FDA Executive Summary

Prepared for the
October 27, 2011 meeting of the
Circulatory System Devices Panel

P100008
Medtronic Ablation Frontiers Cardiac Ablation System
Medtronic, Inc.

Introduction

This is the FDA Executive Summary for the Medtronic Ablation Frontiers Cardiac Ablation System. This device is a percutaneous catheter system intended for the treatment of atrial fibrillation. The feasibility phase of a clinical trial to study the device was approved by the agency on February 7, 2007 under IDE G060175. The pivotal phase of this trial was approved in November 2007 under the same IDE number. Medtronic, Inc. (the Sponsor) has most recently submitted a Premarket Approval Application (PMA) for marketing approval of the device (P100008). This submission has been reviewed by the Division of Cardiovascular Devices (DCD) within the Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA).

This memorandum will summarize FDA's review of the PMA up to this point, highlighting the particular areas for which we are seeking your expertise and input. These topics will include the proposed indications for use and the results of the clinical study conducted by the Sponsor. At the conclusion of your review and discussion of the data presented, FDA will ask for your recommendation regarding whether or not the data demonstrate a reasonable assurance of safety and effectiveness.

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1 PROPOSED INDICATIONS FOR USE

The Medtronic Cardiac Ablation System is indicated for the treatment of symptomatic, drug refractory, persistent atrial fibrillation (AF) or longstanding persistent AF of up to four years in duration.

2 DEVICE DESCRIPTION

The Medtronic Cardiac Ablation System (the System) is a percutaneous catheter system intended to treat symptomatic, drug refractory, persistent or longstanding persistent atrial fibrillation (AF) by creating a series of transmural lesions from the endocardial surface of the left atrium intended to block or destroy electrical conduction patterns characteristic of AF. The system is comprised of the following components:

- The Multi-Array Ablation Catheter (MAAC), designed to create lesions in the left atrium that target Complex Fractionated Atrial Electrograms (CFAEs).
- The Multi-Array Septal Catheter (MASC), designed to create lesions on the septal wall of the left atrium that target CFAEs.
- The Pulmonary Vein Ablation Catheter (PVAC), designed to create encircling lesions to isolate the pulmonary veins (PVs)
- The GENius Multi-Channel RF Generator, designed to deliver radiofrequency (RF) energy in unipolar mode, bipolar mode, or combinations thereof to operator-selected ablation electrodes on any of the three System catheters.
- Associated accessories
    - Ablation Frontiers, ECG Interface Box
    - Ablation Frontiers, Cable, Interface Box to the RF Generator
    - Ablation, Frontiers, Cable, Interface Box to EKG-12 Channel
    - Ablation Frontiers, Cable, Catheter Interface
    - GENius Jr Remote Control
    - Remote Control Cable

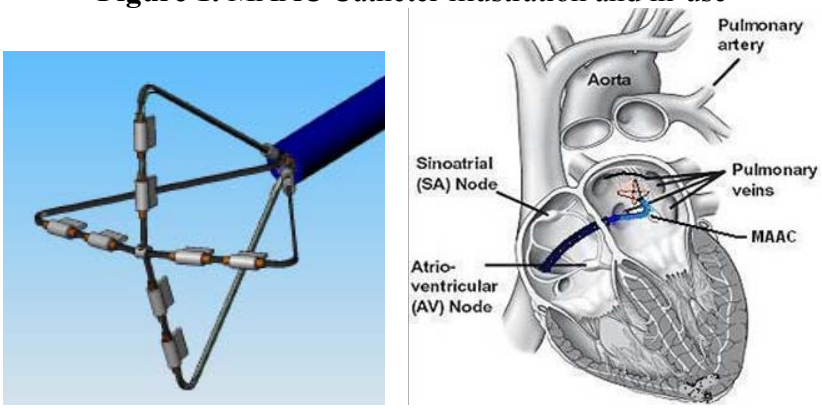
All three System catheters are multi-electrode, non-irrigated RF ablation catheters with the electrodes mounted on Nitinol splines on the distal end of the catheter. Each catheter features a different geometric arrangement of the electrodes. Each arrangement is designed to create part of the lesion set in the left atrium to block conduction of fibrillatory electrical activity in the atria. The generator can be programmed to provide energy to all catheter electrodes simultaneously, or a subset thereof, per the operator preference.

2.1 Multi-Array Ablation Catheter (MAAC)

The MAAC is fitted with 4 pairs of electrodes for delivering energy as shown below. The electrodes are mounted on the distal side of the distal splines in a ‘X’-like configuration. It has a deflectable distal segment and bidirectional steering within a single

plane via controls in the handle. This catheter is intended to create lesions on the left atrium to target CFAEs.

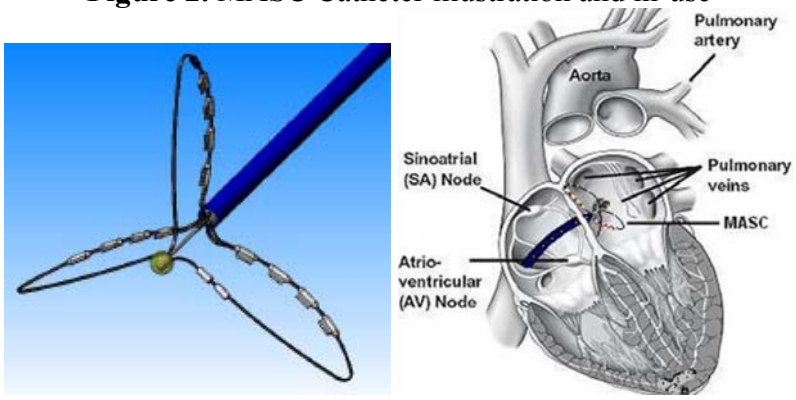
Figure 1. MAAC Catheter illustration and in-use



2.2 Multi-Array Septal Catheter (MASC)

The MASC is a non-steerable catheter fitted with 6 pairs of electrodes for delivering energy as shown below. The electrodes are located on the side of the distal splines facing the proximal catheter shaft. Once the splines emerge from the transseptal sheath they automatically deploy such that when pulled back against the septal wall of the left atrium, the 6 electrode pairs come in contact with the septal wall. This catheter is intended to target CFAE on the septal wall of the left atrium.

Figure 2. MASC Catheter illustration and in-use

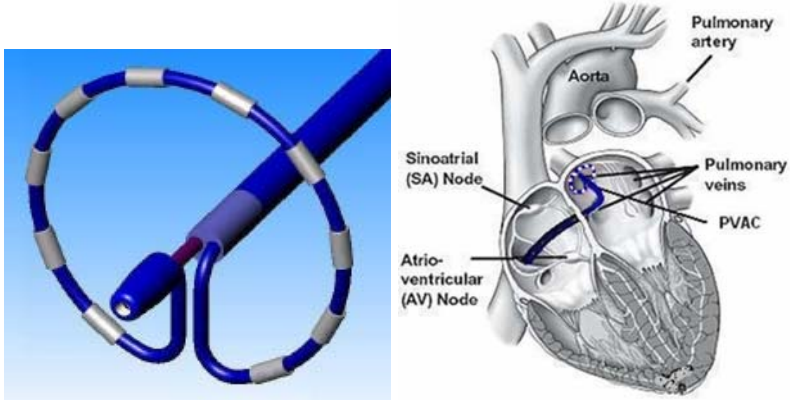


2.3 Pulmonary Vein Ablation Catheter (PVAC)

The PVAC is an over-the-wire catheter fitted with 5 pairs of electrodes for delivering energy. The electrodes are mounted on a circular spline on the plane normal to the axis of the catheter shaft. It has a deflectable distal end, bidirectional steering, and slide mechanism which can be adjusted via controls in the handle to aid in positioning the

electrodes in contact with the antrum around the pulmonary veins as shown below. This catheter is intended to isolate the pulmonary veins.

Figure 3. PVAC Catheter illustration and in-use



2.4 GENius Multi-Channel RF Generator

Each of the three System catheters can be connected to the GENius generator via an accessory cable. The generator has the ability to detect which catheter is connected and set corresponding ablation settings. Energy can be delivered in unipolar or bipolar mode, as well as three different combinations thereof (4:1, 2:1, and 1:1). In unipolar mode, the RF current is delivered to a single electrode on a catheter and returns via two Valleylab Patient Return Electrodes applied to the patient's back. In bipolar mode, the RF current is delivered to one electrode on a catheter and returns via a second adjacent electrode on the catheter. Combination energy modes are created by adjusting the phase angle of the RF between alternating electrode pairs, so that unipolar and bipolar current are delivered simultaneously. The picture below shows the components and accessories that are used with the GENius generator.

Figure 4. GENius Generator and Accessories

Model Name	
GENius Multi Channel RF Ablation Generator	
ECG Interface Box	
ECG Interface Box Cable	
ECG (12 Lead) Amplifier Cable	
Catheter Interface Cable	
GENius Jr Remote Control (Optional)	
Remote Control Cable: 15ft	
Remote Control Cable: 25ft	

For additional information on the system, please see the sponsor's summary.

3 REGULATORY HISTORY

The System was originally manufactured by Ablation Frontiers. The sponsor received the CE Mark for the system in December, 2006. The first US patient was treated with this system on May 18, 2007 under the feasibility phase of the clinical study (approved on February 7, 2007). Twenty (20) subjects were enrolled in a non-randomized feasibility study and were treated with the System. These results, along with a modest cohort from an independent European study were reviewed by FDA, and the sponsor was granted approval to begin enrolling in the randomized, controlled pivotal study on November 14, 2007. The first subject was enrolled in the pivotal study on November 28, 2007. Ablation Frontiers was acquired by Medtronic in February, 2009.

Before any results from the pivotal study had been evaluated, the sponsor requested a change to the protocol to allow for an interim analysis and to implement early stopping rules. At the same time, FDA requested that the sponsor change the definition of "failed

cardioversion" from "recurrence of AF within 30 days following direct current (DC) cardioversion" to "recurrence of AF within 7 days following DC cardioversion". These protocol changes were approved by the FDA and implemented by the sponsor in October 2008.

Because the interim analysis required that all patients complete the acute safety endpoint (a serious adverse procedure and/or device-related event within 7 days of the procedure), the analysis was not performed until the study had been fully enrolled. The sponsor conducted the approved interim analysis after 50% of the subjects had reached their 6 month effectiveness endpoint. Based on the results, the early stopping criteria were determined to have been met. Because the full cohort was enrolled, the remaining subjects were followed as indicated in the protocol. The last index ablation procedure occurred on June 15, 2009. The last retreatment ablation occurred on November 25, 2009. The sponsor submitted the PMA P100008 to FDA on March 2, 2010 with the results of the interim analysis claiming success in the primary effectiveness endpoint. FDA issued a major deficiency letter on June 16, 2010. The sponsor submitted a response to FDA's letter on June 10, 2011.

4 PRE-CLINICAL AND ANIMAL STUDIES

The sponsor has conducted characterization studies, animal studies as well as bench testing of the Medtronic Ablation Frontiers Cardiac Ablation System. The following information was provided, reviewed by FDA, and found to be acceptable:

- Test results demonstrating that the device is compliant with FDA recognized international standards for biocompatibility appropriate for this type of device.
- Test results demonstrating that the packaging and sterilization processes were validated according to FDA recognized international standards.
- Test results demonstrating that the device is compliant with FDA recognized international standards for electrical safety and electromagnetic compatibility.
- Complete software documentation, including test results from complete software verification and validation testing demonstrating acceptable performance
- Test results demonstrating that the catheters maintain their mechanical and electrical integrity under conditions that simulate worse-case clinical use of the device
- Data from animal studies which evaluate the safety of the device in atrial ablation and characterize ablation lesion formation, and maneuverability of the device. Both the MAAC and MASC were used for left atrial ablation. The PVAC was not used for pulmonary vein or left atrial ablation but for superior vena caca ablation.

Please see the Sponsor's Summary of Safety and Effectiveness Data (SSED) for a more detailed description of the pre-clinical testing conducted.

FDA Commentary: FDA has no remaining concerns with regards to pre-clinical testing of the device.

