (2/50)
Current Cardiac Medications				
Anticoagulants	73.6% (39/53)	66.0% (35/53)	68.8% (33/48)	56.0% (28/50)
Antiplatelets	84.9% (45/53)	73.6% (39/53)	68.8% (33/48)	66.0% (33/50)

5.2.7. Clinical Assessments through 6 months

Clinical assessments were required for all visits performed through the six-month follow-up time point. Subjects demonstrated an improvement in their NYHA classification which was linked to the correction their coronary or valvular heart disease Table 37.

Table 37: Clinical Assessment Summary across Visits

Parameter	Discharge N=53	30 Day N=53	3 Month N=48	6 Month N=50
Time to Assessment [days]				
Mean +/- SD (N)	11.4 +/- 9.7 (53)	32.9 +/- 5.0 (53)	97.3 +/- 13.7 (48)	188.4 +/- 11.1 (50)
Median	9.0	34.0	95.5	188.0
Min, Max	3, 55	22, 50	67, 130	162, 225
NYHA Classification [% (n/N)]	Baseline (N=55)			
I	16.4% (9/55)	35.8% (19/53)	60.4% (29/48)	70.0% (35/50)
II	41.8% (23/55)	41.5% (22/53)	27.1% (13/48)	18.0% (9/50)
III	38.2% (21/55)	9.4% (5/53)	6.3% (3/48)	8.0% (4/50)
IV	0.0% (0/55)	1.9% (1/53)	0.0% (0/48)	0.0% (0/50)
Not Done	0.0% (0/55)	11.3% (6/53)	6.3% (3/48)	4.0% (2/50)

5.2.8. Long Term Clinical Assessments (12, 18, 24 months)

The ABLATE protocol requires a phone call assessment at 12 months, 18 months, 24 months and yearly for a total of five years. Table 38 presents an overview of the type of assessment performed and the results. The primary vehicle for each evaluation was via phone call. It can be seen that at this point there have been only 24 subjects evaluated at two years. As indicated in the subject disposition section of this report, only 28 subjects have reached this follow up time point and with 24 subjects having been evaluated. The

observed compliance on the long-term assessments thus far is very good at nearly 86% (24/28).

The clinical results confirm that the subjects continue to feel well, with nearly all of them having their general cardiovascular health graded as either good or very good. Further, the majority of subjects also categorize their health as good, very good or excellent when asked to compare to the prior year. This provides the confirmation that the clinical outcomes are supportive of the primary surgery as well as the concomitant Maze.

There have been only a small number of subjects that have required a cardioversion in the long-term phase (seven subjects underwent eight cardioversion attempts); two between six months and 12 months, five between 12 months and 18 months and one between 18 months and 2 years. In addition, a subsequent treatment via catheter ablation was performed in only one subject at 18 months. The patient was experiencing atrial flutter for which ablation of the cavotricuspid isthmus was performed. The patient was in atrial flutter at the 6-month assessment but with duration < 30 seconds. This patient was successfully cardioverted post catheter ablation at 18 months. All but one of the subjects with cardioversion were either in AF or on AADs at the time of the late rhythm assessment for long term follow-up evaluation and are thus included as failures in the endpoint assessment for AF free off Class I and III AADs at 12 months or later.

This low rate of cardioversion/reintervention also confirms that in this cohort of subjects with a long history of AF, these additional treatments are generally not required to maintain AF free status.

Follow up will continue to be assessed on an annual basis for five years to provide a breadth of understanding on the long term durability of the concomitant Maze procedure.

Table 38: Long Term Follow-up Assessment Summary across Visits

Parameter	12 Months N=46	18 Months N=44	2 Years N=24
Visit Type			
Phone Contact	100.0% (46/46)	93.2% (41/44)	87.5% (21/24)
MD Visit	0.0% (0/46)	6.8% (3/44)	12.5% (3/24)
Time to Assessment [days]			
Mean +/- SD (N)	369.2 +/- 17.3 (46)	547.9 +/- 14.5 (44)	727.2 +/- 9.7 (24)
Median	367.0	548.0	729.0
Min, Max	346, 435	526, 587	711, 743
Recurrence of AF Since Last Follow-up	15.2% (7/46)	20.5% (9/44)	16.7% (4/24)
General Cardiovascular Health			
Current			
Excellent	6.5% (3/46)	6.8% (3/44)	12.5% (3/24)
Very Good	52.2% (24/46)	52.3% (23/44)	37.5% (9/24)
Good	32.6% (15/46)	29.5% (13/44)	45.8% (11/24)
Fair	6.5% (3/46)	9.1% (4/44)	4.2% (1/24)
Poor	2.2% (1/46)	2.3% (1/44)	0.0% (0/24)
Compared to One Year Ago			
Excellent	26.1% (12/46)	6.8% (3/44)	12.5% (3/24)
Very Good	37.0% (17/46)	54.5% (24/44)	50.0% (12/24)
Good	26.1% (12/46)	34.1% (15/44)	33.3% (8/24)
Fair	8.7% (4/46)	2.3% (1/44)	4.2% (1/24)
Poor	2.2% (1/46)	2.3% (1/44)	0.0% (0/24)
Hospitalized	17.4% (8/46)	11.4% (5/44)	12.5% (3/24)
Reoperation/Reintervention	4.3% (2/46)	13.6% (6/44)	8.3% (2/24)
Cardioversion	4.3% (2/46)	11.4% (5/44)	4.2% (1/24)
Catheter Ablation	0.0% (0/46)	2.3% (1/44)	0.0% (0/24)
Other	0.0% (0/46)	2.3% (1/44)	4.2% (1/24)
Medication Usage			
Class I/III Antiarrhythmics	13.0% (6/46)	18.2% (8/44)	20.8% (5/24)
Class IC	2.2% (1/46)	2.3% (1/44)	0.0% (0/24)
Class III	10.9% (5/46)	15.9% (7/44)	20.8% (5/24)
Anticoagulants	56.5% (26/46)	65.9% (29/44)	66.7% (16/24)
Heart Failure	58.7% (27/46)	59.1% (26/44)	58.3% (14/24)

5.3. Safety Results

Safety information is provided based on the safety endpoints as well as the overall presentation of all reported events in the trial. The MedDRA adverse event coding dictionary was utilized to present events in a systematic fashion based on Preferred Term and System Organ Class. These summaries represent the outcome of the adjudication process. Narratives for the endpoint events as well as other significant adverse events are provided in **Appendix G**. It is appropriate to examine the events based on their attribution. A summary of the primary safety endpoint analysis is also presented in this section with the complete Bayesian Analysis report provided in **Appendix K**.

The events were determined to be either serious or non-serious as defined below and attributed to one of the following categories:

Serious Adverse Event: An adverse event is considered serious if it resulted in:

- Death
- Is life-threatening
- Resulted in persistent or significant disability or incapacity
- Required in-patient hospitalization or prolongation of existing hospitalization
- Is an important medical event which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes

Attribution of Events:

Device: An adverse event is considered to be related to the device if the patient experiences any untoward or unintended event that in the opinion of the Independent Physician Adjudicator (IPA) is considered to be related to the AtriCure Synergy Ablation System.

AF Procedure: An adverse event is considered to be related to the AF Procedure if the patient experiences any untoward or unintended event that in the opinion of the Independent Physician Adjudicator (IPA) is considered to be related to the AF Ablation procedure.

Ancillary Device: An adverse event is considered to be related to an Ancillary Device if the patient experiences any untoward or unintended event that in the opinion of the Independent Physician Adjudicator (IPA) is considered to be related to an Ancillary Device used in the procedure.

General Surgical Procedure: An adverse event is considered to be related to the General Surgical Procedure if the patient experiences any untoward or unintended event that in the opinion of the Independent Physician Adjudicator (IPA) is considered to be related to the General Surgical Procedure.

Underlying Disease/Condition: An adverse event is considered to be related to an Underlying Disease/Condition if the patient experiences any untoward or unintended

event that in the opinion of the Independent Physician Adjudicator (IPA) is considered to be related to the Underlying Disease/Condition.
Intercurrent Intervention: An adverse event is considered to be related to an Intercurrent Intervention if the patient experiences any untoward or unintended event that in the opinion of the Independent Physician Adjudicator (IPA) is considered to be related to the Intercurrent Condition.

5.3.1. Summary of Adverse Events

Table 39 provides a summary of all adjudicated events and their attribution. A complete summary of adverse events is provided in a listing format in **Appendix J**. The majority of events that have occurred through 12 months of follow-up are attributed to the general surgical procedure with 146 events out of the total 220 events reported being attributed to the primary surgical procedure more than half of these events are also considered to be serious (122 out of 220). This frequency of adverse events is expected in this patient population with multiple co-morbidities undergoing complex cardiac surgery. It is also noted that the bulk of the events occurred within the first thirty days (166/220) which would be expected for after a major surgical procedure such as cardiac surgery. The events included the expected periprocedural surgically related events such as renal failure, anemia, electrolyte imbalance and respiratory distress resulting in the need for prolonged ventilation support.

The additional events occurring during the follow up phase (additional 25%) were primarily related to the comorbidities of the patient. This is also not unexpected in this population.

Table 39: Summary of Adjudicated Adverse Events based on Attribution

	In Hospital N=55		Cumulative to 30 days N=55		Cumulative to 3 months N=55		Cumulative to 6 months N=55		Cumulative to 12 months N=55	
Parameter	**# 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**	**# of Evts**	**% (n/N) of Pts with Event**
Any Adverse Event	145	85.5% (47/55)	166	89.1% (49/55)	179	90.9% (50/55)	198	90.9% (50/55)	220	92.7% (51/55)
Investigational Device	0	0.0% (0/55)	0	0.0% (0/55)	0	0.0% (0/55)	0	0.0% (0/55)	0	0.0% (0/55)
AF Procedure	8	14.5% (8/55)	8	14.5% (8/55)	8	14.5% (8/55)	8	14.5% (8/55)	8	14.5% (8/55)
Ancillary Device	1	1.8% (1/55)	1	1.8% (1/55)	1	1.8% (1/55)	1	1.8% (1/55)	1	1.8% (1/55)
General Surgical Procedure	127	83.6% (46/55)	140	87.3% (48/55)	143	87.3% (48/55)	144	87.3% (48/55)	146	87.3% (48/55)
Other Relationship	9	10.9% (6/55)	17	20.0% (11/55)	27	27.3% (15/55)	45	41.8% (23/55)	65	54.5% (30/55)
Serious Adverse Event	74	56.4% (31/55)	84	63.6% (35/55)	93	67.3% (37/55)	106	74.5% (41/55)	122	81.8% (45/55)
Investigational Device	0	0.0% (0/55)	0	0.0% (0/55)	0	0.0% (0/55)	0	0.0% (0/55)	0	0.0% (0/55)
AF Procedure	7	12.7% (7/55)	7	12.7% (7/55)	7	12.7% (7/55)	7	12.7% (7/55)	7	12.7% (7/55)
Ancillary Device	1	1.8% (1/55)	1	1.8% (1/55)	1	1.8% (1/55)	1	1.8% (1/55)	1	1.8% (1/55)
General Surgical Procedure	61	54.5% (30/55)	67	60.0% (33/55)	69	60.0% (33/55)	70	61.8% (34/55)	72	61.8% (34/55)
Other Relationship	5	9.1% (5/55)	9	14.5% (8/55)	16	21.8% (12/55)	28	32.7% (18/55)	42	45.5% (25/55)

To fully understand the safety implication of the product/procedure to the patient and to balance the additional risk to the potential clinical benefit, it is appropriate to examine any events that were associated with the Maze procedure.

Table 40 provides an accounting of the events of interest. There are 8 events that were adjudicated to be associated with the Maze Procedure, with 7 of them being determined to be serious. In addition, there was one serious adverse event adjudicated to be associated with an ancillary device (the AtriCure Pen). All events occurred prior to hospital discharge.

Table 40: Events Adjudicated as Associated to the AF Ablation Procedure or Ancillary Device

Subject	Event Name	Adjudication	Relationship	Treatment	Primary Safety Endpoint
	Atrioventricular Block First Degree	Non-Serious AE	AF Ablation Procedure	Recovery	NO
	A-V Node Dysfunction	Serious AE	AF Ablation Procedure	PPM	NO
	A-V Node Dysfunction	Serious AE	AF Ablation Procedure	PPM	NO
	A-V Node Dysfunction	Serious AE	AF Ablation Procedure	PPM	NO
	A-V Node Dysfunction	Serious AE	AF Ablation Procedure	PPM	NO
	Cardiac Akinesis	Serious AE	Ancillary Device Related	CAB x2	NO
	Pulmonary Vein Tear (LPV)	Serious AE	AF Ablation Procedure	Suture	NO
	Torn IVC Cannulation Site	Serious AE	AF Ablation Procedure	Patch	NO
	Left Atrial Tear	Serious AE	AF Ablation Procedure	Suture	DEATH

.

5.3.2. Permanent Pacemaker Implantation

An important consideration that should be evaluated regarding the overall safety of the procedure is the need for a permanent pacemaker after the concomitant surgical ablation procedure. In the STS database analysis performed by Gammie et al. 2008 the need for permanent pacemaker implantation post Maze was the only factor that reached clinical significance after adjustment for baseline differences when compared against a population of subjects with the same surgery without a Maze add on. As highlighted previously, the Odds Ratio for postoperative pacemaker implantation was 1.26.

A summary of the pacemaker implantations is provided in Table 41. In the ABLATE series, a total of 12 subjects required the placement of a PPM within the initial 30 days post procedure (Table 41**).** Of these, four were for A-V nodal dysfunction and eight were for sinus node dysfunction.

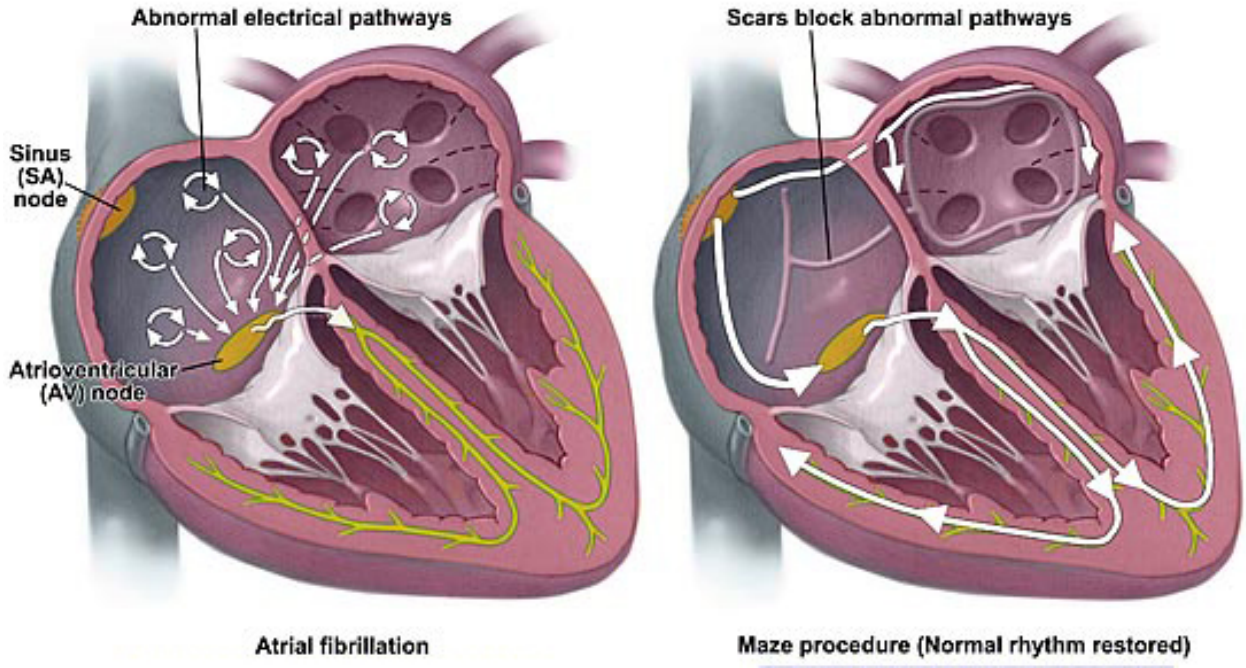
Table 41: Pacemaker Implantation across Visits

	Pre Hospitalization N=55	In Hospital Prior to Discharge N=48 [1]	Cumulative to 30 days N=48 [1]	Cumulative to 6 months N=48 [1]	Cumulative to 12 months N=48 [1]
	% [n/N]	% [n/N]	% [n/N]	% [n/N]	% [n/N]
Permanent Pacemaker Implantation, as Adjudicated	12.7% (7/55)	25.0% (12/48)	25.0% (12/48)	33.3% (16/48)	33.3% (16/48)
For AV node dysfunction		8.3% (4/48)	8.3% (4/48)	8.3% (4/48)	8.3% (4/48)
For Sinus node dysfunction		16.7% (8/48)	16.7% (8/48)	25.0% (12/48)	25.0% (12/48)

[1] Pacemaker implantation rates post procedure exclude the seven patients in whom a permanent pacemaker was present prior to the index procedure hospitalization.

