DIAMOND-AF STUDY

Study Title: A Randomized Controlled Clinical Evaluation of the **Diamond**Temp™ Ablation System for the Treatment of Paroxysmal **A**trial **F**ibrillation

Sponsor:	**Epix Therapeutics (EPIX)** 945 Stewart Drive, Suite 100 Sunnyvale, CA 94085 USA +1 (408) 755-1500
Protocol No:	TP00599
Investigational Device:	**DiamondTemp Ablation System** *(Inclusive of the DiamondTemp Ablation Catheters, DiamondTemp Catheter-to-RFG Cable, DiamondTemp GenConnect Cable, DiamondTemp RF Generator, DiamondTemp Irrigation Pump and DiamondTemp Irrigation Tubing Set)*
Revision Number:	I
Effective Date:	01 APR 2020

1. STUDY CONTACT INFORMATION

Sponsor

Katie Flor
Principal Clinical Research Specialist/Global Study Manager
[redacted]
Email: katie.j.flor@medtronic.com

Coordinating Principal Investigators, US

Tom McElderry, MD, FACC, FHRS
Section Chief, Cardiac Electrophysiology
[redacted]

William Maddox, M.D., FACC, FHRS
Assistant Professor, Electrophysiology
[redacted]

University of Alabama Birmingham (UAB)
930B Faculty Office Tower
510 20th Street South
Birmingham, AL 35294

Coordinating Principal Investigator, OUS

Josef Kautzner, M.D., PhD, FESC
Director, Electrophysiology
Institut klinické a experimentální medicíny (IKEM)
Vitebsk 1958/9
140 21 Prague 4
[redacted]

Steering Committee *Including Coordinating Principal Investigators*	**Andrea Natale, M.D., FACC, FHRS** Director, Electrophysiology Texas Cardiac Arrhythmia Institute at St. David's Medical Center [redacted] **Frank Cuoco, M.D., MBA** Director, Arrhythmia Research Center Trident Medical Center [redacted]
OUS Contract Research Organizations (CRO)	**High Tech Med Consult** Firmlova 1322/4e 15500 Prague 5, Czech Republic Phone: +402 777 671 069 [redacted] **MERC srl** Via Elia Capriolo, 41 25122 Brescia, Italy Phone: +39 030 2754021 [redacted]
Data Management / Biostatistics	**Advanced Research Associates** Data Management / Biostatistics 2350 Mission College Blvd., Suite 825 Santa Clara, CA 94054 Sr. Director, Biostatistics: Jennifer Nezzer Phone: +1 (650) 817-7062 [redacted]
Electronic Data Capture (EDC)	**Medrio** 345 California Street, Suite 325 San Francisco, CA 94104 Phone: +1 (415) 963-3700
ECG Core Lab	**HeartcoR Solutions, LLC** Event Monitor, ECG Core Lab 2403 Harnish Drive #201 Algonquin, IL 60102 Project Manager: Madalina Andreescu, BS, CRA, CCT Phone: +1 (224) 333-3318 [redacted]

Investigator Protocol Signature Page and Agreement

I have read this Investigational Plan and agree to adhere to the requirements. I will share this Investigational Plan and all pertinent information to all site personnel involved in this study. I will discuss this material with them and ensure they are fully informed regarding the study products and the conduct of the study.

I agree to conduct the study as outlined in the Investigational Plan, in accordance with the signed clinical study agreement and to the ethical principles stated in the latest version of the Declaration of Helsinki (2013), the applicable guidelines for good clinical practices, MEDDEV 2.7/4 (Guidelines on Clinical investigations: A Guide for Manufacturers and Notified Bodies) and 2.7/3 (Clinical investigations: Serious Adverse Event reporting), ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice) or the applicable local and international regulations, whichever provide the greater protection of the individual.

I agree to provide all the information requested in the Case Report Forms presented to me by the Sponsor in a manner to assure completeness, legibility and accuracy. I agree to actively enroll subjects into this study.

I also agree that all information provided to me by the Sponsor, including pre-clinical data, protocols, Case Report Forms, and any verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be relayed in confidence to the Institutional Review Board / Ethics Committee.

In addition, no reports or information about the study or its progress will be provided to anyone not involved in the study other than the Sponsor, the Institutional Review Board / Ethics Committee, the core labs, or the Data Safety Monitoring Board. Any such submission will indicate that the material is confidential.

_____ _____

Investigator Signature Date

_____

Investigator Printed Name

_____ _____

Sponsor Signature Date

_____

Sponsor Printed Name

2. REVISION HISTORY

Revision Level	DCO	Description of Change	Reason for Change	Effective Date
A	0426	Initial Release	N/A	08/25/2017
B	0429	a. Update section 7.1, Proposed Intended Use of the Investigational Device to include: accessories (DiamondTemp Cable-to-RFG Cable, DiamondTemp GenConnect Cable, DiamondTemp Irrigation Pump/Tubing Set); removed ablation, RF, and three dimensional descriptors. b. Update SAE rates for 7 and 30 day follow up	a. Clarification of statement; no change to intent. b. Reflects updated results.	08/29/2017
C	0438	Updated Table 4, Summary of Procedural Data, in Section 5.	Reflects updated results.	08/31/2017
D	0608	a. Updated planned subject sample size from 350 to 480. b. Revised primary safety endpoint from 7 days to 30 days and included clinically symptomatic PV stenosis through 6 months. c. Added atrial flutter and atrial tachycardia to primary effectiveness endpoint. Revised effectiveness failure definition to remove time period and add inability to isolate all accessible targeted PV; use of non-study device for AF targets; restricted repeat ablation to 1 procedure during blanking period. d. Defined single procedure success and study success. e. Revised inclusion criteria for PAF history from 12 to 6 months from index procedure and requirement for physician documentation for recurrent, self-terminating AF.	a. Revised statistical calculations in G170227 A001 and A002; FDA approval letter dated February 7 2018. b-g. Feedback from FDA in G170227 amendment responses. h. Supports request from FDA to add PV stenosis to primary safety endpoint. i-o. Feedback from FDA in G170227 amendment responses.	02/20/2018

Revision Level	DCO	Description of Change	Reason for Change	Effective Date
		f. Revised randomization stratification to include failure of AADs. g. Added requirement for bi-monthly periodic event monitoring from 3 to 12 month follow up. h. Added definition of PV stenosis. i. Revised stroke definition. j. Revised sample size justification, modifying estimated attrition rate to 7% and composite safety rate to 6.5%. h. Revised enrolled patient criteria to be the point at which subject is randomized to a treatment arm. i. Revised baseline tests to include TEE and ICE diagnostics and criteria to assess subjects for thrombus. j. Clarified that continuation of AADs should be at the physician discretion and at the failed dose. k. Added instructions for placement of esophageal temp probe and guidance for temperature increase that should terminate energy delivery. l. Clarified that EGM will be used to guide termination of RF delivery within 3-5 seconds after EGM amplitude is achieved. m. Added anticoagulation guidelines based on 2017 HRS Expert Consensus Standard on Catheter and Surgical Ablation of AF. n. Revised physical exam from limited to full. o. Added questionnaire for subjects to ask which treatment they believed		

Revision Level	DCO	Description of Change	Reason for Change	Effective Date
		they received (investigational, control or unknown).		
E	0676	a. Updated address for steering committee member. b. Added DiamondTemp Bidirectional Catheter to section 3 (Protocol Summary), section 7.3 (Investigational Device Description), section 7.4 (DiamondTemp Ablation Catheter) c. Clarification that clinical subjects from US sites will be approximately 50% (from a minimum of 50%). d. Clarification that inclusion criteria of at least one episode of PAF, documented by electrocardiographic data, is sufficient (versus requiring documented duration of a minimum of 30 seconds) in section 3 (Protocol Summary) and section 9.2 (Study Inclusion Criteria). e. Revision of regularly prescribed amiodarone as an exclusion criteria from within 3 months of enrollment to 2 months of enrollment in section 3 (Protocol Summary), section 8.2 (Study Design) and section 9.3 (Study Exclusion Criteria). f. Clarification of randomization stratification in section 8.2 as blocked randomization stratified by site followed by stratification by failure of Class I/III or Class II/IV AADs.	a. Updated hospital association b. Five day notice submitted to FDA on 3/22/2018 as G170227 S002. c. Enrollment rate in Europe at multiple centers is ongoing; a hard stop at exactly 50% of total study subjects (total subjects = 480) may not be possible. Subjects slightly in excess of 50% will not impact overall study conclusions. d. Steering committee feedback that requiring a 30 second recording is impractical. Per the committee, a recording of any duration, with objective electrocardiographic evidence, is sufficient to document PAF. e. Based on steering committee feedback and the pharmacokinetic profile of amiodarone, reducing the exclusion criteria to 60 days still allows for subjects to be amirodarone-free	04/18/2018