5 IDE CLINICAL STUDY DESCRIPTION

The IDE pivotal trial was a prospective, multi-center, randomized, unblinded study designed to show the safety and effectiveness of the Ablation Frontiers Cardiac Ablation System for the treatment of symptomatic, drug-refractory permanent[1] atrial fibrillation. The study involved 24 enrolling centers and 210 subjects with a history of symptomatic permanent atrial fibrillation (AF) who had failed at least one class I or III antiarrhythmic drug (AAD). Subjects were randomized to receive either ablation with the investigational device (Ablation Management Arm) or medical therapy (Medical Management Arm) using a 2:1 allocation ratio, respectively.

The original trial design was intended for patients with "symptomatic, drug-refractory permanent[1] atrial fibrillation" which was defined as:

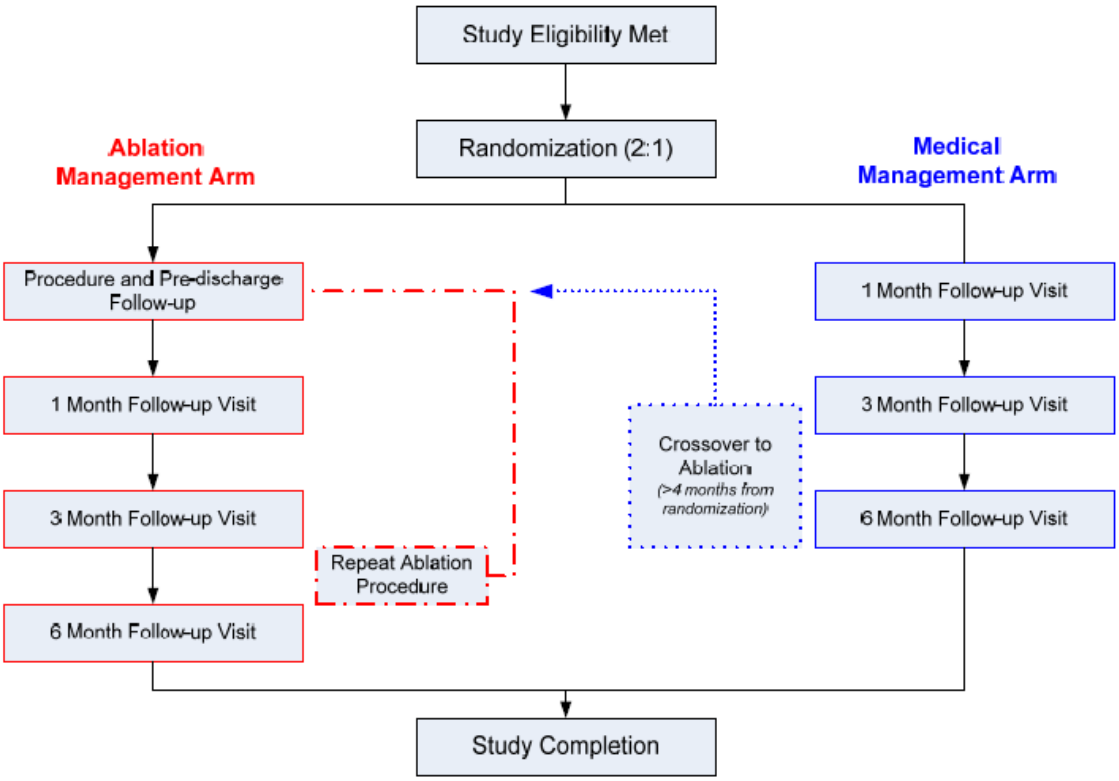
- Non self-terminating AF lasting greater than 7 days but less than 4 years with at least one failed direct current (DC) cardioversion within the previous 2 years. Failure of DC cardioversion is defined as an unsuccessful cardioversion or one in which normal sinus rhythm was established but not maintained beyond thirty days[2];
- AF symptoms defined as the manifestation of: palpitations, fatigue, exertional dyspnea, or increased intolerance to routine activities (exercise intolerance);
- Failure of at least one class I or III rhythm control AAD.

[1] The use of "Permanent" here is used to describe the original clinical protocol population that was requested. This is terminology that was used prior to the HRS Consensus Document of 2007 that provided updated terminology for describing AF populations.

[2] This definition for "failed cardioversion" was changed during the trial to "beyond 7 days". This paragraph, however, describes the protocol in its original format.

5.1 Study Overview

The following flow chart depicts a basic overview of the study



5.1.1 Medical Management Arm

Subjects randomized to the Medical Management Arm of the study were treated with different class I or III AADs from those that may have failed to maintain sinus rhythm prior to enrollment in the study. In addition, the protocol allowed adjustments to the AAD therapy (including changes in dosage) and up to two failed DC cardioversions for management of AF in subjects randomized to the Medical Management Arm. All cardioversions would be separated by at least 30 days. More than two failed DC cardioversions constituted a Medical Management Arm effectiveness failure.

Therapeutic dose ranges of class I and III AADs, based on the recommendations from the Scientific Advisory Board, were provided as guidance to investigational sites. These are tabulated below. However, medication titration was left to the discretion of the investigator.

Table 1. Protocol recommended therapeutic dose ranges.

Medication	Total Daily Dose
Amiodarone (Cordarone)	200mg/day • Increased to 300mg/day for 30 days if the subject enters the study at 200mg/day • A 3 week period of increased dose for loading was at the discretion of the investigator
Dofetilide (Tokosyn)	0.125-0.5 mg BID
Sotalol (Betapace)	120-160 mg BID
Flecainide (Tambocor)	100-150 mg BID
Propafenone	150-300 mg TID
Rhythmol Extended Release	225-425 mg BID

The protocol required a follow-up visit with ECG 30 days after each DC cardioversion. Subjects who failed to maintain sinus rhythm despite antiarrhythmic medication titration and/or DC cardioversion were allowed to crossover and receive ablative treatment for recurrent AF. Crossover could occur no sooner than four months after randomization and only if the subject demonstrated effectiveness failure (< 90% AF reduction) on a 48-hour Holter.

5.1.2 Ablation Management Arm

Subjects randomized to the Ablation Management Arm of the study were treated with the investigational System.

During the first 30 days following the initial ablation procedure, if symptomatic AF recurred such that initiation of AAD therapy was desired, a previously ineffective class I or III AAD was prescribed. Documentation of AF at the one month visit necessitated management with a DC cardioversion and/or repeat ablation. Subjects in whom DC cardioversion failed to restore sinus rhythm or maintain sinus rhythm beyond 30 days would be treated with a repeat ablation. If AADs were restarted after recurrence of AF, discontinuation prior to the 48-hour Holter recording at 6 months was required for a subject to be considered a treatment success. Subjects could undergo a second ablation procedure through the 6 months follow-up period and still be eligible for treatment success. Subjects requiring a repeat ablation restarted the 6 months follow-up period after the second procedure.

5.2 Effectiveness Success Criteria

In the Ablation Management Arm, a subject was considered an acute success if all of the following criteria were met:

- Only System catheters were used to achieve procedure success;
- All accessible PVs were isolated;
- A minimum of a 50% reduction of CFAEs and high frequency intracardiac electrogram amplitude were mapped and ablated with System catheters; and
- Sinus rhythm was achieved upon leaving the EP lab (with or without DC cardioversion).

A 48-hour Holter was performed at baseline and at the 6 month visit to assess the chronic effectiveness. In the Ablation Management Arm, a subject was considered a chronic success if all of the following criteria were met:

- A ninety percent (90%) reduction in clinically significant AF from baseline to the six month time point was observed based on the 48-hour Holter recording. Clinically significant AF is defined as sustained AF lasting more than ten minutes.
- The subject was off all rhythm control AADs at the six month follow-up visit. Success was considered if AADs were discontinued 5 days from the time the 48-hour Holter recording was started, with the exception of Amiodarone. Amiodarone had to be discontinued 28 days prior to the start of the 48-hour Holter recording in order to be considered successful.
- The investigator judged all procedures conducted on a subject during the treatment period to be acutely successful.

In the Medical Management Arm, a subject was considered a chronic success if a ninety percent (90%) reduction in clinically significant AF from baseline to the six month time point was observed based on the 48-hour Holter recording. Clinically significant AF is defined as sustained AF lasting more than ten minutes.

5.3 Key Inclusion Criteria

The complete inclusion and exclusion criteria are summarized in Appendix 9 in the panel pack. FDA would like to highlight the following key entrance criterion:

- History of symptomatic permanent atrial fibrillation defined as:
  - Continuous AF greater than one year but less than four years in duration; or
  - Non self-terminating AF, lasting greater than seven days but no more than one year, with at least one failed DC cardioversion. Cardioversion failure is defined as an unsuccessful cardioversion or one in which normal sinus rhythm was established but not maintained beyond seven days[3].
  - AF symptoms defined as the manifestation of: palpitations, fatigue, exertional dyspnea, and increased intolerance to routine activities (exercise intolerance).

FDA Commentary: FDA believes that this particular criterion is important because of the definition of permanent AF used for trial enrollment and the potential for a heterogenous AF population.

Other key study inclusion criteria:

- Age between 18 and 70
- Failure of at least one class I or III rhythm control AAD

[3] About 2/3 of the study population were enrolled with the original definition of "failed cardioversion" which indicated that "sinus rhythm was established but not maintained beyond 30 days"

The key study exclusion criteria:

- NYHA Class III or IV heart failure and/or left ventricular ejection fraction < 40%.
- Left atrial diameter of > 55 mm
- Moderate to severe mitral or aortic valvular heart disease
- Hypertrophic cardiomyopathy
- Pulmonary hypertension
- Prior ablation for AF
- History of stroke or TIA
- Left atrial thrombus
- Severe COPD

5.4 Cross-over Ablation

Subjects who failed AAD therapy in the Medical Management Arm had the option to be treated with the investigational System device only after they had completed the chronic effectiveness endpoint evaluation. This could not occur earlier than four months after randomization. In order to be considered a failure, the subject would have had to demonstrate effectiveness failure on the 48-hour Holter despite treatment by Medical Management described above (section 5.1.1 Study Overview). Their treatment would be the same as for those subjects who were randomized to the Ablation Management Arm including pre-procedure testing utilized for safety in the Ablation Management Arm. Data was collected for safety and effectiveness but was reported separately.

5.5 Statistical Analysis Plan

The following sections provide an overview of the statistical analysis plan described in the protocol, including interim look and stopping rules.

5.5.1 Analysis Populations

The "intent-to-treat" (ITT) population includes all study subjects that have been randomized. All subjects were analyzed according to their assigned randomization arm.

The statistical analysis plan prespecified that the ITT population would be used for the primary analyses. The pre-specified primary missing data imputation method imputed all missing data for the primary endpoints as failures.

5.5.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint compared the proportion of subjects in each study arm who achieved chronic effectiveness success.

The hypotheses of the primary effectiveness endpoint were:

$$H_0 : p_A \leq p_M \quad vs. \quad H_a : p_A > p_M$$

where p_A and p_M were the proportions of subjects who achieved chronic effectiveness success in the Ablation Management Arm and the Medical Management Arm,

respectively. The hypothesis testing was conducted at a one-sided level of significance 0.0015 for the interim analysis and at a one-sided level of significance 0.0245 for the final analysis using a chi-square test. To evaluate the poolability of the chronic effectiveness data across different centers, a Breslow-Day Test of the homogeneity of odds ratios would be conducted at a level of significance 0.15.

5.5.3 Primary Safety Endpoint

There were two primary safety endpoints. One of the two co-primary safety endpoints was the acute safety, which was defined as a success/failure variable calculated for each subject in the Ablation Management Arm. The hypotheses for the acute safety endpoint were

$$H_0 : p_A \geq .16 \quad vs. \quad H_a : p_A < .16$$

where $p_A =$ the proportion of subjects who experienced acute safety failures in the Ablation Management Arm. The hypothesis testing was conducted using an one-sample exact binomial test at a one-sided level of significance 0.025 and the 95% confidence interval of the proportion of subjects classified as acute safety failures in the Ablation Management Arm would be constructed. To evaluate the poolability of the acute safety data across different centers, a chi-square test was conducted at a level of significance 0.15.