It is helpful to understand the anatomical construct of the surgical procedure to appreciate any potential for correlation to the Maze procedure**.** Figure 10 depicts the lesions that are made in the Maze IV procedure and the location of the SA node as well as the AV node. It can be seen that there are no lesions that are made in close proximity to either the SA node or the AV node. Although attribution to the procedure cannot be definitively ruled out, it is difficult to correlate the need for the PPM to any damage caused by the Maze procedure. It is likely that in many subjects, the long history of AF was associated with a SA node that had been dormant for a period of time. This would take some time to resolve and for the SA node to reactivate.

Figure 10: Atrial Fibrillation vs. Normal Rhythm after Maze Procedure



Taken From MAYO Clinic Website http://www.mayoclinic.org/maze-heart-surgery/enlargeimage1780.html

Evaluations of the pacemaker implant rate by type of surgery performed were undertaken to determine if the rate of pacemaker implant varied according to either site or surgical procedure performed (Table 42). These analyses suggest, as would be expected, that the more complicated surgeries may have an increased requirement for pacemaker implantation. The sample sizes for these surgical subgroups are small, however and the variability associated with these estimates is wide. The apparent high incidence of pacemaker implant in the 10 CABG only patients is likely a small sample phenomenon since only two patients in this group required a pacemaker.

Table 42: Pacemaker Implantation through 30 days by Surgery Type

	Overall N=55	Double Valve Surgery N=14	Mitral Valve Surgery (with or without CABG) N=16	Aortic Valve Surgery (with or without CABG) N=15	CABG Only N=10
	% [n/N]	% [n/N]	% [n/N]	% [n/N]	% [n/N]
Pacemaker Pre-Procedure	12.7% (7/55)	7.1% (1/14)	12.5% (2/16)	13.3% (2/15)	20.0% (2/10)
Permanent Pacemaker Implantation within 30 days, as Adjudicated	25.0% (12/48)	38.5% (5/13)	28.6% (4/14)	7.7% (1/13)	25.0% (2/8)
For AV node dysfunction	8.3% (4/48)	15.4% (2/13)	7.1% (1/14)	0.0% (0/13)	12.5% (1/8)
For Sinus node dysfunction	16.7% (8/48)	23.1% (3/13)	21.4% (3/14)	7.7% (1/13)	12.5% (1/8)

Although the rate is higher than desired, the need for PPM varies based on the individual site experience and may be influenced by hospital practices. Further, it is also likely that it is indicative of the need for patients that have had a long history of AF. Although early data from the cut-and-sew Maze procedure would indicate that the rate is significantly lower, it should be viewed with caution since this surgical cut and sew population included paroxysmal AF subjects who potentially had functioning SA nodes. Further, the rate for PPM placement after complex surgical procedures such as those performed in Ablate without a Maze is highly variable. These references cite rates ranging from 6% to 17% depending on the type of procedure and the severity of the patient's clinical condition. [Matthews 2010; Schurr 2010; Raza 2011; Merin 2009; Emkanjoo 2008; Erdogan 2006; Cook 2005; Lewis 1998] The factors associated with the need for pacemaker implantation are multifactorial so assigning direct relationship is difficult.

5.3.3. Primary Safety Endpoint

The Primary Safety Endpoint for ABLATE has been evaluated in the 55 subjects that were enrolled and treated with the AtriCure Synergy Ablation System (Table 43). Subjects were considered to be safety failures if any of the safety events (Major Adverse Events, MAE) were observed within the initial 30 days of operation. The events consist of: Death within 30 days or beyond 30 days if considered device related, Excessive Bleeding (defined as > 2 units of RBCs with reoperation), Stroke, TIA or MI. A clinic visit was performed at 30 days to fully assess the patient for potential adverse events. All subjects were evaluable for assessment of this primary safety endpoint. The primary analysis of safety outcomes is presented with an intention to treat approach as outlined in the Statistical Analysis Plan. There were five primary safety events in the cohort including two deaths, two excessive bleeds and one stroke. None of the events were attributed to the investigational device. All but one event, a patient death, was attributed to the underlying surgical procedure that was being performed and not to the Maze

procedure. The one death that was related to the Maze portion of the procedure occurred as a result of a bleeding event that was associated with the Maze portion of the operation. A brief summary of this event is provided below.

5.3.3.1. Primary Safety Analysis

The rate for the Primary Safety Endpoint is 9.1% with the 95% one-sided Bayesian credible interval (BCI) upper bound of 17.9%. This upper bound of the BCI is below the threshold of 18.95% established for safety success.

The posterior probability that the safety rate is less than 0.1895 is

$$\Pr(q_T < q_C + \delta_S \mid \text{Trial Results}) = \mathbf{Pr(q_T < 0.1895 \mid Trial\ Results) = 0.967} > 0.95.$$

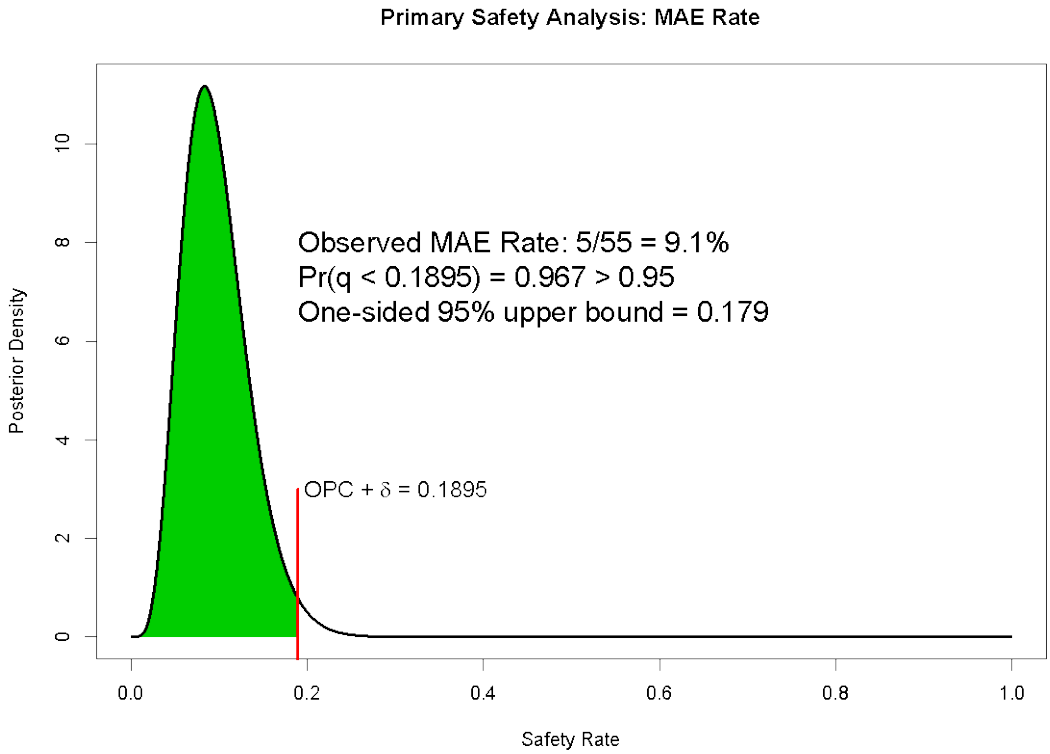
Figure 11 illustrates the Posterior Density function for the safety results and highlights that the defined threshold for safety success has been met since the Posterior Probability is greater than 95%. Therefore, the ABLATE study has demonstrated that the product meets the performance goal established for safety. There are potential criticisms of the use of the cut and sew Maze to establish a threshold for safety.

Table 43: Summary of Primary Safety Endpoint

Primary Safety Endpoint	% (n/N)
Primary Endpoint (primary endpoint events within 30 days post procedure)	9.1% (5/55) BCI = (0.00, 0.179)
Death	3.6% (2/55)
<=30 days	3.6% (2/55)
>30 days, procedure related	0.0% (0/55)
Stroke/TIA	1.8% (1/55)
Stroke (with significant permanent disability)	1.8% (1/55)
TIA	0.0% (0/55)
MI	0.0% (0/55)
Excessive Bleeding (>2 units blood and surgical intervention)	3.6% (2/55)

BCI = 95% upper one- sided Bayesian Credible Interval

Figure 11: Primary Safety Endpoint



5.4. Efficacy Results

5.4.1. Summary of Efficacy Endpoints

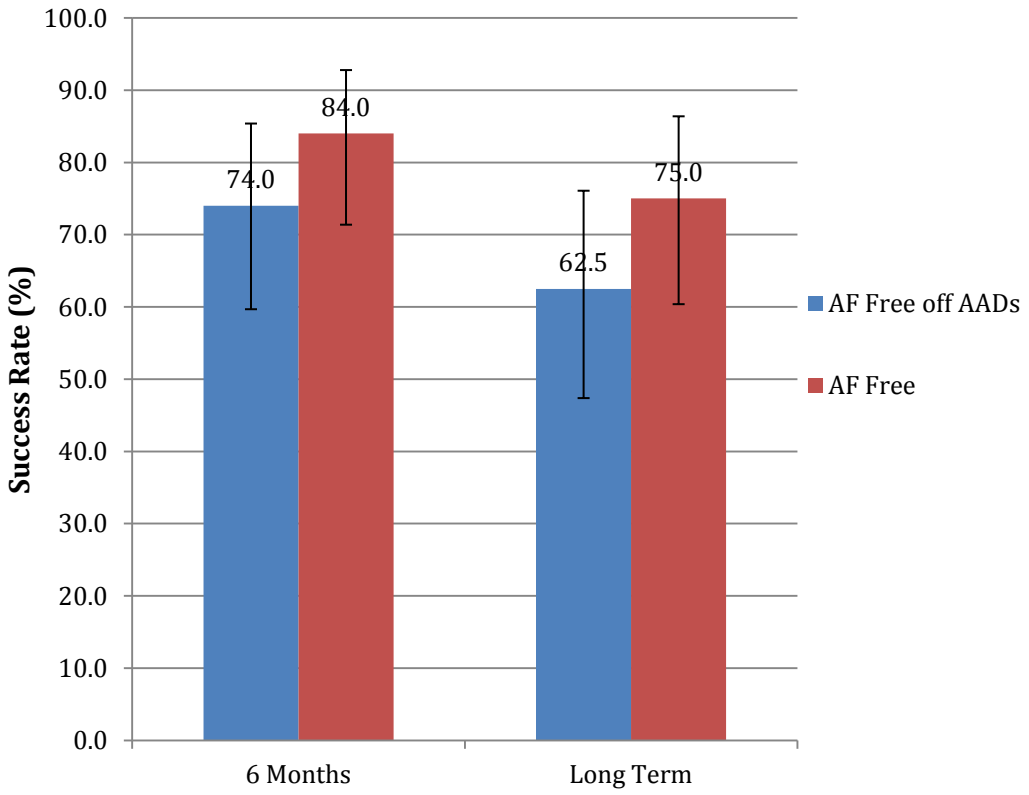
The efficacy of the procedure performed with the AtriCure Synergy Ablation System is based on the establishment of sinus rhythm at select follow up time intervals in an effort to achieve rhythm control. Efficacy was evaluated at two points in time, six months post procedure and at a long term follow up point at twelve months post procedure or thereafter. The Primary Efficacy Endpoint was defined as being AF Free and off Class I and III AADs at six months as assessed by a 24-hour Holter that was reviewed by an independent core laboratory. The state of being AF Free was also determined at a long term follow up point utilizing a 48-hour Holter that was reviewed by the same independent core lab. The rate of subjects that were AF Free irrespective of AAD usage was also calculated. All of these efficacy rates are summarized in Table 44 and are presented graphically in Figure 12.

These results show a rate of AF Free that is consistent with the literature and verifies the outcomes expected for this procedure by the medical community using a multicenter clinical trial with a consistent protocol.

Table 44: Summary of Efficacy

Efficacy Endpoint	% (n/N)
Six Months	N=50
Free of AF and off AAD	74.0% (37/50)
Free of AF [1]	84.0% (42/50)
Long Term	N=48
Free of AF and off AAD	62.5% (30/48)
Free of AF [1]	75.0% (36/48)
[1] Proportion of patients who are free of AF by holter, independent of need for meds.	

Figure 12: Efficacy Endpoint Summary



The rate of subjects AF free and off Class I and III AADs at six months post procedure was 74% (37/50). Evaluation of the proportion of subjects AF Free regardless of any requirement for antiarrhythmic drug medication at 6 months was 84%. Four (4) out of the 50 evaluable subjects were free of AF yet remained on an AAD at the time of the endpoint assessment. At the long-term assessment (median of 21 months), 62.5% of subjects were free of AF without the assistance of any AADs and 75% were AF free independent of the use of AADs. These results are consistent with the literature utilized to establish the performance goal. These results confirm the ability of the Maze add on procedure to provide a clinical benefit to the patient when considering the benefits of not being in AF.

Additional factors associated with the extent of AF are also important when assessing outcomes. The existence of other forms of atrial arrhythmias is also provided in this panel pack since the presence of these arrhythmias is an important consideration for evaluation of product performance and procedural outcomes.

5.4.2. AF Burden/ Duration on Holter or Pacemaker

A total of 41 out of the 50 evaluable subjects (82%) had no residual AF burden at the six-month follow up. One subject had < 5 min of AF on Holter and was considered a success by the Holter evaluation criteria. A second subject had the equivalent of > 5min - 1 hour of AF noted on pacemaker interrogation. The remaining seven subjects with AF by Holter or PM Interrogation were in AF for the duration of the assessment. These results confirm the efficacy results and demonstrate the ability of the procedure to effectively obliterate the AF with or without the use of any AADs.