Revision Level	DCO	Description of Change	Reason for Change	Effective Date
		g. Clarification in Table 6 and section 12.7 (Adverse Event Reporting) of extended hospitalization events that are and are not included in safety endpoints. h. Clarification of AADs during the effectiveness evaluation period as acceptable to discontinue an AAD but not acceptable to add a new class of AAD or to substitute an AAD in Section 11.5 (Post Procedure). i. Clarified early recurrences of atrial arrhythmias within the blanking period (section 11.9, Repeat Ablation Procedure) as AF, AT and AFL, not solely AF.	during the blanking period. f. Change reflects intended stratification protocol and matches actual stratification being done. g. Not all extended hospitalizations meet the intent of the safety endpoints. h. Provides clarification of what constitutes a change in AAD regimen. i. Clarifies the original intent of the statement.	
F	0928	a. Added generator models to sections 7.3, 7.5. b. Clarified secondary endpoints for ablation time in protocol summary and section 8.5. c. Added analysis for catheter model evaluation in section 8.7. d. Added Per Protocol analysis to Section 8.7, Statistical Analysis. Clarified the Safety Analysis Set population in Section 8.7.	a. Study includes generator models CEDTG100 and CEDTG200. b. Assists in secondary endpoint data analysis. c. Provides for analysis by model of catheter used.	11/15/2018
G	1026	Updated company name to Epix Therapeutics or EPIX. Updated company address to reflect new headquarters Updated Company logo in the header of document Updated Sponsor email addresses to reflect @epixthx.com	Epix Therapeutics officially changed names and updated logo and email addresses to reflect name change EPIX moved company headquarters	2/27/2019
H	1036	Updated Section 5, 5.5, 5.6, Table 2 and Table 4 and Table 5. Changed contact info on page 3	Updated final TRAC-AF study data results Project Manager changed	03/18/2019

Revision Level	DCO	Description of Change	Reason for Change	Effective Date
I	1595	• Updated study contact information • Primary effectiveness endpoint definition updated to remove "symptomatic" from the definition (Section 3 and 8.4). • Secondary endpoint bullet number 4 updated to remove "symptomatic and asymptomatic" from the definition (Section 3 and 8.5). • Secondary endpoint bullet number 5 removed altogether (Section 3 and 8.5). • Clarified definition of secondary endpoint bullet number 7- single procedure success, in alignment with revised primary effectiveness endpoint definition (Section 3 and 8.5). • Added new secondary endpoint for single procedure success, in alignment with the composite primary effectiveness endpoint failure criteria (Section 3 and 8.5)	• Changed to reflect primary Sponsor study contact and current Advance Research Associates Contact • Primary effectiveness endpoint definition updated to align with endpoint failure definition and in accordance with study data collection (i.e. symptoms data associated with ECG transmissions not submitted to ECG Core Lab). • Secondary endpoint bullet 4 updated to align with primary effectiveness endpoint definition and in accordance with study data collection. • Secondary endpoint bullet 5 removed as it cannot be reliably analyzed. • Secondary endpoint bullet 7- single procedure success definition updated to clarify scope of analysis. • New secondary endpoint added per FDA feedback.	04/01/2020

3. PROTOCOL SUMMARY

Objective	The objective of this study is to demonstrate the safety and effectiveness of the DiamondTemp Ablation System for the treatment of drug refractory, recurrent, symptomatic paroxysmal atrial fibrillation.
Test Device	DiamondTemp Ablation System consists of: • DiamondTemp Ablation Catheter ○ Unidirectional and Bidirectional models • DiamondTemp Catheter-to RFG Cable • DiamondTemp GenConnect Cable • DiamondTemp Generator with Footswitch • DiamondTemp Irrigation Pump • DiamondTemp Irrigation Tubing Set The investigational device will be used with commonly available: • EP recording systems • Cardiac stimulators • EnSite™ Velocity™ or Precision™ Cardiac Mapping System
Control Device	St. Jude Medical (Abbott) Ablation System ○ TactiCath™ Quartz Contact Force Ablation Catheter ○ AMPERE™ RF Ablation Generator and Cables or equivalent ○ COOL POINT™ Irrigation Pump and Tubing or equivalent The control device will be used with commonly available: • EP Recording Systems • Cardiac Stimulators • EnSite™ Velocity™ or Precision™ Cardiac Mapping System
Study Design	The DIAMOND-AF study is a prospective, single-blind, 1:1 randomized, controlled trial being performed at multiple centers in the United States, Canada and Europe.
Planned Subject Sample Size	A maximum of 480 subjects will be enrolled and randomized in this study.
Planned Number of Global Investigational Sites	Subjects will be enrolled at up to 30 investigational sites in the United States (US) and outside of the US (OUS). Approximately 50% of the data will be generated from sites within the US.
Ablation Procedure	The primary focus of the ablation procedure is to create a series of point-by-point radiofrequency (RF) lesions encircling the left and right PVs to

	achieve electrical pulmonary vein isolation (PVI) from the rest of the left atrium (LA). Investigators may use their preferred approach to obtain PVI, such as antral or wide area circumferential ablation (WACA) targeting PVs individually or PV pairs ipsilaterally. PVI must be confirmed by entrance block at least 20 minutes following the last ablation around the respective PV. Targeting non-PV foci and complex fractionated electrograms (CFAE) is not recommended in this investigation. If the investigator identifies additional focal or macro-reentrant atrial sites to be clinically relevant to AF and requiring ablation, the ablation location will be documented.
Primary Safety Endpoint	The primary safety endpoint is defined as freedom from a composite of serious adverse events (SAE) occurring within 30-days and clinically symptomatic pulmonary vein stenosis through 6-months post-index ablation procedure, as adjudicated by an independent Clinical Events Committee (CEC) for relatedness to the procedure or device. The primary safety device- or procedure-related SAE composite will be the combined rate of the following events: • Atrioesophageal fistula • Bleeding complication • Cardiac tamponade / perforation • Death • Extended hospitalization • Myocardial infarction • Pericarditis • Phrenic nerve paralysis • Pulmonary edema • Pulmonary vein stenosis • Stroke post-ablation • Thromboembolism • Transient ischemic attack (TIA) post-ablation • Vagal nerve injury • Vascular access complications

Primary Effectiveness Endpoint	The primary effectiveness endpoint is defined as freedom from documented atrial fibrillation (AF), atrial flutter* (AFL) and atrial tachycardia (AT) episodes following the blanking period (3-month follow-up post-ablation procedure) through the end of the effectiveness evaluation period (12-month follow-up post-ablation procedure). An effectiveness failure is defined by any of the following events: • Inability to electrically isolate all accessible targeted pulmonary veins during the ablation procedure • Documented episodes of AF, AFL or AT lasting ≥ 30 seconds in duration as evidenced by electrocardiographic data during the effectiveness evaluation period • DC cardioversion for AF, AFL or AT during the effectiveness evaluation period • A repeat ablation procedure to treat AF, AFL or AT during the effectiveness evaluation period • Use of a new or modification to existing Class I-IV anti-arrhythmic drug (AAD) regimen to treat AF, AFL or AT recurrence during the effectiveness evaluation period • Use of a non-study device for ablation of any AF targets during the index or repeat ablation procedure during the blanking period • More than one (1) repeat ablation procedure during the blanking period * *Occurrence and/or ablation of cavotricuspid isthmus (CTI)-dependent AFL, as confirmed by entrainment maneuvers during EP testing at any time during this study is not a primary effectiveness failure because it is not considered an iatrogenic arrhythmia following a left atrial ablation procedure for AF.*
Secondary Endpoints	Secondary endpoints to characterize the performance of the DiamondTemp Ablation System, relative to the control device, will include: • Mean duration of individual RF ablations (seconds). • Mean cumulative RF time per procedure (minutes). • Freedom from a composite of SAE occurring within 7-days post-index ablation procedure as adjudicated by an independent CEC for relatedness to the procedure or device. • Freedom from documented AF, AT and AFL* episodes following the blanking period through 12-month follow-up post-ablation procedure in the absence of class I and III anti-arrhythmic drug therapy.