The second of the two co-primary safety endpoints was the chronic safety, which was defined as a success/failure variable calculated for each subject in both arms. The hypotheses of the chronic safety endpoint were

$$H_0 : p_A \geq p_M + .06 \quad vs. \quad H_a : p_A < p_M + .06$$

where p_A and p_M are the proportions of subjects who experienced chronic safety failures in the Ablation Management and Medical Management arms, respectively. The hypothesis testing was conducted using a chi-square test at a one-sided level of significance 0.0245. To evaluate the poolability of the chronic safety data across different centers, a Breslow-Day Test of the homogeneity of odds ratios was conducted at a level of significance 0.15.

5.5.4 Overall Success Rule

The pre-specified null hypotheses for the chronic effectiveness endpoint and the acute safety endpoint must be rejected in favor of the investigational device to claim the overall study success.

FDA Commentary: Please note that the pivotal trial was not powered for the chronic safety endpoint and the pre-specified overall study success rule did not include the chronic safety endpoint. The hypothesis testing of the chronic safety endpoint should be conducted and reported only when both the pre-specified null hypothesis for the chronic effectiveness endpoint and that for the acute safety endpoint were rejected in favor of the investigational device. By including it as a primary endpoint, it allows for a direct comparison between the safety events that occur after 7 days in the ablation arm and those that occur in the medical management arm.

5.5.5 Interim Analysis Plan

When 130 subjects had been enrolled to the trial and without un-blinding study results, an interim analysis plan for effectiveness was added to the protocol with FDA approval. A single interim analysis was conducted for the effectiveness endpoint when all planned subjects were enrolled and finished follow-up for the acute safety endpoints, and at least 50% of the subjects had reached their chronic effectiveness endpoint. If the primary effectiveness endpoint was met at the interim analysis, the study would be stopped.

An O'Brien-Fleming boundary was used for controlling the overall type I error rate: to claim success at the interim analysis for the chronic effectiveness endpoint, the one-sided p-value needs to be less than 0.0015; to claim success at the final analysis for the chronic effectiveness endpoint, the one-sided p-value needs to be less than 0.0245. There was no planned interim analysis for the primary safety endpoints.

5.6 Ablation Management Arm Procedures

The following sections describe the key pre-ablation and investigational procedures that were either required during the treatment with the investigational device, or left to investigator discretion.

5.6.1 Peri-Procedure Anticoagulation

Management of peri-procedure anticoagulation was not dictated by the study protocol but rather titrated per the investigator's standard of care. Two anticoagulation strategies were allowed during the study. One strategy used bridging therapy with either subcutaneous low molecular weight heparin (LMWH) or IV heparin for subjects who stopped oral anticoagulants before their ablation procedure. LMWH or heparin was resumed following the procedure (see details below). Oral anticoagulation therapy was additionally resumed after the procedure. Another strategy consisted of the continuation of oral anticoagulation throughout the peri-procedure period without LMWH or heparin bridging.

Once transseptal access was obtained, a bolus dose of heparin was introduced either IV or through the sheath. No ablations could occur until the active clotting time (ACT) reached at least 300 seconds. ACT measurements were required approximately every thirty minutes but should not have exceeded forty-five minutes to maintain ACT > 300 seconds.

Upon removal of the catheters and the transseptal sheath from the left atrium, IV heparin was discontinued. The vascular access sheaths were removed when the ACT reaches a clinically acceptable level (<180 seconds). Once the sheaths had been removed and hemostasis had been achieved, heparin or LMWH was restarted. At that time, warfarin oral anticoagulation was initiated. Heparin or LMWH could be restarted three (3) hours after the sheaths had been removed and hemostasis had been achieved and was continued until the INR reached therapeutic range (>2.0). Oral anticoagulation was continued for the length of the follow-up period.

5.6.2 Key Required pre-ablation procedures

Prior to sedation, the subject was asked to swallow barium paste to enable the localization of the esophagus in relationship to atrial structures. In the event general anesthesia was used, an esophageal probe was substituted for the barium paste.

Before beginning the ablation procedure, a transseptal sheath with dilator was inserted into the femoral vein and then through the right atrium into the left atrium by transseptal puncture using a standard transseptal needle under fluoroscopic and/or ultrasound guidance. Pulmonary venograms were made following transseptal access to the left atrium.

5.6.3 Required during the investigational procedure

The following key procedures were required by the study protocol for subjects randomized to the Ablation Management Arm of the study.

- Under fluoroscopic guidance, the System catheters were passed through the transseptal sheath into the left atrium.
- All three of the System catheters were used during the index procedure in the following order to isolate the PVs and modify the left atrial substrate:
    - The PVAC was placed at the antrum of the targeted vein to record intracardiac signals and ablate/isolate the PV from the atrium. Ablations were performed on all channels (5 bipoles) in a 4:1 (bipolar/unipolar) energy mode. The temperature and ablation duration remained constant for each ablation at 60 degrees and 60 seconds. A series of 3 to 5 ablations per vein were performed, by rotating the catheter 90 degrees prior to each ablation. All accessible PVs were ablated following the same procedure.
    - The MASC was used to map and ablate complex atrial fractionated electrograms (CFAEs) located on the septum of the left atrium. The MASC was deployed into the left atrium, the sheath was retracted back into the right atrium and the MASC was pulled back to engage the electrodes against the septum. Once CFAEs were located, ablations occurred on all channels (6 bipoles) for 60 seconds with a target temperature of 60 degrees using an energy mode setting of 1:1 (unipolar/bipolar). A series of ablations occurred, each followed by a slight rotation of the catheter to reposition along the septum and identify additional CFAEs. This continued until the investigator was satisfied that all identified septal CFAEs were eliminated.
    - The MAAC was used to map and ablate all CFAEs on the anterior and posterior wall, the roof, and along the mitral annular region of the left atrium. Ablations occurred selectively on only channels displaying CFAEs, up to 4 bipoles could be ablated simultaneously. Ablation temperature and duration were held constant for each ablation at 60 degrees and 60 seconds. Any ablations occurring on the posterior wall and/or in the vicinity of the esophagus (as identified by a barium swallow or esophageal probe) were at a 1:1 energy mode setting, however, the

duration of ablation was reduced to 30 seconds. Ablations continued until the investigator was satisfied that all CFAEs were eliminated.

- After initial PV isolation and LA substrate modification, if AF continued, DC cardioversion was used to restore sinus rhythm.
- Once in sinus rhythm, the PVAC was again placed in each accessible PV and remapping occurred. All noted PV potentials were ablated with the same settings, but only by selecting the channels where potentials are located. Ablations continued in each PV until it was electrically isolated.

5.6.4 Optional treatments during the investigational procedure

The study protocol allowed investigators to map the right atrium for additional ablation targets. The PVAC was allowed for ablations at the superior vena cava (SVC) but non-investigational RF catheters were used for all other right atrial ablations including the cavo-tricuspid isthmus. The right-sided ablations that were created were not systematically collected on the case report forms and therefore no conclusions can be drawn with respect to the impact of SVC and cavotricuspid isthmus ablations on chronic success.

6 IDE CLINICAL STUDY RESULTS

6.1 Summary of Enrollment and Patient Accountability

A total of 242 study candidates signed an informed consent document, with 210 randomized in a 2:1 fashion to the Ablation Management (n = 138) or Medical Management (n = 72) arms. Thirty-two (32) subjects failed screening or withdrew consent before randomization.

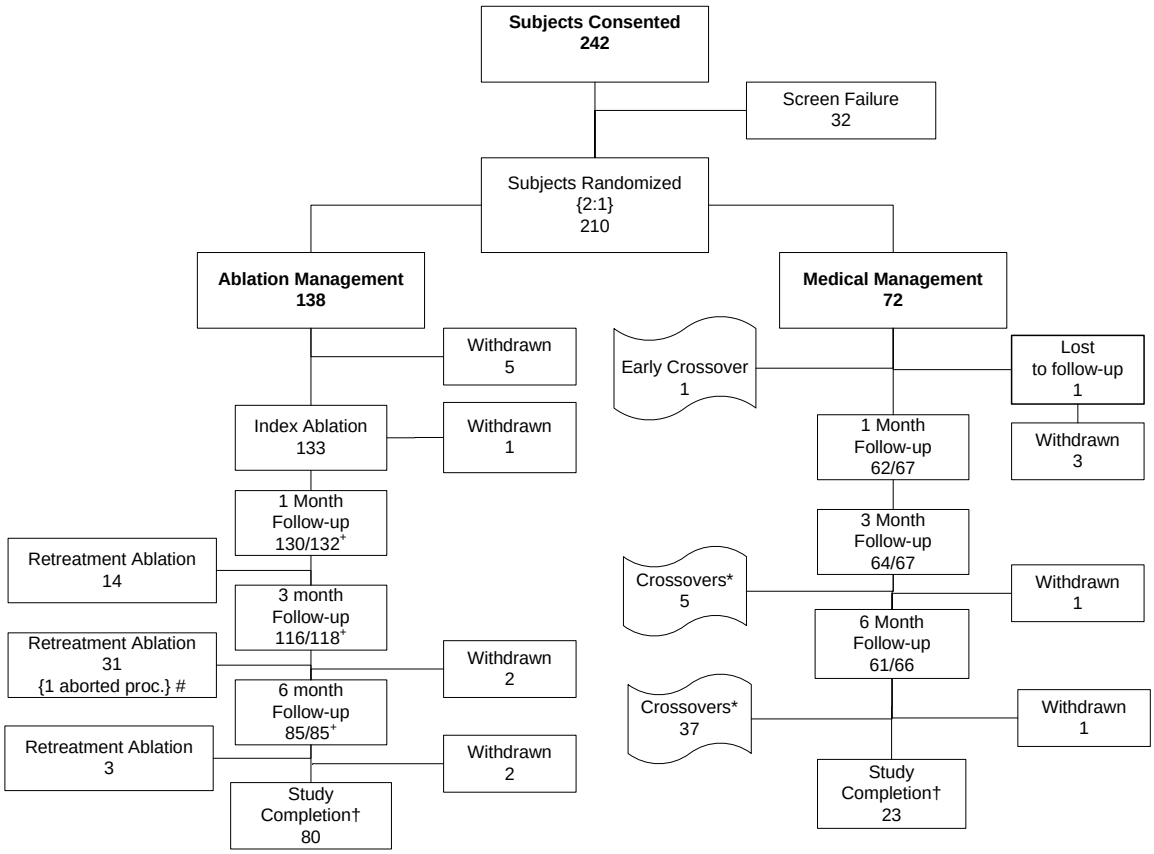
Among the 138 subjects randomized to the Ablation Management Arm, 5 subjects withdrew prior to the ablation procedure, 85 subjects received only the index ablation procedure, and 48 subjects received both the index ablation and the retreatment procedures. Among the 133 subjects treated in the Ablation Management Arm who underwent at least one study procedure, 124 subjects completed the specified 6 months of follow-up, 1 subject died, and 8 subjects were withdrawn from the study.

Among the 72 subjects randomized into the Medical Management Arm, 6 subjects were withdrawn or lost to follow-up, 23 subjects received only the Medical Management treatment and completed the 6-month follow-up. Forty-three (43) subjects were permitted to crossover into the Ablation Management Arm to receive at least one ablation treatment, of which 12 required a second ablation. Four (4) crossover subjects were withdrawn after the ablation treatment, and the other 39 subjects completed the study. Subject accountability throughout the study is summarized in Figure 5.

There were no subjects lost to follow-up in the Ablation Management Arm. One subject in the Medical Management Arm was lost to follow-up at 4.1 months from starting the study. This subject was included in the effectiveness and safety analyses.

Subject demographics and medical history were well matched between the Ablation Management and Medical Management arms. The mean age of the study subjects was 60 +/- 8.5 years old. The majority of the subjects were male (83%) and the population was predominantly Caucasian (97%). The left atrial size and left ventricular ejection fraction averaged 4.5 cm and 0.55, respectively. Coronary artery disease, cardiomyopathy, valvular disease were present in 40 (19%), 19 (9%), and 15 (7.1%) subjects. The majority of the subjects (59%) had a history of hypertension. Persistent or permanent AF had been diagnosed for 10.6 +/- 10.8 and 8.5 +/- 9.5 months in the Ablation Management and Medical Management subjects, respectively. Among the 210 subjects, 153 (73%) were classified as having persistent AF and 57 (27%) were classified as having longstanding persistent AF. Persistent AF was defined as non self-terminating AF lasting greater than seven days but no more than one year. Longstanding persistent AF was defined as continuous AF of greater than one year duration. The Ablation and Medical Management subjects had failed 1.4 +/- 0.9 and 1.1 +/- 0.5 Class I or III AADs and had undergone 2.0 +/- 1.1 and 2.4 +/- 3.5 DC cardioversions, respectively, prior to study enrollment. The $CHADS_2$ scores averaged 0.8 +/- 0.8 and 0.8 +/- 0.7 in the Ablation and Medical Management arms, respectively. The vast majority of subjects (98.6% in both arms) were on warfarin at baseline. Among the 210 study subjects, 27 (13%), 15 (7.1%), 32 (15%), and 25 (12%) subjects were on amiodarone, flecainide, propafenone, and sotalol at baseline, respectively.