Table 45: Atrial Fibrillation Burden (by Holter or Pacemaker)

Efficacy Evaluable at 6 month Follow-up	**N=50**
AF Burden	
= 0 min	82.0% (41/50)
<= 5 min	2.0% (1/50)
> 5 min - 1 hr	2.0% (1/50)
> 1 hr	14.0% (7/50)
Efficacy Evaluable at 12 month Follow-up or greater	**N=48**
AF Burden (initial 24 hrs or >24 - 48 hrs)	
= 0 min	77.5% (31/40)
<= 5 min	0.0% (0/40)
> 5 min - 1 hr	0.0% (0/40)
> 1 hr	22.5% (9/40)

5.4.3. Other Atrial Arrhythmias

Table 46 describes the atrial arrhythmias observed on Holter monitor or pacemaker evaluation for all available subjects. In the subjects who were assessed via pacemaker interrogation, the only atrial arrhythmia observed was atrial fibrillation in two subjects.

At the 6-month follow-up evaluation, two patients had atrial flutter for greater than five minutes (one of whom was on AADs and as such already considered a 6-month failure). No subject had atrial tachycardia through this time frame.

By the time of the long-term assessment, only one subject had atrial flutter (longest duration > 5 minutes) and one subject had atrial tachycardia (longest duration >30 seconds and <=5 minutes).

Table 46: Evaluation of Atrial Arrhythmias by Holter Monitor

	Month 6	Long Term
Parameter	**24 Hour Results**	**48 Hour Results**
Assessed with Holter or Pacemaker Interrogation	100.0% (50/50)	83.3% (40/48)
Holter [1]	88.0% (44/50)	97.5% (39/40)
Pacemaker Interrogation	12.0% (6/50)	2.5% (1/40)
Atrial Fibrillation by PMI	33.3% (2/6)	0.0% (0/1)
Rhythm [% (n/N)]		
Any Atrial Fibrillation (Yes) [% (n/N)]	18.0% (9/50)	22.5% (9/40)
Longest Run		
<= 30 sec	0.0% (0/50)	0.0% (0/40)
> 30 sec, <= 5 min	2.0% (1/50)	0.0% (0/40)
> 5 min	16.0% (8/50)	22.5% (9/40)
Any Atrial Flutter (Yes) [% (n/N)]	4.0% (2/50)	2.5% (1/40)
Longest Run		
<= 30 sec	0.0% (0/50)	0.0% (0/40)
> 30 sec, <= 5 min	0.0% (0/50)	0.0% (0/40)
> 5 min	4.0% (2/50)	2.5% (1/40)
Any Atrial Tachycardia (Yes) [% (n/N)]	38.0% (19/50)	37.5% (15/40)
Longest Run		
<= 30 sec	38.0% (19/50)	35.0% (14/40)
> 30 sec, <= 5 min	0.0% (0/50)	2.5% (1/40)
> 5 min	0.0% (0/50)	0.0% (0/40)

5.4.4. Pulmonary Vein Isolation

Since the investigational system is tightly linked to the Maze IV procedure itself it is somewhat challenging to determine the specific technical efficacy of the device without considering the procedure on the whole. The ability of the AtriCure Synergy Ablation Clamps to effectively isolate the pulmonary veins is a secondary endpoint that provides the only viable assessment of the technical performance of the product itself. PV isolation was confirmed in all subjects that were amenable to having their pulmonary vein lesions assessed. As previously discussed, confirmation of block was not always able to be performed. For the 23 subjects in whom block was evaluated, there was 100% confirmation of pulmonary vein isolation. These results confirm the ability of the investigational product to produce effective lesions.

Table 47: Summary of Pulmonary Vein Isolation

Secondary Efficacy Endpoint	% (n/N)
Both Right & Left Pulmonary Vein Isolation	
Evaluable [1]	41.8% (23/55)
Isolation Confirmed [2]	100.0% (23/23)

[1] Includes patients evaluable on both sides.
[2] Successful Pulmonary Vein Isolation on both left and right side.

5.4.5. Primary Efficacy Endpoint

The primary efficacy endpoint was defined as 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 via Holter monitor assessment (or permanent pacemaker interrogation in the case of those subjects that have a pacemaker implanted).

There were 37 subjects that met the primary efficacy endpoint (Table 48) out of the 50 evaluable subjects utilized in the primary efficacy analysis for a rate of 74%. Failures were noted to occur based on either AF identified on Holter or permanent pacemaker, the need for AAD therapy or a combination of both. In five subjects the failure was based on the subjects being on AADs. In eight other subjects the failure was based on the subjects being noted to have AF, either on Holter or based on permanent pacemaker interrogation. This resulted in the total of 13 failures based on the primary efficacy endpoint.

The resulting rate of Primary Efficacy Endpoint is 74% with the 97.5% one sided Bayesian credible interval (BCI) of [60.4%, 100%]. This lower bound of the BCI is above the threshold of 60% established for efficacy success. The posterior probability that the efficacy rate is greater than 0.6 is

$$\Pr(p_T \geq p_C - \delta_E \mid \text{Trial Results}) = \Pr(p_T > 0.6 \mid \text{Trial Results}) = 0.978 > 0.975.$$

Figure 13 illustrates the Posterior Density function for the efficacy results and highlights that the defined threshold for efficacy success has been met since the Posterior Probability is greater than 97.5%. Therefore, the ABLATE study has demonstrated that the product meets the performance goal established for efficacy. As highlighted in the study design section of this report, the Bayesian Adaptive Design is a method that allows for a study to be sized to meet the performance goal with a precise number of subjects required. Thus the efficacy outcome is near the performance goal bound. Further analyses presented in the next section of this report highlight confirm the outcomes of ABLATE.

Figure 13: AF Free and off Class I and III AADs at 6 month follow-up

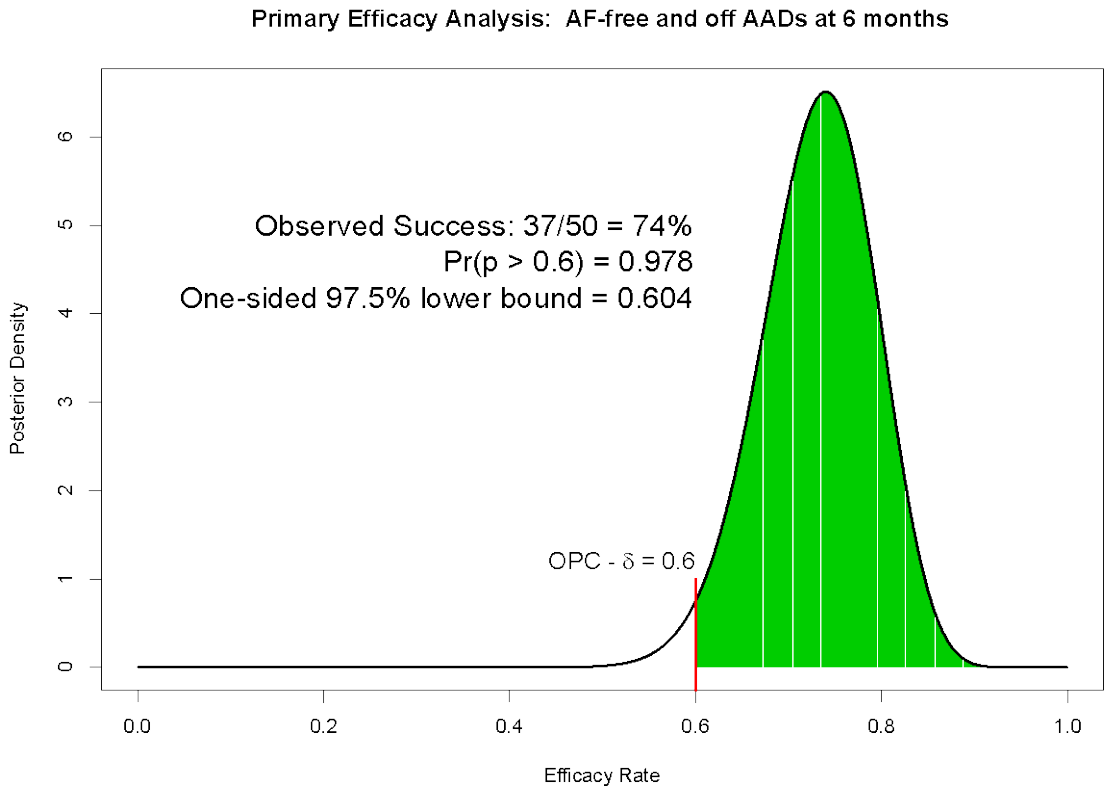


Table 48: Summary of Primary Efficacy Endpoints

Primary Efficacy Endpoint	% (n/N) [1]
Primary Success at 6 months [% (n/N)][1]	74.0% (37/50) BCI = (60.4, 1.0)
Failure by AAD [% (n/N)]	10.0% (5/50)
Failure by Holter/Pacemaker Interrogation [% (n/N)]	16.0% (8/50)

Primary Success: Proportion of patients who are free of AF and off class I and III antiarrhythmic drugs 6 months after procedure.
[1] One patient weaned from AADs late by the referring cardiologist is included as a primary endpoint success based on the outcomes at two subsequent assessment time points (day 630 and day 819).

BCI = 97.5% lower one-sided Bayesian Credible Interval for Primary Efficacy Endpoint

5.5. ABLATE Study Conclusions

5.5.1. Safety Conclusions

The Primary Safety Endpoint goal was achieved in the ABLATE clinical trial. The ABLATE clinical trial did not identify any new safety concerns. The Pacemaker Implantation Rate was within the bounds highlighted in the original clinical protocol but was higher than desired. It has been shown in literature summaries that the Pacemaker Implantation can be higher as a result of the Maze IV procedure. The safety results of ABLATE are therefore consistent with those reported in the literature. It can therefore be concluded that the ABLATE study verified the results from the literature and do not raise any new concerns for safety.

5.5.2. Efficacy Conclusions

The overall efficacy of the product has been established through the demonstration of pulmonary vein isolation using the AtriCure Synergy Ablation System. The efficacy of the Maze IV procedure performed with the AtriCure Synergy Ablation System has demonstrated results that are consistent with those reported in the literature at 74% AF Free and off Class I and III AADs and 84% AF Free independent of AADs at six months. The long term efficacy rate evaluated at a mean follow up time of 21 months was 75% AF Free and off Class I and III AADs and 62.5% AF Free independent of AADs. As highlighted in the RCTs that have been performed with the Maze IV procedure previously, being AF Free can be associated with long term clinical benefits including improved LV Function, stroke prevention and in some cases even mortality benefits. The achievement of effective rhythm control in these patients with a prolonged history of AF in the presence of coronary and/or valvular heart disease is considered a clinical benefit.

5.5.3. Overall Study Conclusions

Both the primary safety and primary efficacy endpoints met the protocol defined performance goals. The Bayesian Adaptive Design enabled these study goals to be achieved through a precise sizing of the trial. Further analyses are provided in this report to present the outcomes for the intended labeling population of persistent and longstanding persistent AF patients. As such, the next chapter will present a summary of the data available from this cohort of subjects from ABLATE as well as from the ongoing registry, ABLATE AF.

6. PROPOSED INDICATION POPULATION RESULTS

The ABLATE study met both of the pre-specified primary safety and primary efficacy study performance goals. The adaptive Bayesian study design allowed for a study to be precisely sized to reach the study goals with the minimum number of subjects. As highlighted previously in this report, the labeling is referring to persistent and longstanding persistent patients (i.e. non-paroxysmal) rather than to the antiquated term, permanent which was utilized in the protocol for ABLATE. After the ABLATE trial was completed, AtriCure established a continued registry study enrolling subjects under the same protocol of ABLATE (entitled ABLATE AF trial) with the clarification of the inclusion criteria to include non-paroxysmal AF rather than permanent AF. This registry is currently ongoing. To provide accurate data for labeling, the results for all persistent and longstanding persistent subjects from ABLATE and available ABLATE AF subjects are summarized together in this section. This analysis is intended to confirm that the conclusions of ABLATE are robust and present the proposed data to include in the labeling.

The analyses presented herein include only the subset of ABLATE and ABLATE AF trial subjects classified as non-paroxysmal. For completeness, the data are provided for each cohort separately as well as for the combined populations.

As described previously, two independent physicians who were masked to study outcomes determined the AF Classification in accordance with the current 2007 HRS guideline definitions utilizing the source documentation for each patient's baseline status. A prospectively designed protocol was utilized for this review process and all results were documented on individual case report forms. A copy of the procedure and case report form is provided in **Appendix H**. The outcome of this independent review provides the most definitive AF Classification for each of the subjects enrolled in the AtriCure IDE trials. Table 49 below outlines the available data for the non-paroxysmal subset from the trials.

Table 49: ABLATE AND ABLATE AF Data Available for Non-Paroxysmal Analysis

	ABLATE	ABLATE AF	ABLATE + ABLATE AF
Trial Enrollment (through AUG 2011)	55	32	87
Clean and monitored through 6 months	55	14	69
AF Classification			
Paroxysmal (PAF)	4	1	5
Persistent (Per)	22	2	24
Longstanding Persistent (LSP)	29	11	40
Non-paroxysmal (Per or LSP)	*51*	*13*	*64*
Evaluable for 30 day Safety Endpoint	*51*	*13*	*64*
Evaluable for 6 month Efficacy Endpoint	*46*	*11*	*57*
Not Evaluable for Primary Efficacy Endpoint			
Reason not Evaluable			
Died prior to 6 months	4	0	4
LTFU prior to 6 months	1	0	1
Not yet presented for 6 month Visit	0	2	2

6.1. ABLATE AF Study Status

ABLATE AF is an ongoing registry intended to enroll only non-paroxysmal cases. It has been expanded to new centers and currently has 15 active enrolling sites. At the time of the database extraction, 32 subjects have been enrolled with 14 subjects through the 6-month follow-up assessment point. As described above, 13 of these 14 subjects were classified as non-paroxysmal based on the independent AF classification assessment. These 13 subjects have complete data (ie: monitored and adjudicated) through 30 days with 11 of the 13 evaluable for the primary efficacy endpoint at six months and nine subjects having data reported in the database on 6-month clinic visit status. The current status for these 13 included non-paroxysmal ABLATE AF subjects is provided in Table 50.

Table 50: Non-paroxysmal ABLATE AF Patient Accountability

Patient Status	Total
Patients Consented [n]	13
Patients Enrolled [n] [1]	13
Procedure and Follow-up visit data available [% (n/N)]	N=13
Procedure	100.0% (13/13)
Discharge	100.0% (13/13)
30 Day	100.0% (13/13)
3 Month	92.3% (12/13)
6 Month or later	84.6% (11/13)
Follow-up Time in Study (Days) [1]	
Mean +/- SD (N)	244.3 +/- 87.7 (13)
Median	272.0
Min, Max	95.0, 386.0
Patients Exited Study [% (n/N)]	
=<30 days	0.0% (0/13)
> 30 days	0.0% (0/13)
[1] Study entry to last follow-up assessment or study exit.	

Table 51 provides the enrollment by site for the non-paroxysmal subset of patients in the trials. Note that the 13 non-paroxysmal ABLATE AF subjects included herein were enrolled at 3 of the sites who were participants in the ABLATE trial.