	• Rate of acute procedural success, defined as confirmation of electrical isolation of PVs via assessment of entrance block at least 20 minutes following the last ablation around the respective PV. • Rate of single procedure success defined as the rate of subjects treated with one single ablation procedure during study participation and with freedom from documented AF, AT and AFL* at 12 months. • Rate of single procedure success defined as the rate of subjects treated with one single ablation procedure during study participation and with freedom from ALL primary effectiveness endpoint failure criteria. • Rate of occurrence of electrically reconnected PVs following a 20-minute waiting period assessed by entrance block at index procedure. • Accumulated changes in QOL using the AF QOL Survey (AFEQT Questionnaire) from baseline through 6 and 12 months following ablation procedure. • Neurological changes measured using the NIH stroke scale between baseline and post-ablation (pre-discharge visit) and at 12 months post-ablation procedure. • Total procedure time (minutes), defined as time of first assigned ablation catheter insertion into the vasculature to time of last procedural ablation catheter removed. • Time to achieve initial PVI at index procedure (minutes), defined as time of delivery of first RF ablation with the assigned ablation catheter until confirmation of PVI. • Total treatment device time (minutes), defined as time of delivery of first RF ablation with the assigned ablation treatment catheter to removal of the treatment catheter. • Total number of RF ablations per procedure. • Total fluid infused through the assigned ablation catheter (mL). • Total fluoroscopy time (minutes). • Number of re-hospitalizations due to atrial fibrillation recurrence after blanking period. **Occurrence and/or ablation of cavotricuspid isthmus (CTI)-dependent AFL, as confirmed by entrainment maneuvers during EP testing at any time during this study is not a primary effectiveness failure because it is not considered an iatrogenic arrhythmia following a left atrial ablation procedure for AF.*

Inclusion Criteria	1. Above eighteen (18) years of age or of legal age to give informed consent specific to state and national law. 2. Subjects with a history of symptomatic, paroxysmal atrial fibrillation (PAF) who have had ≥ 2 episodes of PAF reported within the 6 months prior to index ablation procedure with a physician note indicating recurrent, self-terminating AF. 3. At least one episode of PAF documented by electrocardiographic data within 12 months prior to index ablation procedure. 4. Refractory to at least one Class I-IV anti-arrhythmic AAD for treatment of PAF. 5. Suitable candidate for intra-cardiac mapping and ablation of arrhythmia. 6. Subject agrees to comply with study procedures and be available (geographically stable) for follow-up visits for at least 12 months after enrollment. 7. Subject is willing and able to provide written consent.
Exclusion Criteria	*At time of enrollment and/or prior to procedure:* 1. AF secondary to electrolyte imbalance, thyroid disease or reversible or non-cardiac cause. 2. LA diameter > 5.5 cm. 3. Left ventricular ejection fraction (LVEF) < 35%. 4. Currently NYHA Class III or IV or exhibits uncontrolled heart failure. 5. Body Mass Index (BMI) > 40 kg/m^2. 6. LA ablation, septal closure device or mitral valve surgical procedure at any time prior to enrollment. 7. Presence of intramural thrombus, tumor or abnormality that precludes vascular access, catheter introduction or manipulation. 8. Coagulopathy, bleeding diathesis or suspected procoagulant state 9. Sepsis, active systemic infection or fever (>100.5 ºF / 38 ºC) within a week prior to the ablation procedure. 10. Significant restrictive or obstructive pulmonary disease or chronic respiratory condition. 11. Renal failure requiring dialysis or renal compromise that in the investigator's judgement would increase risk to the subject or deem the subject inappropriate to participate in the study. 12. Known allergies or intolerance to anticoagulant and antiplatelet therapies to be used in conjunction with the study or contrast

<table>
<tr><td></td><td colspan="2">sensitivity that cannot be adequately pre-treated prior to the ablation procedure.
13. Positive pregnancy test results for female subjects of childbearing potential or breast feeding.
14. Enrollment in a concurrent clinical study that in the judgement of the investigator would impact study outcomes.
15. Acute or chronic medical condition that in the judgment of the investigator would increase risk to the subject or deem the subject inappropriate to participate in the study.
16. Life expectancy < 12 months based on medical history or the medical judgement of the investigator.
Within 1 month of enrollment or just prior to procedure:
17. Documented LA thrombus upon imaging.
18. Creatinine >2.5mg/dl or creatinine clearance <30mL/min.
Within 2 months of enrollment:
19. Regularly (uninterrupted) prescribed amiodarone.
Within 3 months of enrollment:
20. Significant gastrointestinal (GI) bleed.
21. Myocardial infarction (MI), unstable angina, cardiac surgery or coronary intervention.
Within 6 months of enrollment:
22. Coronary artery bypass graft (CABG) procedure.
23. ICD, CRT leads or pacemaker implant procedure.
24. Documented stroke, CVA, TIA or suspected neurological event.
Within 12 months of enrollment:
25. An episode of AF lasting >7 days in duration.</td></tr>
<tr><td rowspan="4">Follow-up Visit Schedule</td><td>Subject Visit Description</td><td>Timeframe / Visit Window</td></tr>
<tr><td>Enrollment and Screening Visit(s)</td><td>Within 60 days of ablation procedure</td></tr>
<tr><td>Ablation Procedure (Index)</td><td>Day 0; follow-up visit windows determined by ablation procedure completion date</td></tr>
<tr><td>Pre-Discharge</td><td>Prior to discharge from hospital following ablation procedure</td></tr>
<tr><td></td><td>7 days Follow-Up (Phone)</td><td>7 ± 3 days</td></tr>
</table>

	1 Month Follow-Up	30 ± 14 days
	3 Month Follow-Up	90 ± 21 days
	6 Month Follow-Up	180 ± 28 days
	12 Month Follow-up	365 ± 45 days
	Unscheduled Visits	As needed/necessary
	Repeat Ablation Procedure	Within 90 days of ablation procedure (follow-up visit schedule does not restart)

TABLE OF CONTENTS

4. INTRODUCTION

4.1. Atrial Fibrillation (AF) and Clinical Need

Atrial fibrillation (AF) is the most common clinically-significant cardiac arrhythmia. It is a major public health concern in the United States, affecting an estimated 2.3 million people in North America and 4.5 million people in Europe[1]. It has been projected that the prevalence of AF will increase 2.5 fold during the next 50 years in the United States [2]. AF is associated with increased cardiovascular morbidity and mortality and the prevalence increases over time due to the aging population and an increase in age-specific occurrence of AF [3-5].

Symptoms of AF vary with the ventricular rate, underlying functional status, duration of AF, presence and degree of structural heart disease, and individual patient perception; however, most patients with AF complain of palpitations, angina, dyspnea, fatigue, or dizziness. AF also significantly impairs quality of life, with up to two-thirds of patients reporting it is disruptive and debilitating to their lives [6-8]. AF is an abnormal heart rhythm that has been classified as recurrent when two or more episodes are detected. If these episodes of AF last less than seven days and terminate spontaneously, then it is classified as paroxysmal AF (PAF). PAF accounts for approximately 40 to 45 percent of AF cases. [4, 9]

AF is a sustained arrhythmia characterized by rapid and disorganized atrial activation leading to impaired atrial function, which can be diagnosed on an ECG by lack of a P-wave and irregular QRS complexes. The disorganized atrial activation appears as “fibrillatory” waves activating the atria at a rate generally between 350 and 600 beats/min and the syncytial contraction of the atria is replaced by irregular atrial twitches. While AF can occur in isolation, it may also be associated with other arrhythmias such as atrial flutter or atrial tachycardia.

The electrophysiological mechanisms responsible for AF may include rapid focal tachyarrhythmia in the pulmonary veins (PVs) and/or other atrial regions with fibrillatory conduction, multiple reentrant wavelet conduction initiated by premature atrial complexes (PACs) and/or atrial tachyarrhythmia, and/or formation of stable or unstable reentrant circuits of very short cycle lengths that generate fibrillatory conduction [10, 11].

Of all electrophysiological mechanisms responsible for AF, of significant interest are the PVs which have been identified to play a critical role in triggering and maintaining AF. Haissaguerre and colleagues have demonstrated that in most AF patients, the focus is in one of the PVs [12].

The choice of therapy for AF is influenced by patient preference, associated structural heart disease, severity of symptoms and whether the AF is classified as recurrent paroxysmal, recurrent persistent or permanent. Although AF can be problematic to manage medically due to its progressive nature, there are multiple therapies in current use for the treatment of AF, and many of these therapies are sub-optimal for most patients. Treatment options include medical management, pacing, cardioversion, implantable devices, surgery and ablation therapy to eliminate the arrhythmia [4, 13].