Figure 5. Subject Accountability for Medical Management and Ablation Management Index Procedure Follow-Up Visits



+ The numbers in the follow-up boxes reflects number of actual visits / number of expected visits.

* Data collected on subjects after crossover was evaluated in a separate analysis. A total of 43 subjects crossed over to receive an ablation procedure; all but the 6 crossovers that occurred prior to study completion were evaluated in the Primary Effectiveness Endpoint. The 6 early crossovers were counted as effectiveness failures in the ITT analysis.

†In the Figure above, the number of subjects completing the study for the Ablation Management Arm is all subjects that only had a single procedure and who had a 6 month follow-up visit. The number of subjects completing the study for the Medical Management Arm is only those who did not cross over and who had a 6 month follow-up visit. The total subjects with study completion for the Medical Management Arm is 23 who did not cross over plus 43 who were included in the study endpoints and crossed over Five (5) Medical Management subjects were allowed by the investigator to crossover to Ablation Management without completing all study-related procedures and were considered failures in the ITT effectiveness analysis.

had a retreatment ablation procedure that was aborted prior to investigational catheter deployment. As the patent foramen ovale was crossed into the left atrium with a steerable catheter (no sheath advanced from the right), the ECG monitor demonstrated peaked T-waves in the inferior leads and the ablation procedure was aborted. The subject continued follow-up visits that were accounted for in the index procedure.

6.2 Interim Analysis Results

As prespecified, when all subjects were enrolled and more than 50% of the subjects finished 6-months follow-up, an interim analysis for the primary effectiveness endpoint was performed on July 31, 2009. At the interim analysis, all 138 Ablation Management subjects had reached the acute safety endpoint at 7 days post procedure from the index ablation. Additionally at the time of this interim analysis, 79 of 138 (57%) Ablation Management subjects and 57 of 72 (79%) Medical Management subjects had completed the 6-month follow-up, been withdrawn from the study, or crossed over from failed treatment of medical management and received an ablation. The pre-specified interim analysis results were reviewed during a closed session of the DSMB/CEC on August 23, 2009.

6.2.1 Interim Effectiveness

Chronic effectiveness success was achieved in 44 (55.7%) out of 79 subjects in the Ablation Management Arm, compared to 14 (24.6%) out of 57 subjects in the Medical Management Arm based on the ITT population with all missing data imputed as failures (shown in Table 2). In detail, chronic effectiveness endpoint values for 9 (11.4%) subjects in the Ablation Management Arm and 11 (19.3%) subjects in the Medical Management Arm were missing and imputed as failures. The one-sided p-value was 0.0001, which was lower than the pre-specified significance level of 0.0015. The difference in the proportion of subjects who achieved chronic effectiveness success between the two treatment arms and the unadjusted 95% confidence interval were 31.1%% (15.5%, 46.8%) in favor of the Ablation Management Arm. Therefore, the null hypothesis of the chronic effectiveness endpoint was rejected in favor of the investigational device. The effectiveness results of the interim analysis met the pre-specified effectiveness criteria for stopping the study at the interim time point due to superiority of ablation management versus medical management in the primary effectiveness endpoint.

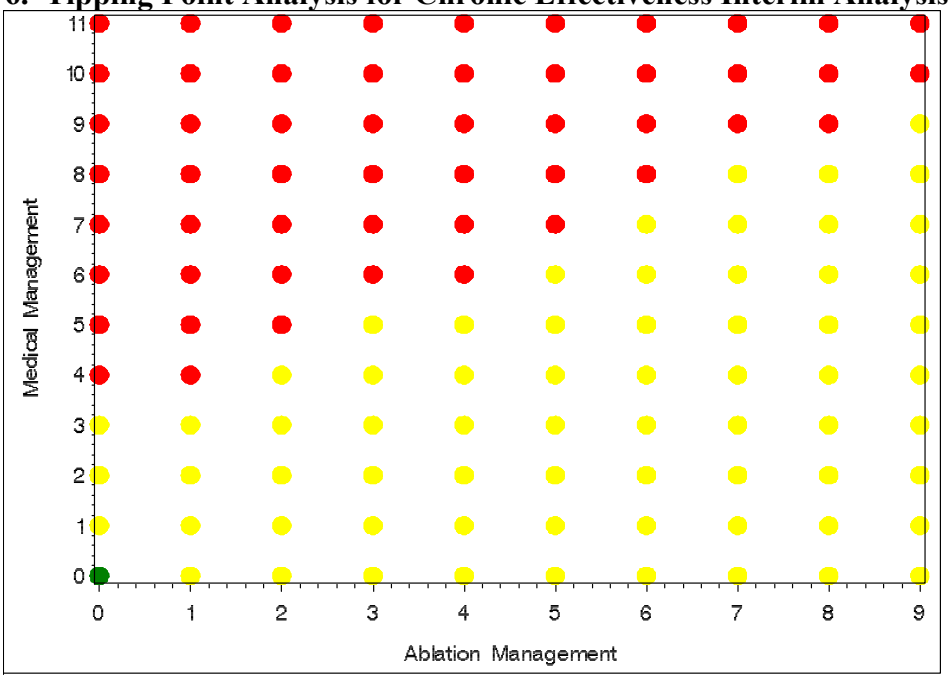
Table 2. Primary Effectiveness at Interim Analysis

	Ablation Mgmt. (n=79)	**Medical Mgmt. (n=57)**
Subject meeting all components of effectiveness endpoint	44	14
Treatment Success by %	55.7%	24.6%
Number of missing endpoints†	9	11
Chi-square one-sided p-value for H_0: $P_A \leq P_M$		P=0.0001

†The primary missing value imputation technique for all primary endpoint analysis is the passive method of imputation.

A tipping point analysis based on the ITT population was conducted by the FDA to assess the likelihood that missing data could bias the conclusion of the chronic effectiveness endpoint from the study, and the result is summarized by the following plot.

Figure 6. Tipping Point Analysis for Chronic Effectiveness Interim Analysis



In the plot, the horizontal axis represents the number of successes among subjects with missing chronic effectiveness endpoints in the Ablation Management arm. Likewise, the vertical axis represents the number of successes among subjects with missing chronic effectiveness endpoints in the Medical Management arm. The area with red dots represents the outcomes in which the trial would fail to conclude the superiority claim of the Ablation Management Arm to the Medical Management Arm in the chronic effectiveness endpoint at one-sided alpha level of 0.0015. For example, the green dot indicated that when all missing data points were failures (the passive imputation), the superiority test would succeed. It also can be found that if 4 out of 11 missing data points in the Medical Management Arm were successes and 1 out of 9 in the Ablation Management was a success, the superiority test would fail. Therefore the tipping point analysis indicates that the extent of missing data could have biased the analysis of the chronic effectiveness endpoint if the Ablation Management subjects with missing data performed relatively worse than the Ablation Management with complete data and the Medical Management subjects with missing data performed relatively better than the Medical Management with complete data. FDA believes that such a difference in performance between subjects with missing versus complete data might be possible, although not very likely.

The sponsor decided to use the interim analysis results to support the PMA submission. The interim analysis results submitted to FDA for review used a July 31, 2009 cutoff date for the chronic effectiveness endpoint and the chronic safety endpoint, and used a November 24, 2009 cutoff date for the acute safety to provide a more complete representation of all acute safety events in the Ablation Management arm.

At the interim analysis point, the CEC/DSMB expressed concerns regarding the acute safety endpoint. The CEC/DSMB expressed particular concern over the 2.9% incidence of peri-procedural stroke (upper 95% confidence limit bound of 7.2%). The CEC/DSMB recommended continued analysis and follow-up of safety issues in both crossover patients and re-treatments in the Ablation Management Arm. The CEC/DSMB further pointed out that these analyses and follow-up activities should include all data, including those beyond the acute safety endpoint time constraints.

6.2.2 Interim Acute Safety

Sixteen (16) of the 138 Ablation Management Arm subjects (11.6%) had one or more serious procedure and/or device-related adverse (SADE) events (occurring within 7 days post-procedure) based on the ITT population. The upper bound of the two-sided, 95% confidence interval of the proportion of subjects who experienced acute safety failures was 18.1%, which was higher than the pre-specified performance goal of 16%. Therefore, the null hypothesis of the acute safety endpoint could not be rejected and it was concluded that the proportion of subjects who experienced acute safety failures in the Ablation Management Arm was not significantly lower than 16%. The acute safety objective was not met in the interim analysis.

6.2.3 Interim Chronic Safety

The chronic safety endpoint for 4 (5.1%) out of 79 Ablation Management subjects and 9 (15.8%) out of 57 Medical Management subjects were missing at the interim analysis. Among the subjects whose chronic safety endpoints were not missing at the interim analysis, 5 (6.7%) out of 75 Ablation Management subjects experienced a SADE and 1 (2.1%) out of 48 Medical Management subjects experienced a SAE. Since the pre-specified null hypothesis for the acute safety endpoint was failed to be rejected in favor of the investigational device and the overall study success was not met in the interim analysis, no hypothesis testing for the chronic safety endpoint was conducted and no corresponding inferential statistics was reported for the chronic safety endpoint in the interim analysis.

6.2.4 Conclusion of Interim Analysis

At the interim analysis, the pre-specified chronic effectiveness objective was met, but the pre-specified acute safety objective was not. Therefore, the overall study success was not met in the interim analysis.

It is important to point out that full enrollment was complete at the interim analysis. 100% of patients had acute safety endpoint data available at that time and therefore there was no interim analysis for the safety endpoints. The early stopping rules allowed the sponsor to claim success for the effectiveness endpoint at the interim analysis and to submit the PMA.

6.3 Entire Cohort Analysis Results of All Enrolled Subjects

The final primary effectiveness analysis was based on an updated dataset submitted per FDA's request and included data up to the time when all enrolled subjects had completed the prespecified 6 month follow-up and had their primary study endpoints evaluated using a March 30, 2011 cutoff date.

6.3.1 Acute Safety Primary Safety Endpoint Analysis

For the acute safety primary endpoint, the study hypothesis was that the 95% upper confidence limit of the proportion of subjects in the ablation management arm who had at least one SADE through seven days post procedure is less than a performance goal of 16%. The performance goal of 16% was obtained from a literature review of complications rates following catheter ablation of AF and a review of acute SAE rates reported in the summaries of safety and effectiveness for ablation catheters approved for typical atrial flutter.

There were 21 SADEs reported for 17 out of 138 (12.3%) Ablation Management Arm subjects within 7 days post-procedure (either index or re-treatment) based on the ITT population as shown in table 3. The two-sided 95% confidence interval for the proportion of subjects who experienced acute safety failures in the Ablation Management arm was (7.3%, 19.0%), the upper bound of which exceeded the pre-specified performance goal of 16%. Therefore, the null hypothesis of the acute safety endpoint could not be rejected, and it was concluded that the proportion of subjects who experienced acute safety failures in the Ablation Management arm was not significantly lower than 16%. In addition, the pre-specified chi-square test indicated that there was significant difference in acute safety endpoint data across different centers (p=0.1028) at the 0.15 significance level (see table 5 below for a summary of events by center). The primary acute safety objective was not met.

Table 3. Acute Safety Results for Ablation Management

Acute Safety Results	Ablation Mgmt. N=138
Number of subjects having one or more acute serious AEs related to the device or procedure	17 (12.3%)
95% Exact Binomial Confidence Interval	(7.3%, 19.0%)
p-value* of H_0: Rate ≥ 16%	0.1427
Number of missing endpoints†	0

*One-sided p-value for exact one-sample binomial test. Binomial test is based on endpoint definition that failures are AEs adjudicated to be both serious and either probably or definitely related to treatment and imputed endpoints.