Table 51: Non-Paroxysmal Cohort Patient Enrollment by Site

Site No.	Site Name	ABLATE (N=51)	ABLATE AF (N=13)	ABLATE + ABLATE AF	Percent of Total N=64 % (n/N)
		3	-	3	4.7% (3/64)
		9	7	16	25.0% (16/64)
		7	2	9	14.1% (9/64)
		7	4	11	17.2% (11/64)
		4	-	4	6.3% (4/64)
		4	-	4	6.3% (4/64)
		9	-	9	14.1% (9/64)
		7	-	7	10.9% (7/64)
		1	-	1	1.6% (1/64)

6.1.1. Demographics and Baseline Status

Table 52 provides a summary of the demographics and baseline status of the non-paroxysmal population for ABLATE study and ABLATE AF registry. Although small numbers, the ABLATE AF group is similar to the ABLATE group. It should be noted that there has been one subject enrolled in ABLATE AF that was classified as paroxysmal and is not included in the analysis. This subject had inadvertently been entered due to an error in the screening documentation on their AF status. Since this occurrence, source documentation from medical records are supplied to confirm AF classification prior to enrollment. The ABLATE AF study is actively screening all patients to ensure that the baseline enrollment criteria are met. In this situation, the screening documentation provided for review highlighted factors that would classify them as persistent but when the source documentation was reviewed during the monitoring and adjudication, the error was discovered. This has been documented as a protocol deviation.

Table 52: Patient Demographics

Parameter	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Age [years]			
Mean +/- SD (N)	70.8 +/- 9.6 (51)	70.7 +/- 7.8 (13)	70.8 +/- 9.2 (64)
Median	73.0	72.0	72.5
Min, Max	45.0, 88.0	52.0, 81.0	45.0, 88.0
Gender [% (n/N)]			
Male	60.8% (31/51)	76.9% (10/13)	64.1% (41/64)
Female	39.2% (20/51)	23.1% (3/13)	35.9% (23/64)
Ethnic Group [% (n/N)]			
Caucasian	90.2% (46/51)	100.0% (13/13)	92.2% (59/64)
Black	3.9% (2/51)	0.0% (0/13)	3.1% (2/64)
Asian	2.0% (1/51)	0.0% (0/13)	1.6% (1/64)
Hispanic	3.9% (2/51)	0.0% (0/13)	3.1% (2/64)
Height [in]			
Mean +/- SD (N)	68.0 +/- 5.1 (51)	69.5 +/- 4.0 (13)	68.3 +/- 4.9 (64)
Median	68.0	71.7	69.0
Min, Max	54.9, 79.0	59.0, 72.5	54.9, 79.0
Weight [lbs]			
Mean +/- SD (N)	200.0 +/- 55.2 (51)	209.7 +/- 51.6 (13)	201.9 +/- 54.2 (64)
Median	185.0	213.4	187.5
Min, Max	113.0, 349.8	128.0, 320.0	113.0, 349.8
BMI			
Mean +/- SD (N)	30.1 +/- 6.6 (51)	30.4 +/- 6.5 (13)	30.2 +/- 6.6 (64)
Median	28.6	30.4	28.8
Min, Max	20.4, 47.4	19.5, 43.4	19.5, 47.4

Table 53: Atrial Fibrillation History

Parameter	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Type of AF [% (n/N)] [1]			
Persistent (7 days continuous)	43.1% (22/51)	15.4% (2/13)	37.5% (24/64)
Longstanding Persistent (1 year continuous)	56.9% (29/51)	84.6% (11/13)	62.5% (40/64)
Time since AF onset (months)			
Mean +/- SD (N)	61.7 +/- 51.1 (51)	94.9 +/- 73.6 (13)	68.4 +/- 57.3 (64)
Median	48.6	77.7	55.8
Percentile: 25th, 75th	19.5, 98.4	40.9, 127.6	19.8, 99.9
Min, Max	1.78, 188.39	11.55, 247.17	1.78, 247.17

[1] Based on HRS guidelines. Calkins, H., et al., HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace, 2007. 9(6): p. 335-79.

The subject medications at baseline are summarized in Table 54. The profile of medications taken by the two study cohorts is similar with only a limited number of subjects being on a Class I/III AAD at baseline. This is either due to the subjects already failing medical therapy or deemed not to be a candidate due to toxicity concerns in this ill population. The majority of subjects are on some form of anticoagulant and/or antiplatelet therapy for stroke prevention.

Table 54: Baseline Medications

Medication	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Current Class I/III AADs	17.6% (9/51)	7.7% (1/13)	15.6% (10/64)
Class I/III AADs			
Class I A	0.0% (0/51)	0.0% (0/51)	0.0% (0/64)
Class I B	0.0% (0/51)	0.0% (0/51)	0.0% (0/64)
Class I C	3.9% (2/51)	0.0% (0/51)	3.1% (2/64)
PROPAFENONE	3.9% (2/51)	0.0% (0/51)	3.1% (2/64)
Class III	13.7% (7/51)	7.7% (1/13)	12.5% (8/64)
AMIODARONE	9.8% (5/51)	7.7% (1/13)	9.4% (6/64)
SOTALOL	3.9% (2/51)	0.0% (0/51)	3.1% (2/64)
Anticoagulants	80.4% (41/51)	76.9% (10/13)	79.7% (51/64)
Antiplatelets	41.2% (21/51)	61.5% (8/13)	45.3% (29/64)

A summary of the various patient baseline characteristics is provided in Table 55 and Table 56. It is difficult to draw definitive conclusions from ABLATE AF since it is a relatively small population.

Table 55: Medical History and Risk Factors

	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Parameter	**% (n/N)**	**% (n/N)**	**% (n/N)**
Alcohol Use	25.5% (13/51)	38.5% (5/13)	28.1% (18/64)
Other Arrhythmia	7.8% (4/51)	38.5% (5/13)	14.1% (9/64)
SICK SINUS SYNDROME	5.9% (3/51)	7.7% (1/13)	6.3% (4/64)
SVT	2.0% (1/51)	0.0% (0/13)	1.6% (1/64)
AV Node Dysfunction	2.0% (1/51)	0.0% (0/13)	1.6% (1/64)
BRADYCARDIA	0% (0/51)	23.1% (3/13)	4.7% (3/64)
VENTRICULAR FIBRILLATION ARREST	0% (0/51)	7.7% (1/13)	1.6% (1/64)
Cardiomyopathy	7.8% (4/51)	15.4% (2/13)	9.4% (6/64)
Cancer	19.6% (10/51)	30.8% (4/13)	21.9% (14/64)
Congestive Heart Failure	37.3% (19/51)	38.5% (5/13)	37.5% (24/64)
Coronary Artery Disease	56.9% (29/51)	84.6% (11/13)	62.5% (40/64)
COPD	15.7% (8/51)	23.1% (3/13)	17.2% (11/64)
Diabetes	21.6% (11/51)	30.8% (4/13)	23.4% (15/64)
Insulin dependent	7.8% (4/51)	15.4% (2/13)	9.4% (6/64)
Endocarditis	2.0% (1/51)	0% (0/13)	1.6% (1/64)
Hyperlipidemia	68.6% (35/51)	92.3% (12/13)	73.4% (47/64)
Hypertension	76.5% (39/51)	100.0% (13/13)	81.3% (52/64)
Ischemic Heart Disease	15.7% (8/51)	30.8% (4/13)	18.8% (12/64)
Myocardial Infarction	7.8% (4/51)	15.4% (2/13)	9.4% (6/64)
Within last 6 weeks	2.0% (1/51)	0% (0/13)	1.6% (1/64)
Obesity	23.5% (12/51)	38.5% (5/13)	26.6% (17/64)
Peripheral Arterial Occlusive Disease	2.0% (1/51)	23.1% (3/13)	6.3% (4/64)
Pacemaker	9.8% (5/51)	23.1% (3/13)	12.5% (8/64)
ICD	2.0% (1/51)	7.7% (1/13)	3.1% (2/64)
Rheumatic Heart Disease	11.8% (6/51)	0% (0/13)	9.4% (6/64)
Smoking	3.9% (2/51)	53.8% (7/13)	14.1% (9/64)
CVA/Stroke	3.9% (2/51)	7.7% (1/13)	4.7% (3/64)
TIA	7.8% (4/51)	23.1% (3/13)	10.9% (7/64)

	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Parameter	**% (n/N)**	**% (n/N)**	**% (n/N)**
Valvular Heart Disease	84.3% (43/51)	76.9% (10/13)	82.8% (53/64)
Aortic Valve	43.1% (22/51)	46.2% (6/13)	43.8% (28/64)
Stenosis	39.2% (20/51)	38.5% (5/13)	39.1% (25/64)
Regurgitation/Insufficiency	11.8% (6/51)	7.7% (1/13)	10.9% (7/64)
Mitral Valve	70.6% (36/51)	69.2% (9/13)	70.3% (45/64)
Stenosis	9.8% (5/51)	7.7% (1/13)	9.4% (6/64)
Regurgitation/Insufficiency	62.7% (32/51)	61.5% (8/13)	62.5% (40/64)
Prolapse	5.9% (3/51)	0 % (0/13)	4.7% (3/64)
Other Valve Disease (Specify)	33.3% (17/51)	0 % (0/13)	26.6% (17/64)
PULMONARY REGURGITATION	3.9% (2/51)	0 % (0/13)	3.1% (2/64)
TRICUSPID REGURGITATION	33.3% (17/51)	0 % (0/13)	26.6% (17/64)
Other Cardiac History [1]	21.6% (11/51)	0 % (0/13)	17.2% (11/64)
Patent Foramen Ovale	2.0% (1/51)	0 % (0/13)	1.6% (1/64)
Left Atrial Thrombus	2.0% (1/51)	0 % (0/13)	1.6% (1/64)
Left Ventricular Hypertrophy	5.9% (3/51)	0 % (0/13)	4.7% (3/64)
Pulmonary Hypertension	11.8% (6/51)	0 % (0/13)	9.4% (6/64)
Other Non-Cardiac History	35.3% (18/51)	30.8% (4/13)	34.4% (22/64)

Table 56: Baseline Clinical Assessment

Parameter	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Resting HR [bpm]			
Mean +/- SD (N)	77.1 +/- 13.4 (51)	75.4 +/- 11.0 (13)	76.7 +/- 12.9 (64)
Median	76.0	80.0	76.0
Min, Max	44, 123	55, 91	44, 123
Systolic Resting BP [mmHg]			
Mean +/- SD (N)	133.4 +/- 20.4 (51)	139.2 +/- 23.6 (13)	134.6 +/- 21.0 (64)
Median	136.0	140.0	137.5
Min, Max	79, 190	100, 182	79, 190
Diastolic Resting BP [mmHg]			
Mean +/- SD (N)	73.9 +/- 11.4 (51)	78.2 +/- 13.9 (13)	74.8 +/- 12.0 (64)
Median	74.0	82.0	75.0
Min, Max	47, 101	55, 106	47, 106
NYHA Classification [% (n/N)]			
I	17.6% (9/51)	38.5% (5/13)	21.9% (14/64)
II	41.2% (21/51)	7.7% (1/13)	34.4% (22/64)
III	39.2% (20/51)	46.2% (6/13)	40.6% (26/64)
IV	2.0% (1/51)	0.0% (0/13)	1.6% (1/64)
Missing	0% (0/51)	7.7% (1/13)	1.6% (1/64)
[xvii]CHADs Score Risk Category			
Low Risk (score=0)	11.8% (6/51)	0.0% (0/13)	9.4% (6/64)
Medium Risk (score=1)	29.4% (15/51)	15.4% (2/13)	26.6% (17/64)
High Risk (score>=2)	58.8% (30/51)	84.6% (11/13)	64.1% (41/64)

[xvii] **CHADS Score** is a clinical prediction rule for estimating the risk of stroke in patients with non-rheumatic atrial fibrillation (AF);

$CHADS_2$ Score		
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age >/=75 years	1
D	Diabetes Melitus	1
S_2	Prior Stroke or TIA	2

The measurements of EF and LA Size are listed in Table 57 for the two groups. The two cohorts appear consistent. The LA Size is slightly lower in the ABLATE AF group but the median value is still representative of subjects with an atrial dimension that is considered large and not be amenable to a catheter based treatment, for example.

Table 57: TEE assessment

Parameter	**ABLATE N=51**	**ABLATE AF N=13**	**ABLATE + ABLATE AF N=64**
Assessment available [% (n/N)]	100.0% (51/51)	100.0% (13/13)	100.0% (64/64)
EF (%)			
Mean +/- SD (N)	49.6 +/- 10.6 (50)	52.5 +/- 8.7 (13)	50.2 +/- 10.2 (63)
Median	50.0	55.0	50.0
Min, Max	20.0, 70.0	30.0, 65.0	20.0, 70.0
Left Atrial Size (cm)			
Mean +/- SD (N)	6.0 +/- 1.0 (46)	5.4 +/- 1.3 (13)	5.9 +/- 1.1 (59)
Median	6.0	5.3	5.8
Min, Max	3.9, 7.7	3.0, 7.3	3.0, 7.7
>= 5 cm	87.0% (40/46)	61.5% (8/13)	81.4% (48/59)

6.1.2. Procedural Information

The procedural details for the non-paroxysmal population are summarized in Table 58 and Table 59. The biatrial lesion set is maintained in ABLATE AF and the lesions are performed with close scrutiny during this registry with a clinical training representative present at each of the cases to ensure protocol compliance. This has reduced the number of deviations on the lesion set and avoided any potential for confusion with regard to the details of the procedure.

Table 58: Summary of Surgical Procedure

	ABLATE N=51	**ABLATE AF N=13**	**ABLATE + ABLATE AF N=64**
Parameter	**% (n/N)**	**% (n/N)**	**% (n/N)**
Surgical Procedure Type(s)			
CABG only	19.6% (10/51)	38.5% (5/13)	23.4% (15/64)
Valve Surgery	37.3% (19/51)	15.4% (2/13)	32.8% (21/64)
Mitral Valve Repair/Replacement	17.6% (9/51)	7.7% (1/13)	15.6% (10/64)
Aortic Valve Repair/Replacement	19.6% (10/51)	7.7% (1/13)	17.2% (11/64)
Double Valve Surgery	17.6% (9/51)	7.7% (1/13)	15.6% (10/64)
Aortic & Mitral	7.8% (4/51)	0% (0/13)	6.3% (4/64)
Mitral & Tricuspid	9.8% (5/51)	7.7% (1/13)	9.4% (6/64)
CABG and Valve Surgery	15.7% (8/51)	38.5% (5/13)	20.3% (13/64)
CABG + Mitral Valve Repair/Replacement	9.8% (5/51)	15.4% (2/13)	10.9% (7/64)
CABG + Aortic Valve Repair/Replacement	5.9% (3/51)	23.1% (3/13)	9.4% (6/64)
CABG + Double Valve Surgery	9.8% (5/51)	0% (0/13)	7.8% (5/64)
Aortic & Mitral	5.9% (3/51)	0% (0/13)	4.7% (3/64)
Mitral & Tricuspid	3.9% (2/51)	0% (0/13)	3.1% (2/64)
Any Mitral Valve Surgery	54.9% (28/51)	30.8% (4/13)	50.0% (32/64)

Table 59: Surgical Procedure Times

	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Parameter	**% (n/N)**	**% (n/N)**	**% (n/N)**
Bypass Procedure			
Total Time on Cardiopulmonary Bypass (min)			
Mean +/- SD (N)	177.3 +/- 62.4 (51)	182.6 +/- 60.5 (13)	178.4 +/- 61.6 (64)
Median	166.0	171.0	166.5
Min, Max	88.0, 427.0	99.0, 275.0	88.0, 427.0
Total Aortic Cross Clamp Time (min)			
Mean +/- SD (N)	128.6 +/- 56.2 (51)	121.2 +/- 50.0 (13)	127.1 +/- 54.7 (64)
Median	116.0	120.0	118.0
Min, Max	42.0, 330.0	50.0, 225.0	42.0, 330.0

The procedural details are presented for ABLATE and ABLATE AF in **Table 60** through **Table 65**. The ABLATE AF subjects all received a complete Maze IV lesion set as prescribed by the protocol. This is in part related to the fact that in ABLATE AF a clinical representative has been at the initial cases for each site to guide them through the details of the procedure to ensure they are performing the operation as designed. This interaction is similar to the type of training that is proposed once the new labeling has been approved. The initial cases in ABLATE AF have highlighted the benefit of such training in terms of compliance with the lesion set.