Of all therapeutic strategies for AF one of interest is radiofrequency catheter ablation (RFCA) as a potential curative treatment. RFCA for the treatment of AF is a commonly performed procedure for symptomatic patients in whom medications are either ineffective or

not tolerated [4, 9, 14]. RFCA restores normal sinus rhythm by delivering RF energy through a catheter at targeted focal sites to disrupt abnormal electrical activity. The most common catheter ablation approach to treat AF is to electrically isolate the PVs (PVI). Other approaches used include WACA and CFAE ablation. Additional focal or macro-reentrant atrial sites may be ablated but the approach varies from center to center.

Despite significant improvements in catheter ablation strategies to treat AF in recent years, Neuzil and colleagues report that refractory recurrence of arrhythmia remains a continuing concern with recurrence rates of AF after RFCA still remaining relatively high (20-55%) [15] and perhaps attributed to lack of transmural lesions during PVI[16]. Technological innovations in RFCA include multi-electrode ablation catheters, high resolution ablation catheters, force-sensing technologies and navigation technologies.

4.2. Prior Clinical Evidence for RF Ablation to Treat PAF

Ablation has become the standard of care in many centers due to the superiority of catheter ablation to AADs. The first two classes of devices to seek and achieve FDA approval for ablation of PAF were an irrigated RF catheter (ThermoCool, Biosense Webster) and a cryoballoon ablation catheter (ArticFront, Medtronic). The prospective randomized studies for these devices demonstrated the safety and efficacy and the superiority of catheter ablation over drug therapy in drug refractory patients.[17, 18]

Subsequent approval studies of new ablation technologies have been either compared with a previously-approved device with the same indications for use in a randomized, controlled non-inferiority study or, in the case of a second-generation RF ablation catheter, compared with predefined performance goals in a single-arm study.

Recently, two catheters have been developed to measure real-time contact force during ablation, a concept where force is one of the primary factors determining lesion size. One catheter uses three optical fibers to measure the micro-deformation of a deformable body in the catheter tip (TactiCath, St Jude Medical, Incorporated), which correlates with tip force [19-21]. The second catheter uses a small spring between the ablation tip electrode and the catheter shaft, with a tiny magnetic transmitter in the tip and magnetic sensors to measure microdeflection of the spring (ThermoCool SmartTouch, Biosense Webster, Inc.), corresponding to tip force[22-24].

The TactiCath catheter was evaluated in the FDA investigational study, TOCCASTAR clinical trial[25]. In this prospective, randomized clinical trial, 300 patients with PAF were randomized to ablation with the TactiCath catheter or to the non-contact force sensing ThermoCool ablation catheter. No difference in efficacy was observed, with success rates of 67.8% and 69.4% in the contact force (CF) and control arms, respectively. When the CF arm was stratified into optimal CF and non-optimal CF groups, effectiveness was 75.9% vs 58.1%, respectively. There was no difference in the rate of complications in the two groups. Cardiac tamponade occurred in one subject in each group.

The ThermoCool SmartTouch catheter was evaluated in a multicenter, prospective, randomized clinical trial performed for FDA approval[24]. The outcomes were compared with the ThermoCool IDE trial[18], in which 170 subjects were enrolled. The 12-month freedom from AF/AT/AFL in SMART-AF was 72.5% at 1-year follow-up, compared with 66%

efficacy for the ThermoCool non-contact force catheter. The average CF per procedure was 18 grams. Four subjects experienced cardiac tamponade. A post hoc analysis revealed that when the CF was between investigator-selected working ranges >80% of the time, outcomes were 4.25 times more likely to be successful.

5. SUMMARY OF FIRST-IN-HUMAN CLINICAL STUDY (TRAC-AF)

EPIX conducted a multi-center First-In-Human clinical study, TRAC-AF, across four European centers to establish evidence of clinical safety and effectiveness of the DiamondTemp Ablation System to treat patients with drug refractory, recurrent, symptomatic paroxysmal atrial fibrillation (PAF).

TRAC-AF (DiamondTemp **T**empe**RA**ture-**C**ontrolled and Contact Sensing RF Ablation Clinical Trial for **A**trial **F**ibrillation, NCT02821351) study was a prospective, multi-center, single-arm feasibility study initiated in 2016 and conducted at four European investigational sites.

Enrollment was performed in two phases. Phase 1 included enrollment of 38 subjects from January through March of 2016 and Phase 2 included enrollment of an additional 34 subjects from June through July 2017. A total of 72 subjects were enrolled in the study and 70 subjects were treated with the study device and analyzed. Enrollment is now closed and all subjects in both phases have completed their 12-month follow-up visits and are now exited from the study.

Primary safety and long-term primary safety endpoints were met through 7-days and 30-days post-procedure, with SAEs reported in two subjects (2.9%) and three subjects (4.3%) respectively, for a total of three subjects experiencing an SAE up to 30 days post-procedure. The primary effectiveness endpoint of acute procedural success was achieved in all 70 subjects (100%) through the demonstration of clinically-relevant pulmonary vein isolation and confirmation 20 minutes after the last delivery of radiofrequency energy. Freedom from AF at 12 months post-procedure was 72.5%.

5.1. TRAC-AF Study Design

Subjects with symptomatic PAF who were refractory or intolerant to at least 1 anti-arrhythmic drug (AAD; class I-IV) were screened for enrollment. Subjects that met the study eligibility criteria and signed the informed consent form (ICF) were enrolled and treated in accordance with the protocol and the HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation [14, 26]. Subjects received ablation using the investigational device which required electrical isolation of all clinically relevant pulmonary veins.

5.2 Investigational Device

The investigational device in this clinical study is the DiamondTemp Ablation System. The investigational device was used with a commonly available EP recording system, cardiac stimulator and mapping device, the EnSite™ Velocity™ or Precision™ Cardiac Mapping System (St. Jude Medical). There were no control devices in this study.

5.3. TRAC-AF Clinical Endpoints

The primary endpoint events for this trial used to assess the safety and effectiveness of the DiamondTemp Ablation System for the treatment of drug refractory, recurrent, symptomatic PAF are as follows:

Primary Safety Endpoint

The safety of the DiamondTemp Ablation System was assessed by evaluating the nature and frequency of serious adverse events (SAEs) and serious adverse device effects (SADEs) during the time of the ablation procedure and within 7 days afterwards.

Long Term Primary Safety

The long-term safety of the DiamondTemp System was assessed by evaluating the nature and frequency of serious adverse events (SAE) and SADEs at 30 days post-procedure.

Primary Effectiveness Endpoint

The effectiveness of the DiamondTemp System was evaluated post-ablation by demonstration of acute procedural success, defined as isolation of clinically relevant pulmonary veins by demonstration of block or isolation of signals confirmed after delivery of the ablation treatment.

Secondary Endpoints

The chronic safety of the DiamondTemp System was assessed by evaluating the nature and frequency of adverse events (AE) and adverse device effects (ADE) at 90 days, 6 months and 12 months post-procedure.

5.4. Study Eligibility Criteria

Subjects presenting with drug refractory, paroxysmal atrial fibrillation requiring treatment and clinically indicated for standard of care pulmonary vein isolation ablation treatment were eligible for screening and potential enrollment in the study. Enrollment was confirmed once the subject signed informed consent, had echocardiographic assessment to confirm final eligibility and the study device was introduced into the subject's vasculature.

Subjects had to meet all of the defined inclusion and none of the defined exclusion criteria to be eligible for enrollment in this study.