†The primary missing value imputation technique for all primary endpoint analysis is the passive method of imputation.

The adverse events included in the acute primary safety endpoint analysis are summarized in Table 4 below.

Table 4. List of adverse events included in the acute primary endpoint analysis.

Description	Number of Subjects with SADEs through 7 Days Post Ablation (%) (N = 138)
Death*	1 (0.7%)
Stroke	4 (2.9%)
Tamponade	2 (1.4%)
Heart failure	1 (0.7%)
Hypotension	2 (1.4%)
Pericarditis	1 (0.7%)
Pseudoaneurysm	2 (1.4%)
Retroperitoneal Bleed	1 (0.7%)
Pneumonia	1 (0.7%)
Pulmonary Infiltrates	1 (0.7%)**
Acute Respiratory Failure	1 (0.7%)
Drop in HCT with Prolonged Hospitalization	1 (0.7%)
UTI with Prolonged Hospitalization	1 (0.7%)
Anesthesia Reaction with Prolonged Hospitalization	1 (0.7%)
Total Subjects Experiencing Acute SADEs	**17 (12.3%, 95% UCB 19.0%)**

* One (1) subject died one day after a repeat ablation procedure. was a with drug refractory symptomatic persistent AF with left bundle branch block. The subject experienced cardiac arrest during PV venograms but before study device deployment to the heart. According to the CEC/DSMB adjudication, heart failure was the cause of the death. The death was considered definitively related to the procedure but not related to the device. FDA has reviewed the case in detail and agrees with the CEC/DSMB that the death was not related to the device but related to the ablation procedure.

** experienced 2 episodes of pulmonary infiltrates (one following index procedure and the other following re-treatment procedure).

The following table tabulates the number of acute safety failures that were seen at each center. This table indicates that not all centers have the same safety outcome. FDA does not believe that there is enough information in order to make a definitive statement regarding the cause of the variability however.

Table 5. Acute Safety Failure Rate by Investigational Centers

Investigational Center	Ablation Management	
	Number of Subjects N	Number of Subjects with Acute Safety Failures n (%)
Center 1	7	0 (0.0%)
Center 3*	4	1 (25.0%)
Center 4	6	0 (0.0%)
Center 5	11	0 (0.0%)
Center 7	9	2 (22.2%)
Center 9	5	1 (20.0%)
Center 10	4	0 (0.0%)
Center 17	11	1 (9.1%)
Center 18	8	1 (12.5%)
Center 21	9	0 (0.0%)
Center 23	12	3 (25.0%)
Center 24	9	1(11.1%)
Center 26	12	0 (0.0%)
Center 27	7	0 (0.0%)
Center 28	6	3(50.0%)
Center 29	6	1(16.7%)
Centers 6, 11, 33**	4	0 (0.0%)
Center s16, 19**	4	1(25.0%)
Center s 31, 32**	4	2(50.0%)
Total	**138**	**17(12.3%)**

* Four of the subjects enrolled at center 3 were transferred to center 12 shortly after enrollment for follow-up and study completion at center 12, due to the transfer of the Principal Investigator. There were no enrollments in Center 12; therefore all patients are listed with Center 3.

** Centers with less than 5 enrollments were combined together to form super centers with at least 5 enrollments.

6.3.2 Chronic Safety Endpoint Analysis

The chronic safety endpoint for 6 (4.3%) out of 138 Ablation Management subjects and 11 (15.3%) out of 72 Medical Management subjects were missing at the final analysis. Among the subjects and whose chronic safety endpoints were not missing at the final analysis, twelve (12) study subjects experienced 13 chronic safety events. There were 9 chronic safety events reported for 9 subjects in the ablation management arm, including pericardial effusion (n = 1), pericarditis/pleuritis (n = 1), PV stenosis (> 70%) (n = 4), symptomatic PV narrowing (50-70%) (n = 1), persistent ASD (n = 1) and stroke (n = 1). There were three chronic safety events in the medical management arm including 2 subjects experiencing 3 episodes of gastro-intestinal bleed secondary to anticoagulation and one subject who was hospitalized for AF. Please note that the missing data (which is treated as failures given the primary imputation method), has a larger impact on the Medical Management Arm than on the Ablation Management Arm as shown in the Table 6 below.

Table 6. Primary Chronic Safety Outcome

	Ablation Management Arm (N = 138)	**Medical Management Arm (n = 72)**
Subjects with Chronic SADEs or SAEs (%)	9 (6.5%)	3 (4.2%)
Subjects with Missing data which is Imputed as Endpoint Failures (%)	6 (4.3%)	11 (15.3%)
Total Number (rate) of Chronic Safety Endpoint Failures	15 (10.9%)	14 (19.4%)

Among the subjects whose chronic safety endpoints were not missing at the final analysis, the proportion of subjects who experienced chronic safety failures ranged from 0.0% to 33.3% in the Ablation Management Arm and in the Medical Management Arm across different centers, and the Breslow-Day Test of the homogeneity of odds ratios failed to indicate a significant difference across centers (p=0.2455) at the 0.15 significance level. Since the pre-specified null hypothesis for the acute safety endpoint was failed to be rejected in favor of the investigational device and the overall study success was not met in the final analysis, no hypothesis testing for the chronic safety endpoint was conducted and no corresponding inferential statistics was reported in the final analysis.

6.3.3 Overall Safety Analysis

There were two pre-specified safety endpoints for this trial that described separately the acute and chronic adverse event rates for the subjects in this study as described in the sections above. However, there was not a single pre-specified endpoint that attempted to characterize the overall safety assessment in this trial. Therefore, an additional post-hoc analysis was performed that combined the acute and chronic safety data. The FDA review team believes that this analysis, although not prespecified, provides the best overview of the safety profile of this device. This analysis was performed to assess the incidence of procedure and/or device related serious adverse events (SADEs) in subjects who underwent at least one study procedure regardless of whether the SADEs occurred within 7 days of the procedure or beyond 7 days through 6 months post procedure.
A total of 176 subjects underwent at least one study procedure, including 133 subjects from the Ablation Management Arm and 43 medical management crossovers. There were 41 SADEs reported for 38 subjects within 6 months of a study procedure. Among the 41 SADEs, 32 occurred within one month of a study procedure, one (AF recurrence with rapid ventricular response (RVR)) occurred 41 days post crossover ablation, and 8 (7 PV stenosis/narrowing and 1 persistent ASD) were identified on 6-month CT or MRI. The overall percentage of subjects who experienced a SADE through 6 months post procedure was 21.6% (38/176).

The adverse events included in the analysis are the following:

Table 7. SADEs in Subjects Who Received at Least One Study Procedure

Description	Number of Subjects with SADEs as Percent of Subjects in Ablation Management Arm to 6m, N = 138	Number of Subjects with SADEs as Percent of Subjects in Medical Management Crossover group to 6m N = 43	Number of Subjects with SADEs Post Ablation to 6m as Percent of Total Number of Subjects Undergoing Ablation (%) (N = 176*)
Death	1	0	1 (0.6%)
Stroke	5	0	5 (2.8%)
TIA	0	2 +	2 (1.1%)
Tamponade	2	1	3 (1.7%)
PV stenosis/ Symptomatic PV narrowing	5	2	7 (4.0%)
Hypotension	2	1	3 (1.7%)
Pericardial effusion	1	1	2 (1.1%)
Pericarditis	2	1	3 (1.7%)
Heart failure	1	0	1 (0.6%)
Hematoma	0	1	1 (0.6%)
Pseudoaneurysm	2	1	3 (1.7%)
Retroperitoneal Bleed	1	0	1 (0.6%)
Persistent ASD	1	0	1 (0.6%)
Pneumonia	1	0	1 (0.6%)

Description	Number of Subjects with SADEs as Percent of Subjects in Ablation Management Arm to 6m, N = 138	Number of Subjects with SADEs as Percent of Subjects in Medical Management Crossover group to 6m N = 43	Number of Subjects with SADEs Post Ablation to 6m as Percent of Total Number of Subjects Undergoing Ablation (%) (N = 176*)
Pulmonary Infiltrates	1[#]	0	1 (0.6%)
Acute Respiratory Failure	1	0	1 (0.6%)
Recurrent AF with RVR requiring hospitalization	0	1	1 (0.6%)
Drop in HCT with Prolonged Hospitalization	1	0	1 (0.6%)
UTI with Prolonged Hospitalization	1	0	1 (0.6%)
Anesthesia Reaction with Prolonged Hospitalization	1	0	1 (0.6%)
Hyperesthesia in right leg and neuropathy	0	1	1 (0.6%)
Total Subjects Experiencing SADEs	**26**	**12**	**38 (21.6%)**

* Number of Ablation Arm subjects who undergoing at least one study procedure (133) plus the number of crossover patients (43).
+ experienced a TIA during a study procedure that was not adjudicated as a SADE by the CEC/DSMB. It was re-classified as a SADE by the FDA.
# experienced 2 episodes of Pulmonary Infiltrates (one following index procedure and the other following re-treatment procedure).

FDA Commentary: FDA is concerned about the overall rate of serious device/procedure related adverse events in the patients that underwent at least one study procedure as indicated in the additional analysis described above. FDA will be seeking Panel input on the acceptability of the adverse overall event rate as described in Table 7 for this device in this population.

6.3.4 Primary Effectiveness Endpoint Analysis

The primary effectiveness endpoint of chronic success was analyzed using the intention-to-treat (ITT) population. The primary effectiveness endpoint was achievement of at least a 90% reduction in clinically significant AF on a 48-hour Holter at 6-months compared to that at baseline. In order to be classified as a chronic success, subjects in the Ablation Management Arm were additionally required to:

1. be off all rhythm control AADs (for at least 28 days for amiodarone, and at least 5 days for others) at the 6-month follow-up visit; and
2. have achieved acute procedural success.

Chronic success was achieved in 77 of 138 subjects (55.8%) in the Ablation Management Arm compared to 19 of 72 subjects (26.4%) in the Medical Management Arm with all missing values imputed as failures. In detail, there were missing values for chronic effectiveness endpoint for 17 (12.3%) subjects in the Ablation Management arm and 15 (20.8%) subjects in the Medical Management arm.

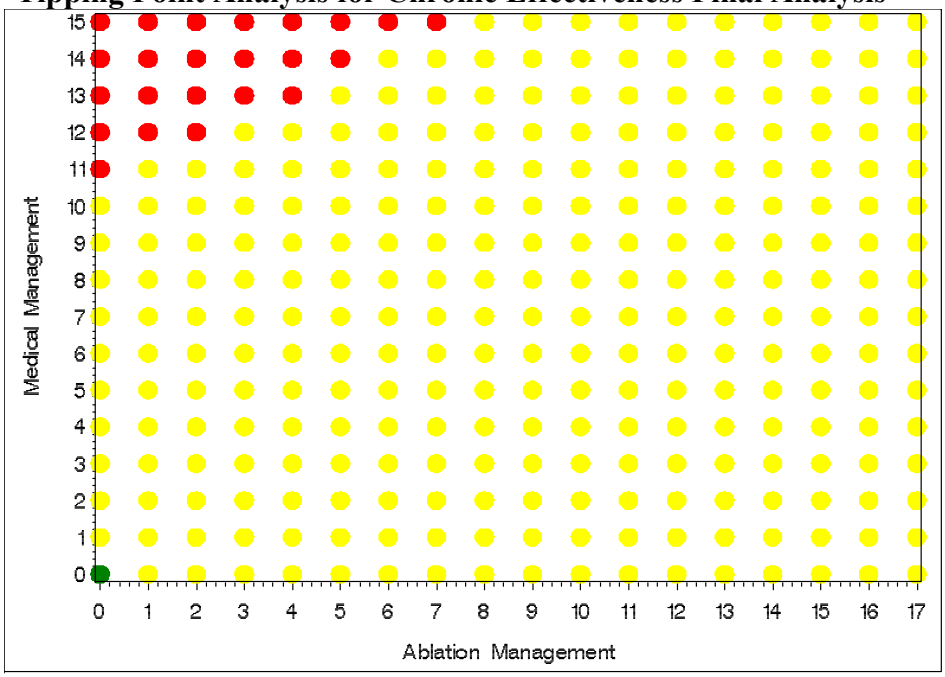
The one-sided p-value was <0.0001, which was lower than the pre-specified level of significance 0.0245. The difference in the proportion of subjects who achieved chronic effectiveness success between the two treatment arms and the unadjusted 95% confidence interval were 29.4% (16.3%, 42.5%) in favor of the Ablation Management Arm. Therefore, the null hypothesis of the chronic effectiveness endpoint was rejected, and as shown in Table 8 below, the primary effectiveness endpoint was met.