Table 60: Ablation Procedure Summary

	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Parameter	**% (n/N)**	**% (n/N)**	**% (n/N)**
Ablation Procedure Summary			
Complete MAZE Procedure	88.2% (45/51)	100.0% (13/13)	90.6% (58/64)
Lesion not Completed			
Right Atrial Ablation Lesions	7.8% (4/51)	0.0% (0/13)	6.3% (4/64)
Right Anterior freewall appendage lesion not done	7.8% (4/51)	0.0% (0/13)	6.3% (4/64)
Lesion from right atrial appendage to tricuspid annulus not done	2.0% (1/51)	0.0% (0/13)	1.6% (1/64)
Left Atrial Ablation Lesions	3.9% (2/51)	0.0% (0/13)	3.1% (2/64)
Completion lesion to mitral valve annulus not done	3.9% (2/51)	0.0% (0/13)	3.1% (2/64)

Table 61: Biatrial Lesion Details - Left Atrial Lesions

	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Parameter	**% (n/N)**	**% (n/N)**	**% (n/N)**
Left Sided Lesions			
I. Mitral Valve Connecting Lesion [1]	100.0% (51/51)	100.0% (13/13)	100.0% (64/64)
AtriCure Clamp	29.4% (15/51)	46.2% (6/13)	32.8% (21/64)
Cryo	2.0% (1/51)	0% (0/13)	23.4% (15/64)
AtriCure Clamp and AtriCure Pen	29.4% (15/51)	0% (0/13)	32.8% (21/64)
AtriCure Clamp and Cryo	31.4% (16/51)	38.5% (5/13)	9.4% (6/64)
AtriCure Clamp and Surgical (cut and sew)	7.8% (4/51)	15.4% (2/13)	1.6% (1/64)
II. Floor Line Lesion	100.0% (51/51)	100.0% (13/13)	100.0% (64/64)
AtriCure Clamp	86.3% (44/51)	76.9% (10/13)	85.9% (55/64)
AtriCure Pen	2.0% (1/51)	0% (0/13)	1.6% (1/64)
Surgical (cut and sew)	11.8% (6/51)	15.4% (2/13)	12.5% (8/64)
III. Roof Line Lesion	100.0% (51/51)	100.0% (13/13)	100.0% (64/64)
AtriCure Clamp	98.0% (50/51)	100.0% (13/13)	98.4% (63/64)
AtriCure Pen	2.0% (1/51)	0% (0/13)	1.6% (1/64)
IV. LAA Appendage to Pulmonary Vein	100.0% (51/51)	100.0% (13/13)	100.0% (64/64)
AtriCure Clamp	96.1% (49/51)	100.0% (13/13)	96.9% (62/64)
Cryo	3.9% (2/51)	0% (0/13)	3.1% (2/64)

[1] 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 62: Biatrial Lesion Details - Right Atrial Lesions

	ABLATE [1] N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Parameter	**% (n/N)**	**% (n/N)**	**% (n/N)**
Right Sided Lesions			
I. Tricuspid Valve Annulus lesion	100.0% (51/51)	100.0% (13/13)	100.0% (64/64)
AtriCure Clamp	43.1% (22/51)	61.5% (8/13)	46.9% (30/64)
AtriCure Pen	15.7% (8/51)	7.7% (1/13)	7.8% (5/64)
Surgical (cut and sew)	2.0% (1/51)	0% (0/13)	9.4% (6/64)
Cryo	15.7% (8/51)	30.8% (4/13)	1.6% (1/64)
AtriCure Clamp and AtriCure Pen	9.8% (5/51)	0% (0/13)	14.1% (9/64)
AtriCure Clamp and Cryo	11.8% (6/51)	0% (0/13)	18.8% (12/64)
AtriCure Clamp and Surgical (cut and sew)	2.0% (1/51)	0% (0/13)	1.6% (1/64)
II. Ablation of SVC / IVC	100.0% (51/51)	100.0% (13/13)	100.0% (64/64)
AtriCure Clamp	100.0% (51/51)	100.0% (13/13)	100.0% (64/64)
III. Freewall Appendage Lesion	92.2% (47/51)	100.0% (13/13)	93.8% (60/64)
AtriCure Clamp	100.0% (47/47)	100.0% (13/13)	100.0% (60/60)
IV. Right Atrial Appendage Lesion	98.0% (50/51)	100.0% (13/13)	98.4% (63/64)
AtriCure Clamp	52.0% (26/50)	46.2% (6/13)	50.8% (32/63)
AtriCure Pen	10.0% (5/50)	7.7% (1/13)	7.9% (5/63)
Cryo	20.0% (10/50)	30.8% (4/13)	6.3% (4/63)
AtriCure Clamp and AtriCure Pen	8.0% (4/50)	7.7% (1/13)	1.6% (1/63)
AtriCure Clamp and Cryo	6.0% (3/50)	7.7% (1/13)	9.5% (6/63)
AtriCure Clamp and Surgical (cut and sew)	2.0% (1/50)	0% (0/13)	22.2% (14/63)
Surgical (cut and sew) and Cryo	2.0% (1/50)	0% (0/13)	1.6% (1/63)

Table 63: Biatrial Lesion Details - Optional Procedures

	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Parameter	**% (n/N)**	**% (n/N)**	**% (n/N)**
Right atrial appendage removal	2.0% (1/51)	0.0% (0/13)	1.6% (1/64)
Surgical (cut and sew)	100.0% (1/1)	0.0% (0/13)	100.0% (1/1)
Septal lesion	21.6% (11/51)	7.7% (1/13)	18.8% (12/64)
AtriCure Clamp	63.6% (7/11)		
Cryo	36.4% (4/11)		

Table 64: Left Atrial Appendage Exclusion

	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Parameter	**% (n/N)**	**% (n/N)**	**% (n/N)**
Left Atrial Appendage			
Excised	88.2% (45/51)	100.0% (13/13)	90.6% (58/64)
Excluded Only	11.8% (6/51)	0.0% (0/13)	9.4% (6/64)

Evaluation of Pulmonary Vein Isolation success is summarized in Table 65. With the aid of a clinical representative available to assist with the pacing protocol, a much higher number proportion of subjects were able to have block confirmed in ABLATE AF as compared with ABLATE (69.9% evaluated in ABLATE AF vs 43.1% evaluated in ABLATE). The ability to achieve block in all those tested confirms the technical capabilities of the product to perform effective lesions.

Table 65: Pulmonary Vein Isolation

	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Parameter	**% (n/N)**		
Right Pulmonary Vein Isolation Evaluated	47.1% (24/51)	76.9% (10/13)	53.1% (34/64)
Right Pulmonary Vein Isolation Confirmed	100.0% (24/24)	100.0% (10/10)	100.0% (34/34)
Left Pulmonary Vein Isolation Evaluated	43.1% (22/51)	69.2% (9/13)	48.4% (31/64)
Left Pulmonary Vein Isolation Confirmed	100.0% (22/22)	100.0% (9/9)	100.0% (31/31)
Both Right & Left Pulmonary Vein Isolation Evaluated [1]	43.1% (22/51)	69.2% (9/13)	48.4% (31/64)
Both Right & Left Pulmonary Vein Isolation Confirmed	100.0% (22/22)	100.0% (9/9)	100.0% (31/31)
[1] Includes patients evaluable on both sides.			

The medication changes over the follow-up course of six months are presented in Table 66 to Table 68. The protocol required the use of a Class III AAD through three months at which time it was discontinued, if possible It can also be seen that there is some reduction in the anticoagulant/antiplatelet medications noted by six months post procedure.

Table 66: Medication Summary across Visits – ABLATE

Medication	Discharge N=49	30 Day N=49	3 Month N=44	6 Month N=46
Current Class I/III AADs	77.6% (38/49)	69.4% (34/49)	18.2% (8/44)	10.9% (5/46)
Class I A	0.0% (0/49)	0.0% (0/49)	0.0% (0/44)	0.0% (0/46)
Class I B	0.0% (0/49)	0.0% (0/49)	0.0% (0/44)	0.0% (0/46)
Class I C	0.0% (0/49)	0.0% (0/49)	0.0% (0/44)	0.0% (0/46)
Class III	77.6% (38/49)	69.4% (34/49)	18.2% (8/44)	10.9% (5/46)
AMIODARONE	71.4% (35/49)	63.3% (31/49)	13.6% (6/44)	6.5% (3/46)
SOTALOL	6.1% (3/49)	6.1% (3/49)	4.5% (2/44)	4.3% (2/46)
Anticoagulants	79.6% (39/49)	71.4% (35/49)	72.7% (32/44)	58.7% (27/46)
Antiplatelets	83.7% (41/49)	71.4% (35/49)	68.2% (30/44)	65.2% (30/46)

Table 67: Medication Summary across Visits – ABLATE AF

Medication	Discharge N=13	30 Day N=13	3 Month N=12	6 Month N=9
Current Class I/III AADs	61.5% (8/13)	61.5% (8/13)	25.0% (3/12)	11.1% (1/9)
Class Ia	0.0% (0/13)	0.0% (0/13)	0.0% (0/12)	0.0% (0/9)
Class Ib	0.0% (0/13)	0.0% (0/13)	0.0% (0/12)	0.0% (0/9)
Class Ic	0.0% (0/13)	0.0% (0/13)	0.0% (0/12)	0.0% (0/9)
Class III	61.5% (8/13)	61.5% (8/13)	25.0% (3/12)	11.1% (1/9)
Anticoagulants	76.9% (10/13)	76.9% (10/13)	58.3% (7/12)	66.7% (6/9)
Antiplatelets	100.0% (13/13)	92.3% (12/13)	91.7% (11/12)	77.8% (7/9)

Table 68: Medication Summary across Visits – Combined

Table 29 Medication Summary across Visits				
Medication	**Discharge N=62**	**30 Day N=62**	**3 Month N=58**	**6 Month N=52**
Current Class I/III AADs	74.2% (46/62)	67.7% (42/62)	19.6% (11/56)	10.9% (6/55)
Class Ia	0.0% (0/62)	0.0% (0/62)	0.0% (0/56)	0.0% (0/55)
Class Ib	0.0% (0/62)	0.0% (0/62)	0.0% (0/56)	0.0% (0/55)
Class Ic	0.0% (0/62)	0.0% (0/62)	0.0% (0/56)	0.0% (0/55)
Class III	74.2% (46/62)	67.7% (42/62)	19.6% (11/56)	10.9% (6/55)
Anticoagulants	79.0% (49/62)	72.6% (45/62)	69.6% (39/56)	60.0% (33/55)
Antiplatelets	87.1% (54/62)	75.8% (47/62)	73.2% (41/56)	67.3% (37/55)

Table 69 through Table 71 present the clinical assessments for patients through the six month follow up in the ABLATE and ABLATE AF cohorts. The data demonstrate the improved clinical status of the subjects over time, indicative of both their primary surgical procedure and potentially the correction of AF.

Table 69: Clinical Assessment Summary across Visits - ABLATE

Parameter	Discharge N=49	30 Day N=49	3 Month N=44	6 Month N=46
Time to Assessment [days]				
Mean +/- SD (N)	11.8 +/- 9.9 (49)	32.9 +/- 5.2 (49)	96.9 +/- 14.1 (44)	188.2 +/- 10.9 (46)
Median	9.0	34.0	95.5	188.0
Min, Max	3, 55	22, 50	67, 130	162, 225
NYHA Classification [% (n/N)]	Baseline (N=51)			
I	17.6% (9/51)	38.8% (19/49)	59.1% (26/44)	71.7% (33/46)
II	41.2% (21/51)	38.8% (19/49)	27.3% (12/44)	17.4% (8/46)
III	37.3% (19/51)	10.2% (5/49)	6.8% (3/44)	6.5% (3/46)
IV	0.0% (0/51)	2.0% (1/49)	0.0% (0/44)	0.0% (0/46)
Not Done	0.0% (0/51)	10.2% (5/49)	6.8% (3/44)	4.3% (2/46)

Table 70: Clinical Assessment Summary across Visits - ABLATE AF

Parameter	Discharge N=13	30 Day N=13	3 Month N=12	6 Month N=9
Time to Assessment [days]				
Mean +/- SD (N)	12.2 +/- 5.8 (13)	34.9 +/- 4.8 (13)	100.3 +/- 4.5 (12)	195.9 +/- 13.3 (9)
Median	11.0	35.0	99.0	194.0
Min, Max	6, 22	27, 48	94, 109	181, 219
NYHA Classification [% (n/N)]	Baseline (N=13)			
I	38.5% (5/13)	38.5% (5/13)	83.3% (10/12)	88.9% (8/9)
II	7.7% (1/13)	23.1% (3/13)	16.7% (2/12)	11.1% (1/9)
III	46.2% (6/13)	23.1% (3/13)	0.0% (0/12)	0.0% (0/9)
IV	0.0% (0/13)	7.7% (1/13)	0.0% (0/12)	0.0% (0/9)
Not Done	7.7% (1/13)	7.7% (1/13)	0.0% (0/12)	0.0% (0/9)

Table 71: Clinical Assessment Summary across Visits- Combined

Parameter	**Discharge N=62**	**30 Day N=62**	**3 Month N=56**	**6 Month N=55**
Time to Assessment [days]				
Mean +/- SD (N)	11.9 +/- 9.2 (62)	33.3 +/- 5.2 (62)	97.6 +/- 12.7 (56)	189.4 +/- 11.5 (55)
Median	9.0	34.0	98.0	188.0
Min, Max	3, 55	22, 50	67, 130	162, 225
NYHA Classification [% (n/N)]	Baseline (N=64)			
I	21.9% (14/64)	38.7% (24/62)	64.3% (36/56)	74.5% (41/55)
II	34.4% (22/64)	35.5% (22/62)	25.0% (14/56)	16.4% (9/55)
III	39.1% (25/64)	12.9% (8/62)	5.4% (3/56)	5.5% (3/55)
IV	0.0% (0/64)	3.2% (2/62)	0.0% (0/56)	0.0% (0/55)
Not Done	1.6% (1/64)	9.7% (6/62)	5.4% (3/56)	3.6% (2/55)

6.2. Safety Outcomes

The Primary Safety Endpoints for the non-paroxysmal population are provided in Table 72. The rate of Primary Safety Endpoint is 7.8% with the combined population.

Table 72: Summary of Primary Safety Endpoint

Primary Safety Endpoint	**ABLATE N=51**	**ABLATE AF N=13**	**ABLATE + ABLATE AF N=64**
Primary Safety Endpoint	**% (n/N)**	**% (n/N)**	**% (n/N) BCI [1]**
Primary Endpoint (Acute MAE within 30 days post procedure)	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)

The ABLATE AF group did not experience any endpoint events in this initial cohort of subjects. It should be noted however that there are additional subjects that have been enrolled but the data are not fully monitored or fully adjudicated at this time. It is known however that there are two endpoint events that have occurred in the additional subjects that have been enrolled at the time of the writing of this document (n = 32 with 27 through 30 days). The specific endpoint events have been reviewed by the independent physician adjudicator and both events were attributed to the underlying primary surgical procedure and not the AF procedure or the investigational device. The data are still preliminary and complete procedural information was not yet available in the database to include in the overall summary. An extrapolated rate for the combined population can be estimated based on the additional ABLATE AF subjects (n = 26 non-paroxysmal through 30 days cohort added to the 51 ABLATE subjects would result in a total of 77 patients through 30 days) to be 9.1% (7/77). This rate remains comparable to the rate identified in ABLATE alone.