Inclusion Criteria

1. Suitable candidate for intra-cardiac mapping and ablation for arrhythmias
2. History of recurrent symptomatic PAF with ≥2 episodes reported within the 365 days (12) months prior to enrollment
3. At least 1 episode of AF documented by Holter monitor, rhythm strip, trans-telephonic monitor (TTM), or 12-lead ECG prior to enrollment
4. Refractory to at least one Class I-IV anti-arrhythmic drug (AAD)
5. Eighteen (18) years of age or above

Exclusion Criteria

1. Previous left atrial ablation procedure
2. Intracardiac thrombus, tumor or other abnormality that precludes catheter introduction and placement
3. Known severe cerebrovascular disease or history of cerebrovascular event (within 1 month)
4. Subjects with severely impaired kidney function as measured by a Cockcroft-Gault Glomerular Filtration Rate (GFR)3 with a GFR ≤ 29. Active gastrointestinal bleeding
5. Active infection or fever (>100.5 F/38 ◦C)
6. Sepsis
7. Cardiac surgery within the past two months.
8. Short life expectancy (<1 yr.) due to other illnesses, such as cancer or pulmonary, hepatic, or renal disease Significant anemia (hemoglobin < 8.0 mg/dL)
9. Severe uncontrolled systemic hypertension (systolic pressure > 240 mm Hg within the last 30 days)
10. Documented anaphylaxis during previous exposure to angiographic contrast media
11. Uncontrolled congestive heart failure (NYHA1 Class III or IV)
12. Unstable angina or acute myocardial infarction within the past three months
13. Bleeding, clotting disorders, or known thrombosis
14. Severe Peripheral vascular disease
15. Uncontrolled diabetes
16. Heart valve replacement
17. Mitral clip (E-valve)
18. Women who are of childbearing potential who are currently pregnant or not willing to use contraception for the duration of the study
19. Active participation in another investigational protocol currently or the last 30 days
20. Unable or unwilling to take anti-coagulants
21. Unwilling or unable to comply with any protocol or follow up requirements

5.5 Study Results

Study Accountability and Disposition

Study enrollment is closed and all subjects in both phases have completed their 12-month follow-up visits and are now exited from the study. Subjects were followed for 7 and 30 days after the index ablation procedure to assess primary safety and effectiveness endpoints. The last subject's 30-day visit was completed on 17 August 2017. **Table 1** provides a summary of the subject disposition for the study. Although a total of seventy-two (72) subjects met the definition for enrollment, analysis of the study results was conducted on seventy (70 subjects).

Table 1. Subject Accountability and Disposition

Subject Accountability	Number
Subjects enrolled in study	72
Subjects who did not have PVI attempted with study device (excluded from the analysis)	2
Analyzable Population	70

Baseline subject demographics for the analyzable subjects are described in **Table 2.** The mean age for subjects in this cohort was 60.5 ± 9.8 years, with a higher incidence of subjects being of males (N=42) vs. females (N=28). Overall the characteristics of the subjects enrolled in the study were representative of the patient population usually undergoing RF ablation for the treatment of paroxysmal atrial fibrillation.

Study Population Demographics

Table 2. Subject Demographics (n=70)

Characteristic	Measurement	Results
Age at Ablation Procedure (years)	Mean ± SD	60.5 ± 9.8
	Range	35 - 76
Gender [N] (%)	Female	28 (40%)
	Male	42 (60%)
Height (cm)	Mean ± SD	173.8 ± 11.7
	Range	115.0 - 194.0
Weight (kg)	Mean ± SD	91.3 ± 17.5
	Range	59.0 - 140.0
Resting Heart Rate (bpm)	Mean ± SD	72.2 ± 17.6
	Range	47.0 - 135.0
Resting Systolic BP (mmHg)	Mean ± SD	142.5 ± 17.6
	Range	110.0 - 135.0
Resting Diastolic BP (mmHg)	Mean ± SD	82.6 ± 10.1
	Range	60.0 - 110.0
Hemoglobin (g/l)	Mean ± SD	140.0 ± 33.5
	Range	13.1 - 176.0
Creatinine (umol/l)	Mean ± SD	88.5 ± 17.8
	Range	54.0 - 140.1
GFR (ml/min/1.73m^2)	Mean ± SD	77.1 ± 19.0
	Range	34.0 - 128.0
LVEF %[i]	Mean ± SD	61.2% ± 7.2%
	Range	25.0% - 72.0%
LA diameter, cm[ii]	Mean ± SD	4.4 ± 0.7
	Range	2.9 - 6.5

[i] *LVEF not recorded on four subjects*
[ii] *LA diameter not recorded on 14 subjects*

The medical history of each subject was assessed including history of atrial fibrillation, cardiovascular disease, non-cardiovascular disease and cardiac surgery at time of the screening visit. **Table 3** lists the pre-existing conditions recorded during the screening visits.

Table 3. Medical History, (N=70)

PAF History	**N (%)**
History of Prior Ablation Treatment	0 (0)
Refractory to Anti-Arrhythmic Drugs	70 (100)
Duration of AF (Mean±SD, years)[1]	2.6 ± 2.4
Medical History	
History of Smoking	21 (30)
Diabetes Mellitus Type II	8 (11.4)
Previous Stroke or TIA	6 (8.6)
Previous Myocardial Infarction	3 (4.3)
Coronary Artery Bypass Grafting (CABG)	0 (0)
Concurrent Medical Conditions	
Hepatic Disease	9 (12.9)
Pulmonary disease	17 (24.3)
Other Relevant Cardiac Diseases	
Hypertension	38 (54.3)
Hypertrophic Cardiomyopathy	0 (0)
Coronary Artery Disease	0 (0)

[1] *Onset date of PAF not collected in first phase subjects; data only available on 30 subjects.*

Study Procedural Results

Pulmonary vein isolation (PVI) was achieved by point-by-point, wide antral ablation encircling each pair of ipsilateral PV's supported by the EnSite Velocity or Precision to collect electrical map of the atrium and assist the navigation of the DiamondTemp to each ablation site. The investigational device was used with the market-approved EnSite Velocity/Precision in 70/70 (100%) of the subjects. A summary of procedural data is listed in **Table 4.**

Table 4. Summary of Procedural Data, (N=70)

Procedure Data (n=70)	Measurement	Results
Mode of Operation	Temperature Control	
Programmed Infusion Rate (ml/min)	Standby Flow Rate – 2 ml/min Therapeutic Flow Rate – 8 ml/min	
No. of RF Applications¥	4662	
Ablation Duration† (sec)	Mean ± SD	17.5 ± 2.4
	Range	10.2 - 22.4
Average Power† (W)	Mean ± SD	36.2 ± 2.7
	Range	31.7 - 41.9
Max Power* (W)	Mean ± SD	50.8 ± 0.5
	Range	50.2 - 53.1
Temperature Set-Point† (°C)	Mean ± SD	58.1 ± 1.6
	Range	51.5 - 60
Max Temperature† (°C)	Mean ± SD	65.0 ± 3.5
	Range	56.8 - 73.8
Average Temperature† (°C)	Mean ± SD	48.2 ± 1.9
	Range	43.3 - 52.5
Max Impedance† (Ω)	Mean ± SD	134.7 ± 31.2
	Range	94 - 239
Average Impedance† (Ω)	Mean ± SD	95.5 ± 8.9
	Range	74.9 - 118.9
Total RF Ablation Time† (min)	Mean ± SD	19.8 ± 8.6
	Range	8.5 - 41.8
Total Procedure Time (mean)	Mean ± SD	2:35 ± 0:47
	Range	1:25 - 4:35
Total Fluoroscopy Time‡ (mins)	Mean ± SD	9:38 ± 6:38
	Range	0:03 - 18:00
Total fluid vol.§ (ablation procedure)	Mean ± SD	322.6 ± 99
	Range	152 - 531

¥RF application count includes all ablations (PVI + atrial tachycardia, etc.)
† These values were generated from the generator, not the database.
‡ Fluoroscopic time not recorded on two subjects.
§ Fluid volume not collected on one subject.

Once electrical isolation was achieved, ablation in the targeted veins was considered complete. Documentation of entrance block into the PVs (PVI) was required for each vein ablated. PVI was confirmed by either testing with an adenosine bolus (n=36 or 51% of subjects) or confirming PVI after a minimum of 20 minutes (n=34 or 49% of subjects) after the last RF application.

Primary Endpoint Results

All primary study endpoints have been met through 30 days. Assessments of primary safety events resulted in a total of two (2) SAEs (2.9%) through the 7-day safety endpoint and three (3) SAEs (4.%) through the 30-day safety endpoint, as adjudicated by an independent CEC (**Table 5**). The primary effectiveness endpoint of acute procedural success was achieved in 100% of subjects.

Table 5. Summary of Primary Safety Endpoint (Analyzable Population)

Event	DiamondTemp N=70 Subjects (%)	Timing
Pericardial Effusion	1 (1.4%)	Prior to 7 days
Hospitalization for AF recurrence	1 (1.4%)	Prior to 7 days
Supraventricular Tachycardia	1 (1.4%)	Prior to 30 days
Total SAEs through 7 days	**2 (2.9%)**	
Total SAEs through 30 days	**3 (4.3%)**	

Long Term Interim Safety Analysis

The chronic safety of the DiamondTemp System is assessed in TRAC-AF by evaluating the nature and frequency of all serious adverse events at 90 days, 6 months and 12 months post procedure, as adjudicated by the CEC.