Table 8. The Proportion of ITT Subjects with Treatment Success at 6 Months

Chronic Effectiveness	**Ablation Mgmt.** **N=138** **n (%)**	**Medical Mgmt.** **N=72** **n (%)**	**One-sided p-value for H_0: $P_A \leq P_M$**
Subjects meeting all success criteria	77 (55.8%)	19 (26.4%)	<0.0001
Number of missing endpoints	17	15	

A tipping point analysis was conducted based on ITT population to evaluate the sensitivity of the study conclusion to the missing data for the chronic effectiveness endpoint for the final analysis, and the result is summarized by the following plot.

Figure 7. Tipping Point Analysis for Chronic Effectiveness Final Analysis



In this plot the horizontal axis represents the number of successes among subjects with missing chronic effectiveness endpoints in the Ablation Management arm. Likewise, the vertical axis represents the number of successes among subjects with missing chronic effectiveness endpoints in the Medical Management arm. The area with red dots represents the outcomes in which the trial fails to conclude the superiority claim of the Ablation Management Arm to the Medical Management Arm in the chronic effectiveness endpoint at one-sided alpha level of 0.0245. It can be seen that the superiority test would fail if 11 (73.3%) or more or more out of 15 missing data points in the Medical Management Arm were successes. Note that the success rate was 33.3% (19 out of 57 subjects) among the Medical Management subjects whose chronic effectiveness endpoint was not missing.

In addition, the chronic effectiveness endpoint data seems poolable, since the pre-specified Breslow-Day Test of the homogeneity of odds ratios failed to indicate a significant difference across centers (p=0.7293) at the 0.15 significance level. The chronic effectiveness objective was met in the final analysis.

The study utilized a core lab for the adjudication of the baseline and 6-month 48-hour Holter recordings. FDA carefully re-reviewed a significant randomly selected portion of the Holter recordings provided by the sponsor. In general, the FDA review confirmed the core lab determinations.

The majority of medical management subjects (54 of 72, 75%) received a new AAD or an AAD dose change and received at least one DC cardioversion over the 6 month study period as recommended in the study protocol. Among the 54 Medical Management subjects, 15 (27.8%) were determined to be treatment successes whereas 39 (72.2%) were determined to be treatment failures due to AF recurrences (n = 33) or missing chronic success data (n = 6). Three (3) subjects received no medical therapy after randomization and were classified as treatment failures.

6.3.5 Conclusion of Final Analysis for All Enrolled Subjects

The pre-specified overall study success was not met in the final analysis because the acute safety endpoint was not met.

6.4 Additional Safety Analyses

6.4.1 Stroke

Among a total of 176 subjects who received at least one study procedure, five (5) subjects experienced a stroke within one month of a study procedure, giving a peri-procedural stroke rate of 2.8% with an upper bound limit of 6.5%.

As shown in Table 9 below, 4 strokes occurred within 12 hours of an ablation procedure and 1 stroke occurred on day 31 post crossover ablation. All stroke subjects received LMWH bridging prior to the procedure. All but one stroke subject had an INR value of < 2 prior to the procedure but there was no protocol recommended pre-procedure target INR value. At the time of stroke, INR values were subtherapeutic (< 2) in all four stroke subjects with available INR data. All stroke subjects received electrical cardioversion for AF at the completion of the procedure. Complete resolution of neurological deficits occurred in two stroke subjects by the 6 months follow-up visit.

All five (5) strokes were adjudicated as SADEs. Three of the 5 strokes were adjudicated by the CEC/DSMB as possibly related to the device and definitely related to the procedure. The remaining two were categorized as possibly related to the device and probably related to the procedure. FDA considers all strokes to be device related because there was no convincing evidence to demonstrate they were otherwise. The table below (Table 9) summarizes the stroke events including the patient characteristics and outcomes.

Table 9. Summary of Subjects with Peri-Procedural Stroke

Subject ID	Age	$CHADS_2$ Score	LA Size (cm)	Baseline INR	LMWH Bridging	Event Onset	INR at Stroke	Cardiac Rhythm at Stroke	Presenting Symptoms/ Signs	SAE Category*	Outcome
	59	1 HTN	5.5	1.5	Yes	< 12 hours	1.1	SR	Dysarthria, some weakness of right lower extremity, apraxia of right hand	I	Complete recovery by 6 mos F/U
	56	1 HTN	5.0	1.1	Yes	12 hours post-procedure	1.1	SR	Diplopia, partial gaze palsy, and mild dysarthria	I†	Diplopia unresolved by 6 mos F/U
	67	2 HTN DM	4.9	1.2	Yes	< 12 hours	1.2	SR	Anomia, visual field deficits, and subtle right hemiparesis	I	Anomia not completely resolved by 6 mos F/U
	49	1 HTN	4.4	1.1	Yes	12 hours post-procedure	1.2	Not Avail-able	Left arm weakness and loss of fine motor skills, left facial paresis	I	Neurological deficits resolved at 6 mos F/U per narrative from the sponsor
	69	3 DM, HTN CHF	4.6	2.3	Yes	Post-procedure day 31	N/A	SR	Visual filed defect	I	Visual field defect remained unchanged at 6 mos F/U

* SAE category I – Death or event with permanent injury or impairment; Category II – Event with temporary or reversible impairment.
† This event was originally categorized at II by the CEC/DSMB. However, FDA has re-adjudicated this event.

Compared to the subjects who received a study procedure but did not experience peri-procedural stroke, stroke subjects had higher $CHADS_2$ scores (1.6 ± 0.9 vs. 0.8 ± 0.8), increased left atrial diameter (4.9 ± 0.4 vs. 4.5 ± 0.5 cm), lower pre-procedure INR values (1.3 ± 0.27 vs. 1.6 ± 0.64), lower ACT values during left atrial access (320 ± 25 vs. 333 ± 35 seconds) and longer left atrial dwell (208 ± 65 vs. 162 ± 48 minutes) and procedure times (243 ± 59 vs. 196 ± 53 minutes).

The peri-procedural anticoagulation strategy was not a data point collected in the case report forms. Therefore, the impact of different anticoagulation strategies (i.e. bridging with LMWH or heparin pre- and post-ablation vs. continuation of oral anticoagulation throughout the peri-procedure period without LMWH or heparin bridging) on the peri-procedural stroke risk could not be assessed.

An additional from the Ablation Management arm experienced a stroke on day 40 post procedure, which was adjudicated by the CEC/DSMB as not related to procedure or device but related to recurrent AF and subtherapeutic anticoagulation. FDA agrees with CEC/DSMB's adjudication.

FDA Commentary: FDA is concerned about the high incidence of peri-procedural stroke observed in this trial. The incidence of peri-procedural stroke commonly reported in the catheter AF ablation literature ranged from 0 to 1.7%.[4,5,6,7,8,9,10,11]. FDA will be requesting Panel input on the significance of the peri-procedural stroke rate observed in this trial.

In addition to the data collected on stroke within this study, there have been two published peer-reviewed manuscripts[12,13] that have reported on the incidence of new asymptomatic cerebral embolic lesions identified on postprocedural DW-MRI after PV isolation for the treatment of paroxysmal or persistent AF. These studies compared the PVAC, one of the study catheters, with an irrigated RF ablation catheter and with a cryoballoon catheter. Their results showed that the PVAC catheter was associated with 37.5% and 38.9% incidence of new asymptomatic cerebral embolic lesions which was significantly higher than that associated with an irrigated RF ablation catheter (7.4% and 8.3%) and cryoballoon catheter (4.3% and 5.6%). Another recently published peer-reviewed manuscript also reported a higher incidence of new asymptomatic cerebral embolic lesions following AF ablation using phased RF technology with the PVAC alone or in combination with MAAC and MASC when compared with AF ablation using an irrigated RF catheter (41.7% vs. 21.4%)[14]. Although the long-term risks of silent cerebral infarct following AF ablation are unknown, the findings from the two studies

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[4]Cappato et al. Updated worldwide survey on the methods, efficacy, and safety of catheter ablation for human atrial fibrillation. Circulation: Arrhythmia and Electrophysiology. 2010; 3:32-38.
[5] Hunter RJ and Schilling RJ. Long-term outcome after catheter ablation for atrial fibrillation: safety, efficacy and impact on prognosis. Heart. 2010; 96(16): 1259-63.
[6] Oral H et al. Risk of thromboembolic events after percutaneous left atrial radiofrequency ablation of atrial fibrillation. Circulation 2006; 114: 759-765
[7] Calkins H et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systemic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol. 2009; 2: 349-61.
[8] Biase L et al. Periprocedural stroke and management of major bleeding complications in patients undergoing catheter ablation of atrial fibrillation. Circulation 2010; 121: 2550-2556.
[9] Scherr D et al. Incidence and predictors of periprocedural cerebrovascular accident in patients undergoing catheter ablation of atrial fibrillation. J Cardiovasc Electrophysiol 2009; 20: 1357-1363
[10] Oral H et al. Radiofrequency catheter ablation of chronic atrial fibrillation guided by complex electrograms. Circulation 2007; 115: 2606-12.
[11] Patel D et al. Long-term functional and neurocognitive recovery in patients who had an acute cerebrovascular event secondary to catheter ablation for atrial fibrillation. J Cardiovasc Electrophysiology 2010; 21(4):412-417
[12] Siklody C et al. Incidence of asymptomatic intracranial embolic events after PV isolation: comparison of different AF ablation technologies in a multicenter study. J Am Coll Cardiol 2011; 58: 681-8.
[13] Gaita F et al. Incidence of silent cerebral thromboembolic lesions after AF ablation may change according to technology used: comparison of irrigated RF, multipolar nonirrigated catheter and cryoballoon. J Cardiovasc Electrophysiol 2011 e-pub ahead of print.
[14] Deneke T et al. Post-ablation asymptomatic cerebral lesions: long-term follow-up using magnetic resonance imaging. Heart Rhythm 2011, July 1, (Epub ahead of print)

suggested that the use of the PVAC for AF ablation may have substantially greater embolic risk than open irrigated RF and cryoballoon ablation catheters.

FDA Commentary: FDA is concerned about the high incidence (up to 41.7%) of asymptomatic cerebral embolic lesions observed following the use of the PVAC catheter for the treatment of AF as reported in three separate clinical studies published in 2011[12,13,14]. FDA will be requesting Panel input on the emphasis that should be given to these published findings for assessing the approvability of this application.

6.4.2 PV stenosis

All subjects who received a study procedure underwent a CT or MRI at baseline and post-ablation study completion for assessment of PV stenosis. PV stenosis (defined as > 70% reduction in diameter) of one PV was identified in 6 subjects (3.4%) including 4 from the ablation arm and 2 crossovers. PV narrowing (50%-70%) of one PV was identified in 12 subjects (6.8%) including 9 from the ablation arm and 3 crossovers. Two subjects with PV stenosis (n = 1) or narrowing (n = 1) had symptoms related to PV stenosis. Therefore, among the 176 subjects who underwent a study procedure, 7 (4% with upper bound limit of 8.1%) had PV stenosis/symptomatic PV narrowing.

No PV angioplasty or stenting was performed for any of the subjects with PV stenosis or narrowing.

FDA Commentary: FDA is concerned about the high rate of PV Stenosis which was observed in this trial. The incidence of PV stenosis (defined as > 70% reduction in diameter) commonly reported in the catheter AF ablation literature ranged from 0% to 1.6%.[15,16,17,18] FDA will be requesting Panel input on the significance of the PV stenosis event rate observed in this trial.

6.4.3 Serious adverse events for Medical Management Arm

During the first 6 months of study follow-up, a total of 6 SAEs were reported for 4/69 (5.8%) subjects who were randomized to the Medical Management arm and received medical therapy. Of note, the events summarized in the table below do not include those SAEs that occurred after crossover ablation.