In addition to the summary of Primary Safety Adverse events, it is appropriate to summarize any event that was associated with the device or the AF procedure. A summary of the specific attribution for each event and a highlight of whether the events are Serious or Non Serious is presented in Table 73. Also included is a review of

whether the event of interest was also a Primary Safety Endpoint event. This table includes the same events described in the ABLATE Clinical Trial Report (see Chapter 5). The ABLATE AF study has not reported any device or AF Procedure related events to this point.

Table 73: Device or AF Procedure Related AEs through 6 months

	Serious Adverse Event (SAE)		Non-Serious Adverse Event		Number of Events that are also Primary Safety Endpoint Events	
	ABLATE	ABLATE AF	ABLATE	ABLATE AF	ABLATE	ABLATE AF
AF Procedure Related	3 cardiac structure damage 4 - AV Block 1 - Death	0	1 - AV Block	0	1 Death	None
Investigational Device Related	0	0	0	0	None	None
Ancillary Device Related	1 – cardiac structure damage	0	0	0	None	None

For labeling purposes it is most important to identify those device or procedure related events that are Serious. Table 74 summarizes the serious device or procedure related events for the non-paroxysmal population.[xviii] There have been no device related adverse events in the series. There are a total of seven serious procedure related events. Further, there is one event that is associated with an ancillary device that caused an indirect harm (see Chapter 5, ABLATE Clinical Trial). This should be included in the overall rate for safety events. The resulting overall rate for serious adverse events associated specifically with the addition of the Maze IV procedure in the target non-paroxysmal population is 12.5% (8/64).

[xviii] **Serious Adverse Event:** An adverse event is considered serious if it resulted in:

- Death
- Is life-threatening
- Resulted in persistent or significant disability or incapacity
- Required in-patient hospitalization or prolongation of existing hospitalization
- Is an important medical event which may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes

Table 74: Serious Device or Ablation Procedure Related Events

	ABLATE N=51		ABLATE AF N=13		ABLATE + ABLATE AF N=64	
Parameter	**# 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 Serious Device or Procedure Related Adverse Event (Includes Ancillary Device)	8	15.7% (8/51)	0	0.0% (0/13)	8	12.5% (8/64)
Investigational Device	0	0.0% (0/51)	0	0.0% (0/13)	0	0.0% (0/64)
AF Procedure	7	13.7% (7/51)	0	0.0% (0/13)	7	10.9% (7/64)
Ancillary Device	1	2.0% (1/51)	0	0.0% (0/13)	1	1.6% (1/64)

For completeness, a summary of events from the non-paroxysmal population based on attribution is provided in Table 75 for each study as well as combined.

Table 75: Summary of Adverse Events by Attribution

	ABLATE Cumulative to 30 Days N=51		ABLATE AF Cumulative to 30 Days N=13		ABLATE+ABLATE AF Cumulative to 30 Days N=64		ABLATE Cumulative to 6 mos. N=51	
Parameter	**# 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	160	92.2% (47/51)	47	84.6% (11/13)	207	90.6% (58/64)	188	94.1% (48/51)
Investigational Device	0	0.0% (0/51)	0	0.0% (0/13)	0	0.0% (0/64)	0	0.0% (0/51)
AF Procedure	8	15.7% (8/51)	0	0.0% (0/13)	8	12.5% (8/64)	8	15.7% (8/51)
Ancillary Device	1	2.0% (1/51)	0	0.0% (0/13)	1	1.6% (1/64)	1	2.0% (1/51)
General Surgical Procedure	134	90.2% (46/51)	35	84.6% (11/13)	169	89.1% (57/64)	138	90.2% (46/51)
Other Relationship	17	21.6% (11/51)	12	69.2% (9/13)	29	31.3% (20/64)	41	43.1% (22/51)
Serious Adverse Event	80	64.7% (33/51)	14	69.2% (9/13)	94	65.6% (42/64)	99	76.5% (39/51)
Investigational Device	0	0.0% (0/51)	0	0.0% (0/13)	0	0.0% (0/64)	0	0.0% (0/51)
AF Procedure	7	13.7% (7/51)	0	0.0% (0/13)	7	10.9% (7/64)	7	13.7% (7/51)
Ancillary Device	1	2.0% (1/51)	0	0.0% (0/13)	1	1.6% (1/64)	1	2.0% (1/51)
General Surgical Procedure	63	60.8% (31/51)	11	53.8% (7/13)	74	59.4% (38/64)	66	62.7% (32/51)
Other Relationship	9	15.7% (8/51)	3	23.1% (3/13)	12	17.2% (11/64)	25	33.3% (17/51)

6.2.1. Permanent Pacemaker Implantation

Table 76 and Table 77 provide the information on pacemaker implantations through 30 days for this non-paroxysmal cohort of subjects. There have been no pacemakers deemed necessary in the ABLATE AF cohort to date so the impact of ABLATE AF on pacemaker conclusions is minimal.

Table 76: Pacemaker Implantation Through 30 days

	ABLATE N=51	**ABLATE AF N=13**	**ABLATE + ABLATE AF N=64**
	% [n/N]	**% [n/N]**	**% [n/N]**
Pacemaker Pre-procedure	9.8% (5/51)	23.1% (3/13)	12.5% (8/64)
Post Procedure			
Permanent Pacemaker Implantation, as Adjudicated	26.1% (12/46)	0.0% (0/10)	21.4% (12/56)
AV node dysfunction	8.7% (4/46)	0.0% (0/10)	7.1% (4/56)
Sinus node dysfunction	17.4% (8/46)	0.0% (0/10)	14.3% (8/56)

Table 77: Pacemaker Implantation through 30 days by Surgery Type

	ABLATE N=51		**ABLATE AF N=13**		**ABLATE + ABLATE AF N=64**		
	AV Node	**SA Node**	**AV Node**	**SA Node**	**AV Node**	**SA Node**	**Total**
Surgical Procedure	**% [n/N]**	**% [n/N]**	**% [n/N]**	**% [n/N]**	**% [n/N]**	**% [n/N]**	**% [n/N]**
CABG Only	12.5% (1/8)	12.5% (1/8)	0.0% (0/4)	0.0% (0/4)	8.3% (1/12)	8.3% (1/12)	16.7% (2/12)
Aortic Valve Surgery (with or without CABG)	0.0% (0/12)	8.3% (1/12)	0.0% (0/4)	0.0% (0/4)	0.0% (0/16)	6.3% (1/16)	6.3% (1/16)
Mitral Valve Surgery (with or without CABG)	7.7% (1/13)	23.1% (3/13)	0.0% (0/1)	0.0% (0/1)	7.1% (1/14)	21.4% (3/14)	28.6% (4/14)
Double Valve Surgery (with or without CABG)	15.4% (2/13)	23.1% (3/13)	0.0% (0/1)	0.0% (0/1)	14.3% (2/14)	21.4% (3/14)	35.7% (5/14)

6.3. Efficacy Outcomes

The Primary Efficacy Outcome for the non-paroxysmal population is provided in Table 78 and Figure 14. The success rate of patients that are AF Free and off Class I and III AADs at six months in the intended population is 75.4%. This is increased to 84.2% when considering subjects being AF Free regardless of their need for AADs. The success rate for the long term assessment of AF Status is only based on ABLATE non-paroxysmal subjects since the ABLATE AF study patients have not reached the one year evaluation point yet (see Table 79). The success rate for AF Free and off Class I and III AADs at the long-term point (21 months post procedure) is 62.2%, which increases to 73.3% when success is determined as AF Free regardless of AAD dependency.

Table 78: Summary of Primary Efficacy Endpoints

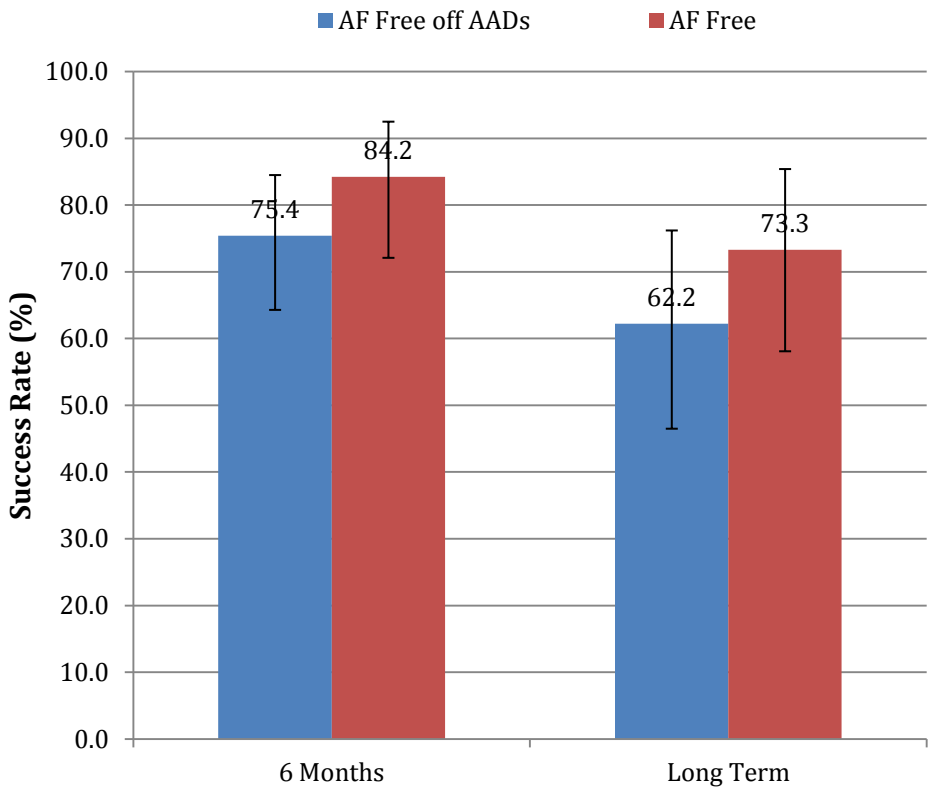
	ABLATE N=46	**ABLATE AF N=11**	**ABLATE + ABLATE AF N=57**
Primary Efficacy Endpoint	**% (n/N) [1]**	**% (n/N)**	% (n/N) [1]
Primary Success at 6 months [% (n/N)] [2][3]	73.9% (34/46)	81.8% (9/11)	75.4% (43/57)
Failure by AAD [% (n/N)]	8.7% (4/46)	9.1% (1/11)	8.8% (5/57)
Failure by Holter/Pacemaker Interrogation [% (n/N)]	17.4% (8/46)	9.1% (1/11)	15.8% (9/57)

[1] Denominators are patients who are evaluable for primary efficacy endpoint.
[2] Primary Success: Proportion of patients who are free of AF and off class I and III antiarrhythmic drugs 6 months after procedure.
[3] One patient weaned from AADs late by the referring cardiologist is included as a primary endpoint success based on the confirmation of outcomes at two subsequent assessment time points (day 630 and day 819).

Table 79: Summary of Primary and Secondary Efficacy Endpoints

	ABLATE	**ABLATE AF**	**ABLATE + ABLATE AF**
Summary of Efficacy Endpoints			
Efficacy Evaluable at 6 month Follow-up	N=46	N=11	N=57
Free of AF and off AAD	73.9% (34/46)	81.8% (9/11)	75.4% (43/57)
Free of AF	82.6% (38/46)	90.9% (10/11)	84.2% (48/57)
Efficacy Evaluable at 12 month Follow-up or greater	N=45	N=0	N=45
Free of AF and off AAD	62.2% (28/45)	-	62.2% (28/45)
Free of AF [4]	73.3% (33/45)	-	73.3% (33/45)

Figure 14: Efficacy Endpoint Summary



6.3.1. Other Efficacy Assessments

A summary of PV Isolation, AF Burden and other atrial rhythms is provided in Table 80 through Table 82 for the non-paroxysmal population. The results confirm the technical performance of the Synergy Ablation Clamp to achieve an effective lesion with 48.4% (31/64) of the cases able to have block evaluated and effective block demonstrated in 100% of these cases.

6.3.1.1. Pulmonary Vein Isolation

The rate of PV Isolation was highlighted previously as improved between ABLATE and ABLATE AF most likely due to closer scrutiny and training of the sites and physicians. This was reflected in more of the subjects being evaluated for block and therefore demonstrating the technical capabilities of the device to produce effective lesions.

Table 80: Pulmonary Vein Isolation Summary

	ABLATE N=51	ABLATE AF N=13	ABLATE + ABLATE AF N=64
Parameter	**% (n/N)**	**% (n/N)**	**% (n/N)**
Both Right & Left Pulmonary Vein Isolation Evaluated [1]	43.1% (22/51)	69.2% (9/13)	48.4% (31/64)
Both Right & Left Pulmonary Vein Isolation Confirmed	100.0% (22/22)	100.0% (9/9)	100.0% (31/31)
[1] Includes patients evaluable on both sides.			

6.3.1.2. AF Burden/Duration on Holter or Pacemaker Interrogation

A summary of the overall AF Burden is provided in Table 81 for the two cohorts. Since only one of the subjects in ABLATE AF had AF detected at six month follow-up, the results are consistent with those presented in the Chapter 5, ABLATE Clinical Trial; albeit these data now only reflect the non-paroxysmal cohort.

Table 81: Summary of Atrial Fibrillation Burden

	ABLATE	ABLATE AF	ABLATE + ABLATE AF
Efficacy Evaluable at 6 month Follow-up	N=46	N=11	N=57
AF Burden			
= 0 min	82.6% (38/46)	90.9% (10/11)	84.2% (48/57)
<= 5 min	0.0% (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)
Efficacy Evaluable at 12 month Follow-up or greater	N=45	N=0	N=45
AF Burden (initial 24 hrs or >24 - 48 hrs)			
= 0 min	76.3% (33/45)	--	76.3% (33/45)
<= 5 min	0.0% (0/45)	--	0.0% (0/45)
> 5 min - 1 hr	0.0% (0/45)	--	0.0% (0/45)
> 1 hr	20.0% (9/45)	--	20.0% (9/45)

A relevant presentation of efficacy is to summarize the outcome based on the most contemporary definition of AF Free. The 2007 HRS guideline highlights that to be AF Free, the patient should exhibit less than 30 seconds of any atrial arrhythmia including atrial fibrillation, atrial flutter or atrial tachycardia. Table 82 provides the data on the

incidence of any atrial arrhythmias and the outcome based up this contemporary definition.