5.6. Conclusion from Clinical Study

The objective of this First-In-Human study was to substantiate the safety and effectiveness of the DiamondTemp Ablation System use to ablate cardiac tissue in patients with paroxysmal atrial fibrillation. The study endpoints achieved the efficacy performance goal demonstrating 100% effectiveness by confirming PVI isolation in all subjects treated as intended under this study protocol. Freedom from AF 12 months post-procedure was 72.5%. The safety profile demonstrated in this study indicates the DiamondTemp System can be used safely in cardiac ablation procedures in this patient population, with no incidences of acute serious adverse device-related events (SADEs) and a 2.9% to 4.3% safety endpoint rate through 7 and 30 days, respectively.

The safety results observed in these seventy (70) subjects treated with the DiamondTemp System up to 30 days are well within the recommendations of the published literature and documented safety and efficacy rates of catheter ablation for PAF[26].

6. TACTICATH CONTROL DEVICE

6.1. Indications for Use

The TactiCath Quartz Contact Force Ablation Catheter is indicated for use in cardiac electrophysiological mapping and for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used in conjunction with a compatible radiofrequency generator and three-dimensional mapping system.

TactiSys Quartz Equipment and accessories are indicated for use in conjunction with a TactiCath Quartz Contact Force Ablation Catheter. TactiSys Quartz Equipment allows the visualization of the force information coming from the catheter tip.

6.2. Product Classification, Code, Regulation

Device Name:	TactiCath Quartz Contact Force Ablation Catheter
Classification:	Catheter, Percutaneous, Cardiac Ablation, for Treatment of Atrial Fibrillation
Product Code:	OAE
Device Class:	3
Submission Type:	PMA (P130026, Approved)

6.3. Control Device Description

The TactiCath Quartz Contact Force Ablation System is comprised of the following components:

- TactiCath Quartz Contact Force Ablation Catheter
- TactiSys Quartz CF Equipment hardware inclusive of:
  - TactiSys Quartz Unit
  - TactiSoft Software
  - TactiSys Quartz RF Cable
  - TactiSys Quartz Ethernet Cable
  - Equipotential Cable
  - Mains Cord and Adapter
- Optional Accessories:
  - TactiSys Quartz Mount
  - TactiSys Analog Output Cable
  - TactiSys Quartz Integration Module

6.4. TactiCath Quartz Contact Force Ablation Catheter

TactiCath Quartz Contact Force Ablation Catheter (TactiCath) is a sterile, 7F steerable, open-irrigated, multi-electrode RF ablation catheter with a deflectable tip incorporating a force sensor and a thermocouple temperature sensor. The catheter is designed to facilitate electrophysiology mapping of the heart chambers and to transmit RF current to the catheter tip electrode for intracardial ablation. The deflectable distal section of the catheter shaft includes four platinum-iridium electrodes (three ring electrodes and one tip electrode) and is available in 65 mm or 75 mm length, with a total usable length of 115 cm. At the proximal end of the catheter, a saline port is used to deliver isotonic saline solution to irrigate and cool the tip electrode and ablation site, through a 0.7 mm diameter catheter lumen and six small holes on the distal electrode tip. The catheter features a tri-axial optical force sensor embedded in the tip section which transmits contact force information to the TactiSys Quartz Equipment.

6.5. TactiSys Quartz Equipment

The contact force visualization equipment associated with TactiCath is comprised of the TactiSys Quartz (TactiSys) unit (hardware and associated cables) and TactiSoft (stand-alone software). The TactiSys unit is a non-sterile active signal and data processing unit that interconnects the TactiCath catheter to an external RF generator and collects data from the catheter to compute contact force and related information transmitted from the catheter. The optical measurement system, which is compatible with the force sensing technology incorporated in the TactiCath catheter, is comprised of three optical sensor analyzer modules. The TactiSoft software displays the contact force information transmitted from the catheter through an Ethernet connection on a dedicated, properly configured computer.

6.6. Additional Required Equipment

The following devices are required in addition to the TactiCath Quartz System to perform catheter ablation procedures:

- AMPERE Generator (St. Jude Medical) or Stockert Generator (Biosense Webster)
- Cool Point Irrigation Pump (St. Jude Medical) or CoolFlow Irrigation Pump (Biosense Webster)
- Electrophysiology recording system and cardiac stimulators
- Dedicated Personal Computer with display screen to run TactiSoft software
- St. Jude EnSite Velocity or Precision Cardiac Mapping System

Optional accessories include choice of RF cable, Ethernet cables available in different lengths, an analog output cable, a mount and an integration module (Ethernet - switch) that will allow the integration of contact force information with third party equipment (e.g. integration in the screen of 3D mapping system for enhanced electrophysiology laboratory set-up).

7. DIAMONDTEMP INVESTIGATIONAL DEVICE

7.1. Proposed Intended Use of the Investigational Device

The DiamondTemp Catheter is indicated for use in cardiac electrophysiological mapping (stimulation and recording) and for treatment of drug refractory, recurrent, symptomatic paroxysmal atrial fibrillation when used in conjunction with the DiamondTemp Generator and accessories (DiamondTemp Cable-to-RFG Cable, DiamondTemp GenConnect Cable, DiamondTemp Irrigation Pump/Tubing Set) and compatible mapping system.

7.2. Product Classification, Code, Regulation

Device Name:	DiamondTemp Ablation Catheter
Classification:	Catheter, Percutaneous, Cardiac Ablation, for Treatment of Atrial Fibrillation
Product Code:	OAE
Device Class:	3

Submission Type: PMA

7.3. Investigational Device Description

The EPIX DiamondTemp Ablation System investigational device includes:

- DiamondTemp Catheter
  - Unidirectional and Bidirectional models
- DiamondTemp Catheter-to RFG Cable
- DiamondTemp GenConnect Cable
- DiamondTemp RF Generator
  - Model CEDTG100
  - Model CEDTG200
- DiamondTemp Irrigation Pump
- DiamondTemp Irrigation Tubing Set
- DiamondTemp Footswitch (optional)

The DiamondTemp Ablation System can be used with the St. Jude EnSite Velocity or Precision Cardiac Mapping System and commonly available EP recording systems and cardiac stimulators.

A representative DiamondTemp Ablation System is illustrated in **Figure 1.**

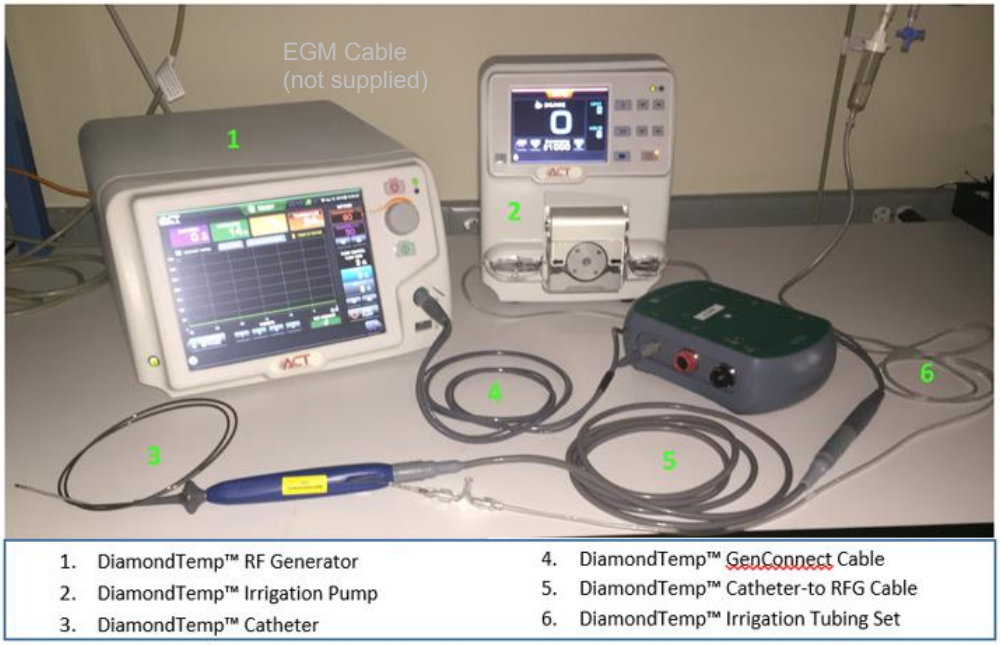

Figure 1. DiamondTemp Ablation System

Key features of the DiamondTemp System:

- The DiamondTemp System allows for cardiac mapping, pacing and ablation when connected to the St. Jude EnSite Velocity or Precision Mapping System and commercially-available cardiac stimulators and recording systems.
- The DiamondTemp Catheter design, materials and composite tip geometry allow for the recording of local electrograms at the ablation site.
- Six thermocouples at the DiamondTemp Catheter tip provide surface temperature feedback.
- The DiamondTemp Generator modulates power to maintain catheter-tissue interface temperature at a set point optimal for creating an effective lesion without char or thrombus formation.
- The DiamondTemp Generator displays the ablation parameters and the composite temperature recorded from the thermocouples.