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[15] Scharf C et al. Anatomy of the pulmonary veins in patients with atrial fibrillation and effects of segmental ostial ablation analyzed by computed tomography. J Cardiovas Electrophysiol 2003; 14: 150-5.
[16] Dong J et al. Incidence and predictors of pulmonary vein stenosis following catheter ablation of atrial fibrillation using the anatomic pulmonary vein ablation approach: Results from paired magnetic resonance imaging. J Cardiovasc Electrophysiol 2005; 16: 845-52.
[17] Calkins H et al. Treatment of atrial fibrillation with antiarrhythmic drugs or radiofrequency ablation: two systemic literature reviews and meta-analyses. Circ Arrhythm Electrophysiol. 2009; 2: 349-61
[18] Wilber DJ et al. Comparison of antiarrhythmic drug therapy and RF catheter ablation in patients with paroxysmal AF: a randomized controlled trial. JAMA. 2010; 303: 333-40

Table 10. SAEs in Medical Management Subjects Who Received Medical Therapy

Description	Number of Subjects with SAE (%) (N = 69)
GI bleed secondary to anticoagulation	2
Hyperkalemia	1
AF with rapid ventricular response	1
Chest discomfort related to CAD	1
Total SAEs	**4 *(5.8%)**

* Two events occurred in one patient. Therefore, the number of subjects is 4 even though the number of events is 5.

Of note, no death, stroke, TIA, myocardial infarction, or thromboembolism occurred during study follow-up in the Medical Management Arm (excluding crossovers).

6.5 Additional Effectiveness Analyses

6.5.1 Gender Analysis

Males accounted for the majority of subjects enrolled in the TTOP-AF study. One hundred fifteen (115) out of 138 (83.3%) Ablation Management Arm subjects and 60 out of 72 (83.3%) Medical Management Arm subjects were male.

As shown in the table below, the chronic success rate was higher in male subjects than that in female subjects in the Ablation Management Arm, and the reverse was the true in the Medical Management Arm. For male subjects, the chronic success rate was higher in the Ablation Management Arm than that in Medical Management Arm (58.3% vs. 23.3%). For female subjects, chronic success was similar between the Ablation Management arm and the Medical Management Arm (43.5% vs. 41.7%). These calculations were based on the ITT population with all missing data imputed as failures.

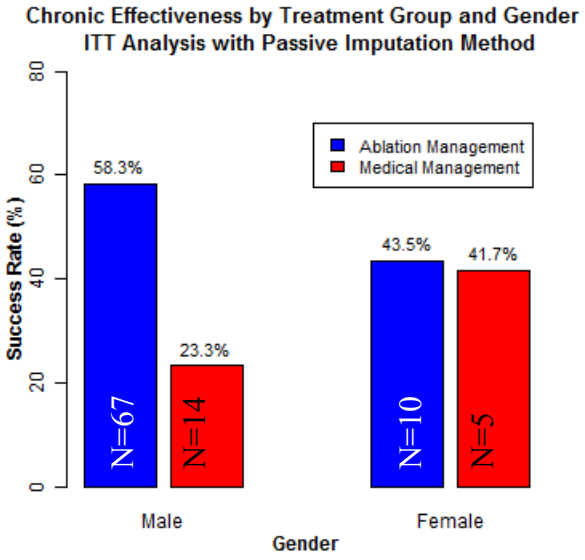
Table 11. Chronic Effectiveness by Treatment Group and Gender

Chronic Effectiveness Criteria	Ablation Management Arm (N = 138)		Medical Management Arm (N = 72)	
	Males N= 115 n (%)	Females N= 23 n (%)	Males N= 60 n (%)	Females N= 12 n (%)
≥ 90% reduction in clinically significant AF	81 (70.4%)	12 (52.2%)	14 (23.3%)	5 (41.7%)

Chronic Effectiveness Criteria	Ablation Management Arm (N = 138)		Medical Management Arm (N = 72)	
	Males N= 115 n (%)	Females N= 23 n (%)	Males N= 60 n (%)	Females N= 12 n (%)
Off all AADs at 6 month F/U	79 (68.7%)	16 (69.6%)		
Acute success of all ablation procedures	109 (94.8%)	19 (82.6%)		
Subjects meeting all success criteria	**67 (58.3%)**	**10 (43.5%)**	**14 (23.3%)**	**5 (41.7%)**
Number of missing endpoints	13	4	13	2

The difference in the proportion of male subjects who achieved chronic effectiveness success between the two treatment arms and the corresponding 95% confidence interval were 34.9% (20.9%, 48.9%).
The difference in the proportion of female subjects who achieved chronic effectiveness success between the two treatment arms and the corresponding 95% confidence interval were 1.8% (-32.7%, 36.3%). Please note that no multiplicity adjustment was applied to the subgroup analysis. The chi-square test for the interaction between treatment arm and gender was conducted by the FDA and the corresponding p-value was 0.0720.

Figure 8.



In the Ablation Management arm, the proportion of subjects who experienced acute safety failures was 21.7% (5 out of 23) for females, which was higher than that for males

(10.4%, 12 out of 115). The FDA conducted a Fisher's exact test to compare the acute safety failure rate between two arms, and the corresponding two-sided p-value was 0.1618. However, because of the number of females enrolled, no conclusions can be drawn from this data.

FDA Commentary: Because of the small numbers and inability to adjust for covariates, FDA is not able to determine if there is a different treatment effect observed in this study between males and females.

6.5.2 Performance of the Crossover Subjects

A total of 43 Medical Management subjects that were deemed study failures with <90% AF reduction by Holter monitoring at the 6 month follow-up visit and met all exclusion criteria were allowed to crossover to receive an ablation procedure for treatment of their AF.

The chronic effectiveness success was achieved in 22 (51.2%) out of 43 Crossover subjects, which seems consistent to the results observed in the Ablation Management arm. Eight (18.6%) Crossover subjects experienced at least one SADEs within the 7 days post-ablation procedure and 4 (9.3%) Crossover subjects failed to remain free of SAEs during the 6-month post-ablation follow-up.

6.5.3 Chronic effectiveness for those who received study treatment

An additional analysis was performed to assess chronic success after excluding 6 subjects who did not receive ablation with the investigational device and 3 subjects who did not receive medical therapy. Chronic success was achieved in 77 of these 132 subjects (58.3%) who received ablations using the study device and 19 of the 69 subjects (27.5%) who received medical therapy.

6.5.4 Chronic effectiveness stratified by AF types

An additional analysis was also performed to assess chronic effectiveness stratified by AF types as defined by the HRS Consensus Document of 2007. The chronic success rate in the Ablation Management Arm was similar for persistent AF subjects (54.6%) and longstanding persistent AF subjects (58.5%). Persistent AF was defined as non self-terminating AF lasting greater than seven days but no more than one year. Longstanding persistent AF was defined as continuous AF of greater than one year duration. In the Medical Management Arm, chronic success was higher for persistent AF subjects (28.1%) than longstanding persistent AF subjects (20%). Per the pre-specified passive imputation method, missing endpoints are treated as failures.

Table 12. Primary Effectiveness by Treatment Group and AF Type

Chronic Effectiveness	Ablation Management Arm (N = 138)		Medical Management Arm (N = 72)	
	Persistent AF N= 97 n (%)	**Longstanding persistent AF N= 41 n (%)**	**Persistent AF N= 57 n (%)**	**Longstanding persistent AF N= 15 n (%)**
≥ 90% reduction in clinically significant AF	64 (66.0%)	29 (70.7%)	16 (28.1%)	3 (20.0%)
Off all AADs at 6 month F/U	66 (68.0%)	28 (68.3%)		
Acute success of all ablation procedures	91 (93.8%)	37 (90.2%)		
Subjects meeting all success criteria	**53 (54.6%)**	**24 (58.5%)**	**16 (28.1%)**	**3 (20.0%)**
Number of missing endpoints	13	4	11	4

FDA Commentary: FDA believes that the patient population for this trial is heterogenous because it contains both persistent AF patients and long-standing persistent AF patients. Patients with persistent AF may respond differently to catheter ablation than those with long-standing persistent AF according to the HRS Consensus Statement on Catheter and Surgical Ablation of AF. However, the data from this trial could not support or refute that conclusion as the trial was not powered to examine the treatment effect across AF populations. FDA will be asking the panel to comment on the description of the population provided in the Indications for Use statement and whether it adequately reflects the population that was actually enrolled. Furthermore, the panel will be asked to comment on whether the study results demonstrated a treatment effect for both the persistent AF population and the longstanding persistent AF population.

6.5.5 Chronic effectiveness per HRS Expert Consensus Statement

The PMA study protocol including the definition of chronic success was fully approved in April 2007. After that, the Heart Rhythm Society (HRS) published a HRS Expert Consensus Statement on Catheter and Surgical Ablation of AF (HRS Expert Consensus

Statement[19]) in which the definition of success and the use of a blanking period were recommended for AF ablation trial. The HRS Expert Consensus Statement recommended ablation success be defined as freedom from 30 seconds or more AF/AFL/AT off Class I and III AAD therapy following a 3 months blanking period after ablation.

Per FDA's request, additional post-hoc analyses were performed to assess the chronic effectiveness by retrospectively applying the success definition recommended in the 2007 HRS Expert Consensus Statement. This would result in the primary effectiveness successes in the Ablation Management Arm being classified as treatment failures if they had any of the following:

1. ECG documented AF/AFL/AT recurrences following 3 month post ablation through 6 month visit;
2. DC cardioversion or ablation for AF/AFL/AT following 3 mos through 6 month visit;
3. more than 30 seconds of continuous AF/AFL on 6-month Holter; or
4. on Class I or III AAD at any time following the 3-month visit through 6-month visit

As shown in Table 13 below, chronic effectiveness at 6-month post-ablation would decrease to 37% if success required < 30 seconds of continuous AF/AFL/AT and off all class I and III AAD after a 3-month blanking period.

Table 13. Chronic Effectiveness Per HRS Expert Consensus Statement Definition

Chronic Success Criterion	6-month Success for Ablation Management Arm (n = 138)
Off AAD Success: (1) No ECG documented AF/AFL/AT recurrences following 3 months through 6 months visit; (2) No DC cardioversion / ablation for AF/AFL/AT following 3 months through 6 months; (3) < 30 seconds of continuous AF/AFL on 6-month Holter; and (4) Off all Class I and III AADs following the 3-month visit through 6-month visit.	51 (37%)

[19] Calkins H, et al. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures, and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2007; 4(6):816-61.

FDA Commentary: The sponsor met the pre-specified endpoint using the protocol defined definition of treatment success in the ablation management group as measured in a 48-hour Holter. However, when using a more conservative definition of treatment success as recommended by the HRS Expert Consensus Statement, the success rate in the Ablation Management Arm drops from 55.8% to 37%. FDA recognizes that the 37% success rate may have underestimated the treatment effect of the device because the protocol did not require discontinuation of Class I and III AAD at the 3 months follow-up visit. In fact, 15 (10.9%) subjects were classified as failures only because they were on a Class I or III AAD before the 6 months visit. Therefore, FDA considers that the true 6-month success rate per HRS Consensus Statement definition was somewhere between 37% and 47.8%. FDA will be seeking advice from the panel regarding the appropriateness of using the protocol defined treatment success, which includes a reduction in AF burden on a single 48-hour Holter, as the appropriate endpoint for the study population that included a large proportion of patients with persistent AF versus applying the treatment success rules from the 2007 HRS Expert Consensus Statement retrospectively. Moreover, the panel will be asked to comment on whether FDA should accept a 6 month ablation success rate, which could be as low as 37%, as evidence of effectiveness for the study device.

6.5.6 Chronic effectiveness for Medical Management Arm using 30 seconds criterion

Among 72 subjects from the Medical Management arm, 19 had no more than 30 seconds of continuous AF/AFL on 6-month Holter. Thus, the 6-month success rate would remain at 26.4% if success required no more than 30 seconds of continuous AF/AFL on 6-month Holter.

6.5.7 Chronic Effectiveness Outcomes of the Subjects with 12-Month Holter Recording Data

Per FDA's recommendation, study subjects were approached to obtain 12-month follow-up data to assess long term outcomes of ablation.