Table 82: Summary of All Atrial Arrhythmias – 6 months

Parameter	ABLATE	ABLATE AF	ABLATE + ABLATE AF
Assessed with Holter or Pacemaker Interrogation	100.0% (46/46)	100.0% (11/11)	100.0% (57/57)
Holter [1]	87.0% (40/46)	90.9% (10/11)	87.7% (50/57)
Pacemaker Interrogation	13.0% (6/46)	9.1% (1/11)	12.3% (7/57)
Atrial Fibrillation by PMI	33.3% (2/6)	0.0% (0/1)	28.6% (2/7)
Time to Holter Assessment (days)			
Mean +/- SD (N)	217.0 +/- 89.5 (46)	208.0 +/- 52.4 (11)	219.4 +/- 87.1 (51)
Median	188.5	195.0	190.0
Min, Max	162.0, 630.0	142.0, 349.0	142.0, 630.0
Any Atrial Fibrillation (Yes) [% (n/N)]	17.4% (8/46)	9.1% (1/11)	15.8% (9/57)
Longest Run			
<= 30 sec	0.0% (0/46)	0.0% (0/11)	0.0% (0/57)
> 30 sec, <= 5 min	0.0% (0/46)	0.0% (0/11)	0.0% (0/57)
> 5 min	17.4% (8/46)	9.1% (1/11)	15.8% (9/57)
Any Atrial Flutter (Yes) [% (n/N)]	4.3% (2/46)	0.0% (0/11)	3.5% (2/57)
Longest Run			
<= 30 sec	0.0% (0/46)	0.0% (0/11)	0.0% (0/57)
> 30 sec, <= 5 min	0.0% (0/46)	0.0% (0/11)	0.0% (0/57)
> 5 min	4.3% (2/46)	0.0% (0/11)	3.5% (2/57)
Any Atrial Tachycardia (Yes) [% (n/N)]	34.8% (16/46)	45.5% (5/11)	36.8% (21/57)
Longest Run			
<= 30 sec	34.8% (16/46)	36.4% (4/11)	35.1% (20/57)
> 30 sec, <= 5 min	0.0% (0/46)	0.0% (0/11)	0.0% (0/57)
> 5 min	0.0% (0/46)	0.0% (0/11)	0.0% (0/57)
Unknown	0.0% (0/40)	9.1% (1/11)	1.8% (1/57)

Based on the alternate definition of success at 6 months, one additional patient in ABLATE would be considered a failure due to atrial flutter (n=1) [Note, one additional patient with atrial fibrillation was already categorized as a failure due to AAD use]. For ABLATE AF, one additional patient would conservatively be classified as a failure due reported atrial tachycardia on a pacemaker interrogation that is of unknown duration. The rate of subjects AF Free and off Class I and III AADs at 6 months post procedure remains high at 71.9% (41/57) with the contemporary definition. The rate of subjects AF Free independent of AAD dependency is 78.9% (45/57) based on the more rigorous

definition. These results continue to support that a high proportion of patients with atrial fibrillation prior to the Maze IV procedure have been converted to sinus rhythm by 6-month follow-up, with the majority of these subjects maintained in sinus rhythm without a need for class I or III AADs.

6.4. Conclusions

The outcomes of non-paroxysmal subjects is consistent with the outcomes from the total ABLATE cohort and supports the conclusions already made by the study. The summary of these non-paroxysmal subjects is more appropriate for a refined label to ensure the most accurate information in accordance with the current terminology utilized by the medical field. The data tables summarized in this section have been incorporated into the proposed labeling that is supplied as a supplement to this panel pack.

Since the product has pervasive utilization in the marketplace, it is appropriate to corroborate the results of the study further with evidence from other sources. A hierarchical model was performed which utilizes data from a variety of sources to confirm the ABLATE series and demonstrated consistency from all scientifically valid sources of data. A presentation of the Hierarchical model is provided in **Appendix L** for reference.

To determine the overall acceptability of the AtriCure System as a tool for performing the Maze IV procedure as a means of achieving rhythm control in persistent or longstanding persistent AF, a risk to benefit analysis has been completed. The results of this analysis support the need for a refined label and ability for training to be implemented in the marketplace.

7. RISKS AND BENEFITS

In this section a presentation is provided of the risks and clinical benefits of the procedure and device in order to understand the clinical utility of the product for use as a tool to perform the Maze IV procedure as an add-on to a primary cardiac surgical operation. This analysis has been performed using subjects from both ABLATE and ABLATE AF presenting with non-paroxysmal AF.

7.1. Risks of the Maze IV Add On Procedure

The best way to determine if the Maze IV component of the procedure adds any significant risk to the primary surgical operation is to compare the Maze IV safety outcomes to the outcomes of patients who are receiving the operation in the absence of the Maze IV. Gammie et al conducted such an analysis utilizing data extracted from the STS database. They compared results from patients that had a mitral valve procedure with or without a concomitant Maze procedure. Several differences between the two groups that favored the overall safety of the AF procedure were identified as highlighted in Table 3 from the article (see Figure 3: Operative Characteristics – STS Database). After adjusting for baseline characteristics, an important step because the subjects in the STS database were not randomly assigned to each treatment, the odds ratio for the need for a permanent pacemaker demonstrated a statistically higher rate in the AF group. The adjusted odds ratio was 1.26, with a slightly increased risk for pacemaker implant when a Maze IV procedure was performed. (see Figure 4: Risk-Adjusted Mortality & Morbidities – STS Database). No other increased risks were identified after adjustment for baseline characteristics.

To provide some perspective on the safety outcomes from the ABLATE/ABLATE AF cohort of non-paroxysmal subjects, the safety data from the STS 2009 report (Wilber 2010) were abstracted for comparison of the safety endpoints from the ABLATE series. Because the complete STS dataset was not available for analysis, a fully adjusted analysis could not be conducted. Complication rates are, however, summarized for each major surgical procedure reported on by the cardiac surgery centers that supply data to the STS. Since the primary surgical procedure performed is a significant contributor to the complication profile, a weighted average reference rate from STS was calculated for each safety outcome event based on the frequency of the procedures that were performed in the ABLATE/ABLATE AF trial. For any surgical procedures that are not supported by the STS database the rates of a less complicated operation were utilized. For instance, in the case of double valve plus CABG which is not supported by the STS, the rates for double valve were used instead.

Figure 15 presents a comparison of the rate of occurrence for each primary endpoint event for the ABLATE series of subjects against the weighted STS rate. The same

analysis has also been performed with ABLATE non-paroxysmal data alone which is depicted in Figure 16**.**

Figure 15: STS Comparison: ABLATE and ABLATE AF Combined
(Non-Paroxysmal Only)

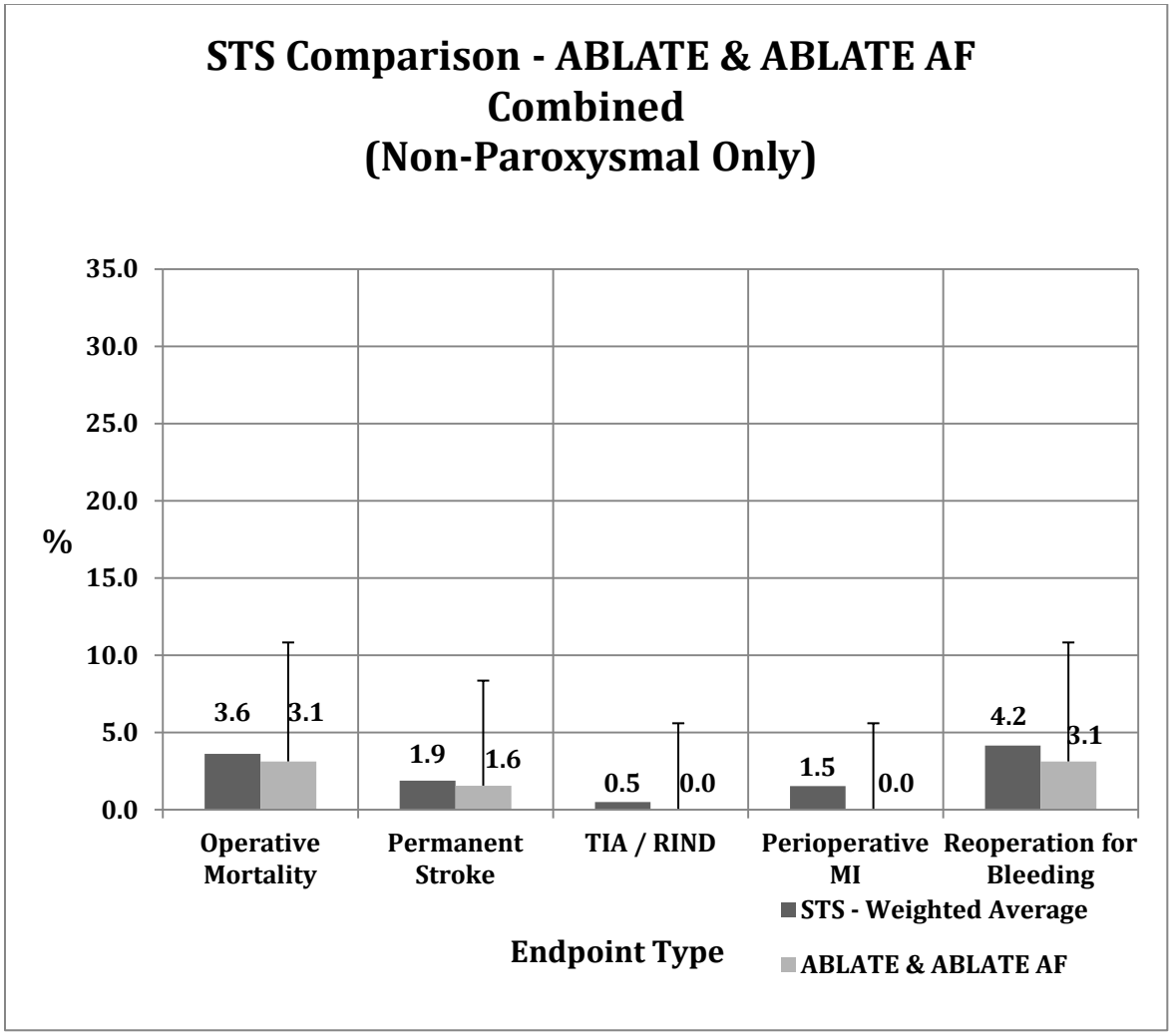
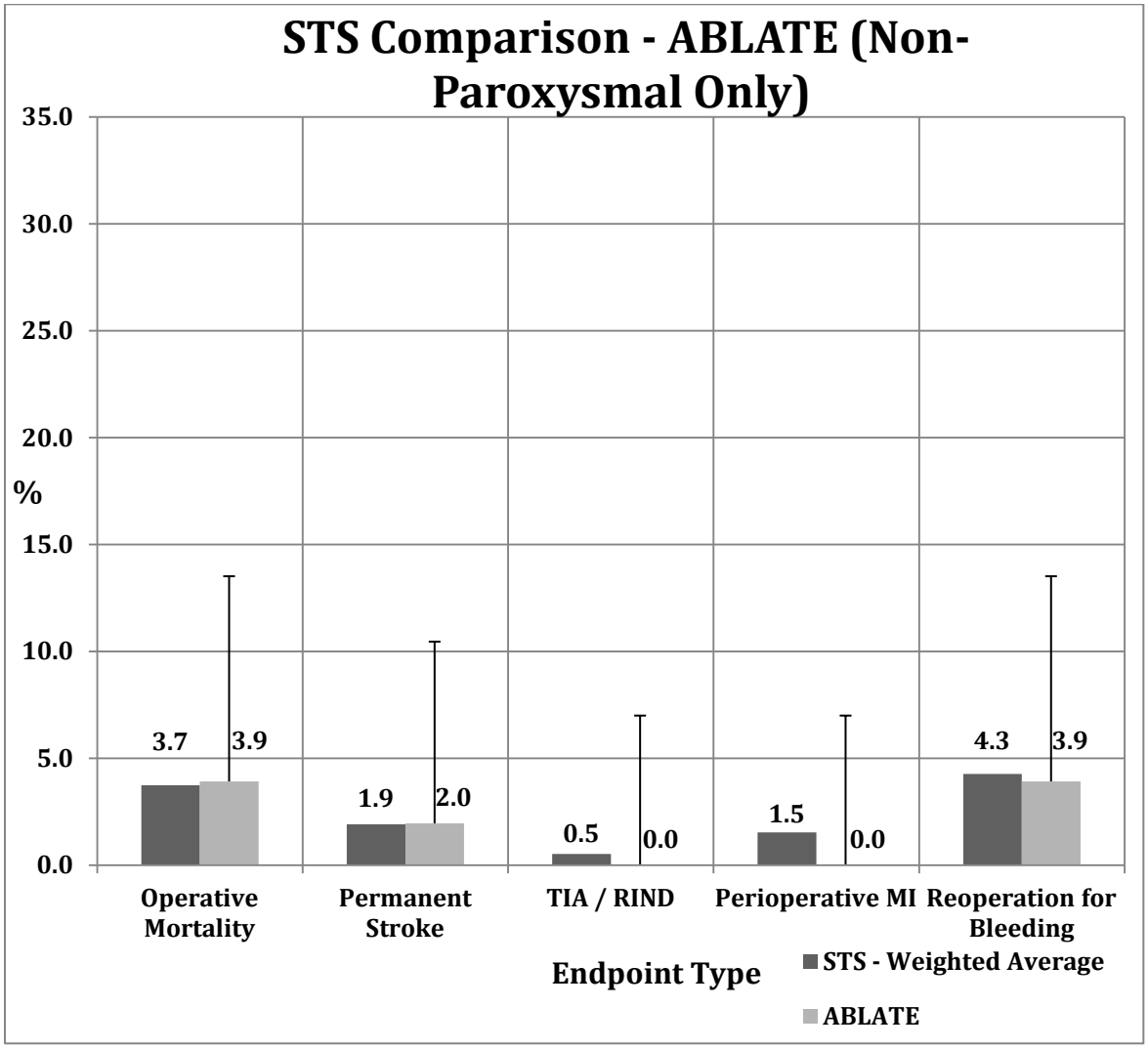


Figure 16: STS Comparison: ABLATE (Non-Paroxysmal Only)



The results highlight that the observed rates from non-paroxysmal subjects in ABLATE combined with ABLATE AF are consistent with those from the STS database rates for the primary surgery alone. Although there are limitations to this analysis (e.g., the inability to adjust for all measures of illness severity and a small sample size), the STS database provides a large body of data that is from a contemporary experience and from a cross section of surgical operators in the United States that can be used as a frame of reference when considering product safety in general terms.

Permanent pacemaker implantation rates were not directly available through the STS 2009 report, however this outcome was studied as previously described by Gammie et al. As previously presented, the need for pacemaker implantation was demonstrated in their

adjusted analysis to be the only significantly increased risk in subjects receiving a Maze add on procedure. The clinical significance of this is unknown and the question remains as to whether the clinical benefit outweighs this potential increase in pacemaker implantation.

The subjects in ABLATE that required placement of a pacemaker were all evaluated at a point later in time to assess whether the pacemaker was still necessary for rhythm support as a way to determine if there was any permanent damage to the AV or SA node. In every ABLATE subject with a permanent pacemaker implanted, the pacemaker has been shown to no longer be necessary with all patients being in an unpaced rhythm. It is recognized that subjects that have been in AF for a protracted length of time such as those enrolled in ABLATE have a sinus node that may have been dormant. A significant amount of time for recovery may be required for the SA node to be fully functional again. This recovery may take an extended period of time, necessitating the need for a pacemaker to be implanted in order for patients to be discharged from the hospital in a timely fashion. It can be concluded that at least for the cohort of subjects in ABLATE, the procedure did not cause permanent damage to either the SA or AV node. This does not obfuscate the need for the pacemaker being implanted as a bridge to patient mobilization, hospital discharge and initial rhythm stability but it does provide support to the premise that permanent damage is not caused by the product or procedure.