All investigational devices for use in the clinical study are identified with model, lot or serial number and will be tracked for dispositioning throughout the study. For the DiamondTemp Ablation Catheter and DiamondTemp Catheter-to-RFG Cable, in addition to the model and lot number, a unique serial number will be used. System Accessories used in the clinical study will be identified by lot and/or serial number.

7.4. DiamondTemp Ablation Catheter

The DiamondTemp Ablation Catheter (DiamondTemp Catheter) is a sterile, single use, externally-irrigated cardiac ablation catheter, 110 cm in length, designed to deliver RF energy at the catheter tip electrode for mapping and cardiac ablation. The DiamondTemp Ablation Catheter is a 7.5F externally-irrigated catheter, with either unidirectional (**Figure 2a**) or bidirectional (**Figure 2b**) steering, designed to deliver RF energy to the composite tip electrode of the catheter for mapping and cardiac ablation. The unidirectional catheter is deflected in one direction using an actuation piston; the bidirectional catheter has a steering knob to actuate the curve in either direction and a tension knob to lock the curve. The distal tip and ring electrodes are designed to record electrocardiogram (EGM) signals for mapping and deliver stimulus for pacing. RF emission from the composite tip is similar to commercially-available, externally-irrigated catheters.

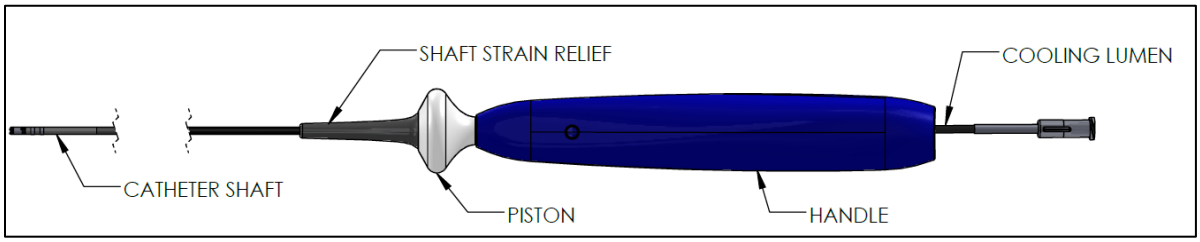

Figure 2a. DiamondTemp Ablation Catheter, Unidirectional

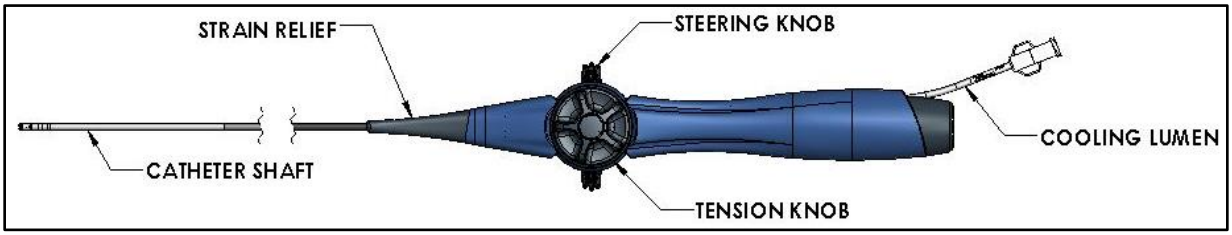

Figure 2b. DiamondTemp Ablation Catheter, Bidirectional

7.5. DiamondTemp RF Generator

The DiamondTemp RF Generator (**Figure 3**) is a temperature-controlled RF generator and provides power to the DiamondTemp Catheter at approximately 460 kHz. It has a universal AC power supply and provides isolated communication ports to the DiamondTemp Irrigation Pump and serial output to an external monitor which can mirror the RF Generator front panel information (**Figure 3b**) such as temperature, power and impedance curves resulting during RF delivery.

There are two generator models for use in this investigation: model CEDTG100 and model CEDTG200. The DiamondTemp Generator model CEDTG100, upon initiation of RF energy and contact with the target tissue, reaches the user-selected temperature set point in approximately five (5) seconds. The DiamondTemp Generator model CEDTG200, under the same conditions, reaches the user-selected temperature set point in approximately one (1) second. All other control features, feedback and safety features are the same between the two models. It is the discretion of the investigator to select which generator model is used.

Figure 3. DiamondTemp RF Generator (a) and Front Panel Display (b)

7.6. DiamondTemp Irrigation Pump

The DiamondTemp Irrigation Pump (**Figure 4**) is a peristaltic pump designed to deliver normal saline (0.9%, with heparin 1 IU/ml) when used in conjunction with the DiamondTemp Irrigation Tubing Set. The Irrigation Pump can be controlled to deliver the

prescribed therapeutic flow rate of 8 ml/min at all power levels up to 50 Watts. The DiamondTemp Irrigation Pump can also be controlled using the touch-screen display on the front panel of the DiamondTemp RF Generator or Irrigation Pump.

Figure 4. DiamondTemp Irrigation Pump

7.7 DiamondTemp Tubing Set

The DiamondTemp Tubing Set is a disposable, one-time use, one-piece tubing that connects the DiamondTemp Ablation Catheter to the DiamondTemp Irrigation Pump.

7.8. DiamondTemp Footswitch

The DiamondTemp Footswitch (**Figure 5**) is an optional accessory used for On/Off control of RF power delivery. Pressing the footswitch turns RF energy ON. Releasing the footswitch terminates delivery of RF energy.

Figure 5. DiamondTemp Footswitch

7.9. Diamond Temp Cables

DiamondTemp Catheter-to-RFG Cable

The DiamondTemp Catheter-to-RFG Cable (**Figure 6**) is 2.4 meters in length, supplied sterile, and contains no latex. The cable distal end has a 19-pin connector that connects to the DiamondTemp Catheter. The cable proximal end, identified by a green band, has

a 26-pin connector that connects to either the DiamondTemp RF Generator or to the DiamondTemp GenConnect Cable when a mapping system is used.

Figure 6. DiamondTemp Catheter-to-RFG Cable

DiamondTemp GenConnect Cable

The DiamondTemp GenConnect Cable (**Figure 7**) is 2 meters in length and has 4 connectors. The cable connects the DiamondTemp Catheter-to-RFG Cable to a commercially-available mapping system (e.g. St. Jude EnSite Velocity or Precision) GenConnect Box (Maestro/EPT) and to the DiamondTemp RF Generator. The cable is supplied non-sterile and contains no latex.

Figure 7. DiamondTemp GenConnect Cable

7.10. Mapping System and EP Recording System Compatibility

The DiamondTemp System is used with the St. Jude EnSite Velocity and Precision Cardiac Mapping Systems and commonly available EP recording systems and cardiac stimulators.

8. STUDY PROTOCOL AND METHODS

8.1. Study Objective

The objective of this study is to demonstrate the safety and effectiveness of the DiamondTemp Ablation System for the treatment of drug refractory, recurrent, symptomatic paroxysmal atrial fibrillation (PAF). The study will be considered successful if the investigative device is considered non-inferior to the control device for the primary safety and effectiveness endpoints.

8.2. Study Design

The DIAMOND-AF study is a prospective, single-blind, 1:1 randomized, controlled trial being performed at multiple centers in the United States, Canada and Europe to evaluate the safety and effectiveness of the DiamondTemp Ablation System for the treatment of drug refractory, recurrent, symptomatic paroxysmal atrial fibrillation compared to the TactiCath Quartz Contact Force Ablation Catheter and compatible ablation system.

This study will enroll up to 480 subjects diagnosed with PAF at up to 30 investigational sites in the US, Canada and Europe. Investigational sites will have a principal investigator (PI) that is responsible for the conduct of a research study as well as sub-investigators. It is anticipated that approximately 50% of the randomized subjects will be enrolled at centers within the United States.