Although the TTOP-AF protocol defined a 6 month follow-up period for all subjects, the sponsor claims that every attempt was made to obtain 12-month follow-up data for all pivotal subjects who completed the trial for evaluation of effectiveness as recommended in the 2007 HRS/ EHRA/ ECAS/Expert Consensus Statement that were published after the TTOP-AF trial began. A post-study CRF form was created for data collection and was sent to investigational centers prefaced with a letter requesting 12 month data for all 210 pivotal subjects. If there was no response, follow-up e-mails and phone calls were made until a response was obtained.

By March 30, 2011, 12-month Holter recording was completed from 106 subjects, including 71 out of 138 Ablation Management subjects, 23 out of 43 Medical

Management subjects who crossed over to the ablation treatment, and 12 out of 29 Medical Management subjects who did not cross over to the ablation treatment.

Table 14. Summary of 12-Month Holter Requests

Outcome of Holter Request	Ablation Management N=138	Medical Management N=72		Total N=210
		Medical Therapy N=29	Crossover N=43	
Completed	**71 (51.4%)**	**12 (41.4%)**	**23 (53.5%)**	**106 (50.5%)**
Subjects withdrawn	13 (9.4%)	6 (20.7%)	4 (9.3%)	23 (11.0%)
Subject/Site refusal	46(33.3%)	9 (31.0%)	13 (30.2%)	68 (32.4%)
Visit done, Holter not completed	8 (5.8%)	2 (6.9%)	3 (7.0%)	13 (6.2%)

Among the 106 subjects who completed the 12-month Holter recording, there were 94 from Subjects Treated with Ablation (including 23 subjects randomized to Ablation Management and crossover subjects). Of the 94 available 12-month Holter recordings from Subjects Treated with Ablation, 62 demonstrated a ≥90 % reduction of clinically significant AF with or without AADs on 6-month Holters. Of these 62 6-month successes in the ablation group, 50 achieved ≥90% reduction in clinically significant AF without AAD on a 12-month Holter.

There were 12 subjects not treated with ablation that completed 12-month Holter recordings. None of the 12 Medical Management successes who completed the 12-month follow-up visit with 48-hour Holter had DC cardioversion after the 6 months follow-up visit. On the 48-hour Holter at 12 months follow-up visit, none of the 12 subjects had greater than 10 minutes of continuous AF/AFL. Therefore, the long-term success rate for the Medical Management arm would be at least 12/72 (16.7%).

Table 15. Treatment Success Evaluated at 12-Months

Follow Up Efficacy Success Criteria	Subjects Treated With Ablation On or Off AAD with Success at 6 months (N=62)			Medical Mgmt. Subjects
	Randomized (N=48)	Crossover (N=14)	Total (N=62)	(N=12)
90% reduction in clinically significant AF at Post Study Completion Follow Up:				
With antiarrhythmic drug	2 (4.2%)	1 (7.1%)	3 (4.8%)	12 (100.0%)
Without antiarrhythmic drug	39 (81.3%)	11 (78.6%)	50 (80.6%)	0 (0.0%)

The results provided by the sponsor have several shortcomings:

- Because there was not a 12 month endpoint included as part of the protocol, the data provided is incomplete and could be subject to substantial selection bias.
- The analysis did not take into account AF recurrences or AAD therapy/DC cardioversion for AF between the 6- and 12-month Holter recordings.

Of the 19 subjects from the Medical Management arm who were treatment successes at 6 months, 12 completed the 12-month follow-up visit with a 48-hour Holter. The remaining 7 subjects either refused to attend the 12-month follow-up visit (n = 6) or did not complete a 48-hour Holter at the 12-month follow-up visit (n = 1). One of the 7 subjects was reported to receive AF ablation following the 6-month visit.

FDA Commentary: It should be noted that the 12-month Holter recordings were not completed for 104 (49.5%) out of the 210 randomized subjects who either withdrew from the study (23 subjects), refused to participate or the site refused to participate (68 subjects), or completed the 12-month visit without obtaining Holter recording (13 subjects). The large proportion of missing data, some of which may be missing not at random, might introduce significant bias into the results of the 12-month Holter recording data.

FDA Commentary: Based on the limited 12-month data available, it seems that the AF recurrence rate among subjects treated with the investigational device and not using AAD is approximately 19.4% between 6 and 12 months following the last ablation procedure. However, given the serious limitations of this data, FDA requests input on the emphasis that should be given to the 12-month data that could be collected.

7 Post Approval Study

Note: The inclusion of a Post-Approval Study section in this summary should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device. The presence of a post-approval study plan or commitment does not in any way alter the requirements for premarket approval and a recommendation from the Panel on whether the risks outweigh the benefits. The premarket data must reach the threshold for providing reasonable assurance of safety and effectiveness before the device can be found approvable and any post-approval study could be considered. The issues noted below are FDA's comments regarding potential post-approval studies, for the Panel to include in the deliberations, should FDA find the device approvable based upon the clinical premarket data.

The FDA review team has made the recommendation that if the Medtronic Catheter Ablation System (System) device is approved, a post-approval study (PAS) should be required as a condition of approval for this ablation system. Through review of the Premarket Data, FDA has identified the following postmarket concerns and recommends that a PAS be conducted to:

- Assess the long term performance of the device.
- Assess device performance in a representative population of providers and patients.
- Assess if there is a difference in effectiveness across gender, as suggested by small numbers in the premarket study data

Throughout the premarket review of the PMA, FDA and the Sponsor have worked closely to design this potential study. However, there are still outstanding issues that require panel input. An overview of the proposed PAS protocol is provided below. The sponsor's PAS protocol has been developed interactively and is currently being negotiated.

7.1 Overview of Proposed Post-Approval Study

Study Design and Study Population
The sponsor proposes a prospective, multicenter, non-randomized observational postapproval study, in order to evaluate the safety and effectiveness of the device in a real-world setting over a longer period than was evaluated in the pre-market study. Patients will be enrolled who meet the study eligibility criteria, which include symptomatic persistent and long-standing persistent AF, age between 18 and 70, and intolerance or failure of at least one Class I or Class III anti-arrhythmic drug.

Hypotheses

Effectiveness hypothesis
The sponsor proposes testing an effectiveness hypothesis that states that there will be a 40% treatment success rate at 12-months.

Safety hypothesis
The sponsor proposes testing a safety hypothesis that states that the combined serious procedure- and device-related adverse event rate at 12 months will be less than 16%.

Enrollment Plan and Follow-up
Subjects enrolled and treated with the study ablation system will be required to attend regular follow-up visits to monitor their condition. Follow-up visits are expected to occur at baseline, study ablation procedure, discharge, 3, 6 and l2 months and annually thereafter until subjects complete 5 years of follow-up from their index procedure. Data collection will consist of, but will not be limited to:

- History and physician exam
- Review of arrhythmic symptoms
- Anticoagulation use
- Review of anti-arrhythmic drug use
- 12-lead ECG
- Neurologic exam
- 48-hour Holter monitoring (12 months, 2, 3,4 and 5 years)

Primary Endpoints
The primary effectiveness outcome is treatment success rate at 12-months. Treatment success is defined as a 90% reduction in AF burden, which is defined as cumulative time

in AF with a minimum 30 seconds of AF based on 48-hour Holter monitoring outside the 180-day blanking period OR no interventions for AF (except for repeat ablation using the Medtronic CAS or cardioversion within the 180-day blanking period after the index procedure).

The primary safety outcome is the proportion of patients who experience a serious procedure- or device-related adverse events within 12 months. A serious adverse event is defined as an event that is life threatening, results in permanent impairment of body structure or function, requires hospitalization or prolongation of an existing hospitalization, requires intervention to prevent any of the above, or leads to fetal death, distress, congenital abnormality or birth defect.

Secondary Endpoints
Secondary endpoints include major atrial fibrillation events (MAFE) at 1, 2, 3, 4, and 5 years, where MAFE is defined as a non-procedure- or device-related event, including any of the following

- Cardiovascular death
- Hospitalization for:
    - AF recurrence or ablation
    - Atrial flutter ablation (excluding Type I)
    - Systemic embolization
    - Congestive heart failure
    - Hemorrhagic event
    - Anti-arrhythmic drug initiation, adjustment or complication
- Myocardial infarction
- Stroke

<u>Primary Effectiveness</u>
Using a one-sided exact test of binomial proportions and assuming a 80% power, one-sided alpha of 0.025, underlying effectiveness rate 50%, performance goal 40%, and attrition of 20% at one year the sponsor states the resulting sample size is 263.

<u>Primary Safety</u>
Using a one-sided exact test of binomial proportions and assuming a 80% power, one-sided alpha of 0.025, underlying safety rate 10%, performance goal 16%, and attrition of 20% at one year the sponsor states the resulting sample size is 239.

Statistical Plan
The sponsor did not provide a statistical analysis plan.

7.2 FDA Comments on Proposed Post-Approval Studies

Study Design and Study Population
The sponsor has not proposed a plan to ensure a balanced enrollment of subjects by gender. Historically, clinical cardiovascular studies often include a paucity of female

subjects. In the premarket study done to support this application, the data suggest that there may be a different treatment effect between males and females. Because of the small number of female subjects enrolled in the premarket study, and because of potential confounding covariates, it is difficult to draw conclusions regarding a gender difference in effectiveness from the premarket data. Therefore, balanced enrollment by gender would be an important aspect to consider for a post-approval study.

FDA Commentary: Due to the limitations of the data in the premarket study, FDA requests panel input on the appropriateness of including a balanced gender enrollment and pre-specified analyses that will allow for a reasonable comparison of treatment effect between males and females.

Primary Endpoints

The proposed performance goal for both safety and effectiveness should be justified by the sponsor. Furthermore, FDA believes that the one year follow-up period proposed for the post-approval study to assess the primary effectiveness endpoint is insufficient to assess the durability of effect. FDA is also concerned that the definition of treatment success is suboptimal because (1) it is based on > 90% AF burden reduction rather than freedom from AF/AFL/AT (> 30 seconds) as recommended by the HRS Expert Consensus Document; and (2) it uses a 6 months rather than 3 months blanking period recommended by the HRS Expert Consensus Document.

FDA Commentary: FDA is concerned that the length of follow-up proposed in the primary endpoint is not adequate in order to assess the durability of the ablation treatment. FDA requests input on the appropriate length of follow-up in the primary endpoint for this patient population.

FDA Commentary: FDA is concerned about the definition for treatment success which has been proposed for the post-approval study. FDA requests input on the appropriate definition for treatment success.

FDA Commentary: The SADE rate that was accepted for the IDE study was not met. Therefore, FDA seeks panel input on the appropriateness of this rate given the results of the trial in this population.

FDA Commentary: The upper confidence limit for both stroke and PV Stenosis in the premarket trial was higher than expected as discussed in the safety analysis section above. FDA is considering whether the post approval study should be adequately powered to better define the confidence limit for these important safety events.

8 Conclusions

The Sponsor met the primary effectiveness endpoint and failed the primary safety endpoint in the population studied, based upon their pre-specified hypotheses. Although Ablation Management using the System was found to be superior to the Medical Management control at 6 months (55.8% vs 26.4%), the superiority is decreased substantially if a more recently accepted criteria to assess ablation treatment success were used, retrospectively, to assess effectiveness at 6 months (37% vs 26.4%).

FDA is concerned about the overall safety profile of the System. When using an analysis that includes all safety events observed in the trial for subjects that underwent at least one study procedure, 38 subject with at least one serious device/procedure related event out of 176 patients (133 Ablation Arm Subjects + 43 crossover subjects) were observed for an overall safety assessment rate of 21.6%.

Of particular concern is the high peri-procedural stroke rate observed in the trial (2.8% with an upper bound limit of 6.5%). This concern is echoed by the recently published peer-reviewed reports suggesting that the PVAC (one of the three catheters included in this PMA) is associated with up to a five-fold higher incidence of asymptomatic cerebral embolic lesions as assessed by pre-and post ablation diffusion weighted MRI imaging when compared to other ablation catheters.

In addition, there was a higher than expected rate of PV stenosis/symptomatic PV narrowing (4% with upper bound of 8.1%) associated with the use of the System.

Given these concerns, FDA would like panel input on the overall risk/benefit profile and approvability of the device.