The need for pacemaker implantation is highly variable and may be increasing as the initiative to discharge patients earlier increases due to the financial strain on the medical system in general. It is also clinically relevant to shorten patient immobility to reduce the risk of other post surgical complications related to prolonged bedrest. The literature highlights the rate of pacemaker implantation in subjects that undergo cardiac surgery. [Matthews 2010, Schurr 2010, Raza 2011, Merin 2009, Emkanjoo 2008, Erdogan 2006, Cook 2005, Lewis 1998] For patients undergoing complex cardiac procedures without Maze IV, the rate is consistently above 6% and is reported in some settings to be as high as 17% depending upon the operation. The rate for the ABLATE cohort of non-paroxysmal subjects was 26.1% within 30 days and in the combination of ABLATE/ABLATE AF non-paroxysmal subjects was 21.4% within 30 days. This is somewhat higher than the rates referenced for the procedures without a Maze but the decision for pacemaker implantation is multifactorial and, as such, it is difficult to understand the direct implication of the rate. Pacemaker implantation is a frequently required supplemental procedure for many patients undergoing any form of cardiac surgery. This requirement needs to be offset by the potential benefits of the procedure.

7.2. Benefits

The benefit of the concomitant Maze IV procedure has been highlighted in Chapter 2 of this Executive Summary. Changing a patient's primary rhythm status from AF to sinus rhythm is believed to be a substantial benefit to physicians that care for patients with a poorly managed form of this illness. The majority of patients achieve restoration of sinus rhythm using the Maze IV procedure as a supplement to an open cardiac surgical operation and maintain sinus rhythm for an extended duration. This benefit has also shown to be achieved with minimal added risk to the procedure.

There have been a number of articles that have attempted to determine if the benefit of this procedure translates into other clinical advantages such as a reduction in mortality. Randomized controlled trials of RF ablation technology have compared patients with AF at baseline receiving a concomitant Maze to those with no AF correction added to the procedure. All studies demonstrated stroke reduction at a long-term follow-up of five to ten years post surgery.

These studies provide strong evidence that correcting AF is translated into clinical benefits ranging from improvement in symptoms, improvement in LV function, reduced risk of stroke and in some studies even a demonstration of improved survival [Denekd 2002; Abreu Filho 2005; Doukas 2005; Chevalier 2009]. A recent meta-analysis looking at both RCTs and Non-RCTs concluded that restoration of sinus rhythm conferred protection against stroke when examined over an extended period of time beyond one year, $p = 0.007$. [Cheng 2010]

We should also consider the risk to the patient if their AF is left uncorrected. This has been carefully studied in the series of research efforts that reviewed case matched outcomes for patients with underlying AF that received a surgical procedure versus those that did not have AF at baseline but had the same operation.[Ngaage 2006; Ngaage Jan 2007; Ngaage Apr 2007; Quader 2004] The conclusion for each of the surgical procedures was that there was a higher incidence of stroke with those subjects that remained in AF after their operation. Further, the operations for CABG and Aortic Valve Replacement also demonstrated a mortality benefit as well. It may be that in mitral valve subjects their underlying LV dysfunction was so well established that it was more of an overriding influence in predicting death than their AF rhythm.

The results from non-paroxysmal subjects in ABLATE as well as ABLATE combined with ABLATE AF are shown for all efficacy endpoints in comparison to the results of the randomized trials that aided in the adoption of the procedure in the marketplace. Figure 17 through Figure 19 are forest plots showing the consistency of the clinical trial results to the RCTs available from the literature. This analysis, together with the hierarchical

model results presented in **Appendix L**, support that the ABLATE and ABLATE AF results are consistent with the outcomes that have been reported in the literature and for other similar series of patients. This provides the verification that the ABLATE series results for non-paroxysmal subjects are appropriate to be utilized in product labeling.

Figure 17: AF Free at 6 Months Efficacy Rates Observed Across Studies

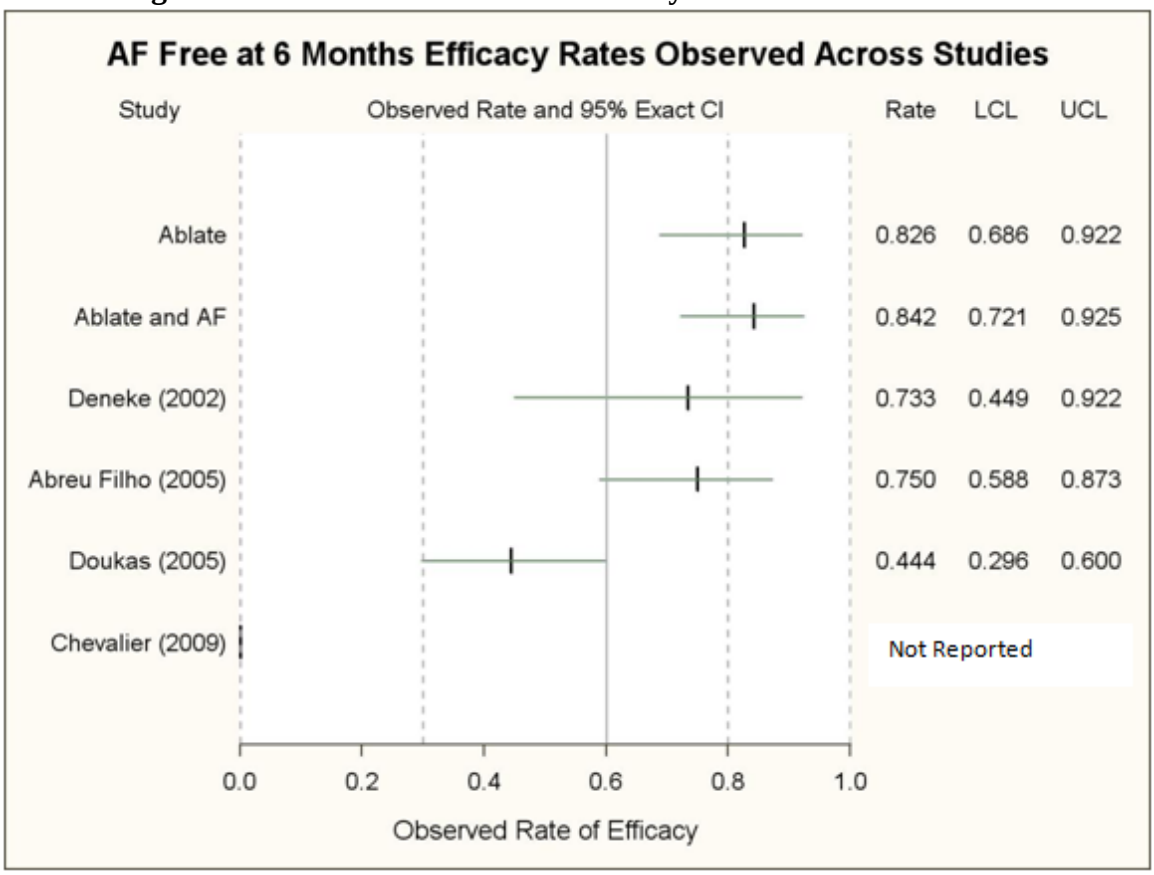


Figure 18: AF Free at 12 Months Efficacy Rates Observed Across Studies

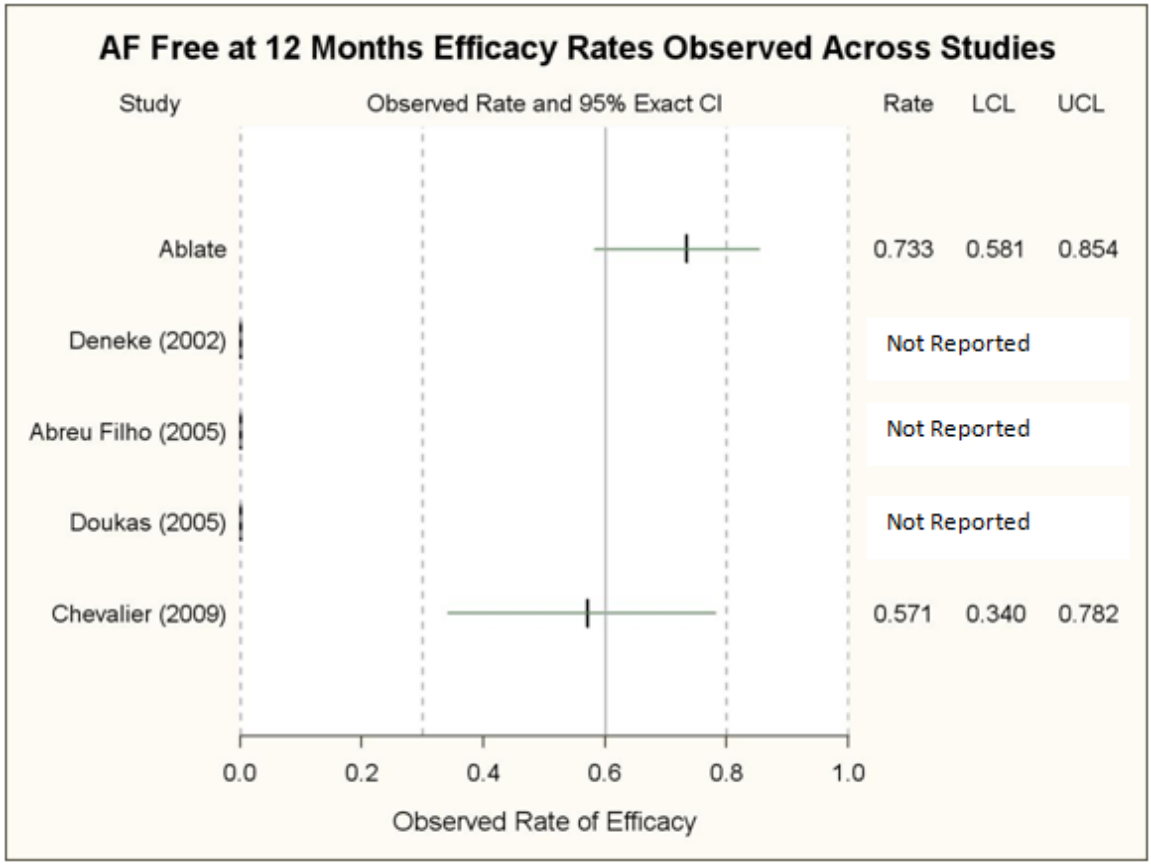
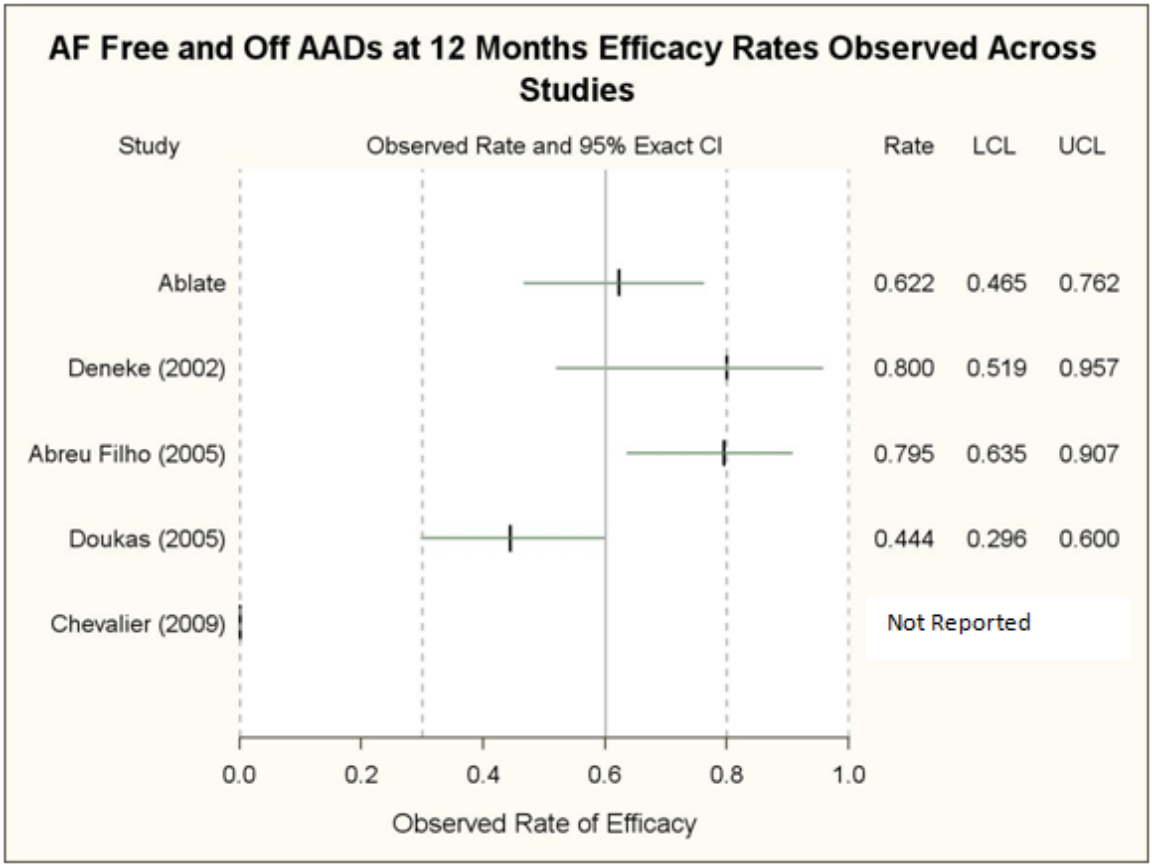


Figure 19: AF Free and Off Class I and III AADs at 12 Months Efficacy Rates Observed Across Studies



The clinical experience highlighted in this panel pack taken as a whole, provides the evidence that supports the risk/benefit evaluation of the concomitant Maze IV procedure. The clinical benefit, coupled with the demonstration that the procedure performed with the AtriCure Synergy Ablation System has minimal added risk, establish the favorable risk to benefit profile for the device and procedure. These data are valid to use in a refined product label to enable the sponsor to conduct training programs.

The FDA has recently issued a Guidance Document (provided in **Appendix M**) that outlines the decision making process that is being adopted for new PMA products. The guidance has a series of question and answers with a tabular format. The risk-based approach has been summarized in this section and a copy of the tabular format is provided in **Appendix N** for review. This evaluation is supplemental to the discussion provided in this section.

7.3. Overall Conclusions

The Maze IV procedure is the current standard of care procedure for the treatment of AF as a supplement to an open-heart operation for a patient with coronary or valvular heart disease. It is recommended by all of the major medical societies including HRS [Calkins 2007], AHA/ACC [Fuster 2006] and ISMICS. [Ad 2009] RF ablation technology, such as the AtriCure Synergy Ablation System, has been shown to be the most prevalent type of product used for the operation. The current label claim for the device is limited in that it does not allow the company to legally train and educate physicians on the benefits of treating AF and the details of the surgical procedure. The ABLATE clinical trials coupled with the other clinical science that has been performed with the technology over the past ten years provide the valid scientific evidence to enhance the product labeling and support education and training. Product and procedure promotion will result in more consistent surgical techniques and highlight the need to correct AF in patients that have the diagnosis at the time of their evaluation for coronary or valvular heart disease. Without the enhanced labeling, the health care provided and patient awareness will remain unchanged and there will continue to be a problem with patients being untreated or undertreated.

AtriCure has conducted a prospective clinical trial that met FDA-agreed upon safety and efficacy criteria. Other valid sources of clinical data have been compiled from the literature, known physician databases, and prior and ongoing clinical registries to provide additional support for the requested label change. The sponsor believes that the benefit of restoring sinus rhythm in the majority of these difficult to treat subjects sufficiently outweighs the risk to subjects of the additional component of an already planned procedure. A change to the label will enable the sponsor to improve training and education to optimize the treatment of atrial fibrillation in subjects undergoing surgery for their coronary or valvular heart disease.

8. POST APPROVAL STUDY

AtriCure is proposing to conduct a post approval study

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