After providing consent, subjects will undergo screening and baseline tests. Subjects that meet the eligibility criteria will be randomly assigned to either treatment with the investigational or control device only after completion of all screening and eligibility procedures. A randomization module within the Electronic Data Capture (EDC) system will be used to randomize subjects 1:1 to one of two treatment groups using a blocked randomization stratified by site followed by stratification by failure of Class I/III or Class II/IV AADs. Since full eligibility for the study may not be confirmable until pre-ablation procedure tests are performed, subjects will only count towards the enrollment ceiling once final eligibility is confirmed and they are randomized. Once randomized, a subject will be considered enrolled in the study.

The primary focus of the left atrial ablation procedure is to create a series of point-by-point RF lesions encircling the left and right PVs to achieve electrical PVI from the rest of the left atrium (LA). Investigators may use their preferred approach to obtain PVI, such as antral or WACA ablation targeting PVs segmentally or PV pairs ipsilaterally. PVI must be confirmed by entrance block at least 20 minutes following the last ablation around the respective PV. Targeting non-PV foci and complex fractionated electrograms is not recommended in this investigation. If the investigator identifies additional focal or macro-reentrant atrial sites to be clinically relevant to AF and requiring ablation, the ablation location will be documented.

All subjects will be followed per protocol in relation to the date of the index ablation procedure. Follow up will be required prior to hospital discharge and at 7 days, 1 month, 3 months, 6 months and 12 months post-ablation.

Subjects will be given a cardiac event monitor (Sentinel Wireless ECG Recorder System or equivalent, HeartcoR Solutions, LLC.) at the hospital pre-discharge visit to be used throughout the duration of the study. If subject exhibits symptoms (e.g. palpitations, dizziness, tiredness, lightheadedness, shortness of breath, chest pain, fatigue, syncope) associated with AF recurrence at any time after the ablation procedure, they will be instructed to record their heart rhythm using their cardiac event monitor and to contact the site investigator. This data will be transmitted to and read at an ECG core lab. If a subject has an arrhythmia recurrence within the first 90 days after the ablation procedure (blanking period), one repeat ablation procedure is allowed per protocol. Investigators should make every attempt to schedule a repeat ablation procedure on or before day 90. The repeat ablation procedure must be performed with the assigned investigational or control catheter. Repeat ablation procedures performed with a catheter different than originally assigned will be a protocol deviation. Subjects will also be required to perform bi-monthly periodic event recording from the 3-month follow up visit to the 12-month follow-up visit to detect possible asymptomatic atrial tachycardias. The event recordings, Holter recordings and 12-lead ECG data collected between the 3 and 12 month post ablation procedure timepoints will be reviewed, analyzed and reported on by an ECG core lab to determine the study effectiveness.

To evaluate the success of subject blinding to treatment assignment, all subjects will be asked whether they think they were in the investigational group, control group or if they don't know at the 12-month follow-up visit.

The duration of the study is projected to span approximately 36 months. The duration accounts for:

- Approximately 12-15 months to enroll all subjects in the trial;
- Approximately 12 -15 months subject participation from consent to end of 12-month follow-up visit window;
- Approximately 3-6 months to analyze, report on study results and close the study.

8.3. Primary Safety Endpoints

The primary safety endpoint is defined as freedom from a composite of serious adverse events (SAE) occurring within 30-days and clinically symptomatic pulmonary vein stenosis through 6 months post-index ablation procedure, as adjudicated by an independent Clinical Events Committee (CEC) for relatedness to the procedure or device.

The primary safety device- or procedure-related SAE composite will be the combined rate of the following events in **Table 6.**

Table 6. Primary SAE, Classification and Definition

Primary SAE	Severity Classification / Definition[26]
Atrioesophageal fistula	Creation of direct communication between the left atrium and esophagus as documented by esophageal erosion combined with evidence of a fistulous connection to the atrium (e.g. air emboli, an embolic event or direct observation at the time of surgical repair). A CT or MRI scan is recommended to document event.
Bleeding complication	Major bleed that requires a transfusion or results in a ≥ 20% fall in hematocrit
Cardiac tamponade / perforation	Significant pericardial effusion with hemodynamic compromise that requires elective or urgent pericardiocentesis or results in a 1-cm or more pericardial effusion as documented by echocardiography.
Death	Cardiovascular-related death post ablation that is related to the procedure or device
Extended hospitalization	Extended hospital stay or re-hospitalization that is related to the procedure or device.*
Myocardial infarction	MI as it relates to AF ablation resulting in the presence of any one of the following criteria: • ECG changes indicative of new ischemia that persist for > 1 hour • development of new pathological Q waves on an ECG • imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Pericarditis	Pericarditis resulting in an effusion that leads to hemodynamic compromise, requires pericardiocentesis, prolongs hospitalization > 48 hours or persists for more than 30 days following procedure.
Phrenic nerve paralysis	Absence of phrenic nerve function assessed by a sniff test that persists > 7 days. A phrenic nerve paralysis is considered to be permanent when it is documented to be present ≥ 12 months following ablation.
Pulmonary edema	Pulmonary alveolar fluid accumulation accompanied by typical symptoms (dyspnea), physical findings (rales, hypoxemia), radiologic findings, and response to diuretic therapy and requiring or prolonging hospitalization.
Pulmonary vein stenosis	A severe or clinically symptomatic PV stenosis verified by a chest CT or MRI will be classified as a SAE. PV stenosis symptoms are shortness of breath, cough and hemoptysis. Pulmonary vein stenosis is defined as a reduction of the diameter of a PV or PV branch. PV stenosis will be categorized as mild <50%, moderate 50%–70%, and severe >70% reduction in the diameter of the PV or PV branch when compared to the proximal reference diameter.
Stroke post-ablation	Stroke Diagnostic Criteria: • Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the

	body, dysphasia or aphasia, hemianopia, amaurosis fugax or other neurological signs or symptoms consistent with stroke • Duration of a focal or global neurological deficit ≥24 hours; or <24 hours if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); or available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death • No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences).^ • Confirmation of the diagnosis by at least one of the following: neurology or neurosurgical specialist; neuroimaging procedure (MRI or CT scan or cerebral angiography); lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) Stroke will be determined by the consulting neurologist using diagnosis criteria above and subsequent neuroimaging procedure (MRI or CT scan or cerebral angiography). ^ *Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based on neuroimaging studies.*
Thromboembolism	Occurrence of deep vein thrombosis or pulmonary embolism post ablation
Transient ischemic attack (TIA) post-ablation	Rapid onset of new focal neurological deficit with immediate symptom resolution (usually 1 to 2 hours), always within 24 hours as determined by consulting neurologist and neuroimaging without tissue injury.
Vagal nerve injury	Esophageal dysmotility or gastroparesis requiring or prolonging hospitalization following an ablation procedure
Vascular access complications	Resulting in development of a hematoma, an AV fistula or a pseudoaneurysm that requires intervention, such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.

* Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan (including repeat ablation procedure), without serious deterioration in health, will not be included in the primary safety endpoint analysis. Hospitalizations due to recurrent AF/AT/AFL or prolonged hospitalization during the 30 days following procedure to adjust anticoagulation regimen or to administer diuretic medication are not considered part of the combined primary safety endpoint.

8.4. Primary Effectiveness Endpoints

The primary effectiveness endpoint is defined as freedom from documented atrial fibrillation (AF), atrial flutter* (AFL) and atrial tachycardia (AT) episodes following the blanking period (3-month follow-up post-ablation procedure) through the end of the effectiveness evaluation period (12-month follow-up post-ablation procedure).

An effectiveness failure is defined by any of the following events:

- Inability to electrically isolate all accessible targeted pulmonary veins during the ablation procedure
- Documented episodes of AF, AFL or AT lasting ≥30 seconds in duration as evidenced by electrocardiographic data during the effectiveness evaluation period
- DC cardioversion for AF, AFL or AT during the effectiveness evaluation period
- A repeat ablation procedure to treat AF, AFL or AT during the effectiveness evaluation period
- Use of a new or modification to existing Class I-IV anti-arrhythmic drug (AAD) regimen to treat AF, AFL or AT recurrence during the effectiveness evaluation period
- Use of a non-study device for ablation of any AF targets during the index or repeat ablation procedure during the blanking period
- More than one (1) repeat ablation procedure during the blanking period

* *Occurrence and/or ablation of cavotricuspid isthmus (CTI)-dependent AFL, as confirmed by entrainment maneuvers during EP testing at any time during this study is not a primary effectiveness failure because it is not considered an iatrogenic arrhythmia following a left atrial ablation procedure for AF.*

8.5. Secondary Endpoints

Secondary endpoints to characterize the performance of the DiamondTemp Ablation System, relative to the control device, will include

- Mean duration of individual RF ablations (seconds)
- Mean cumulative RF time per procedure (minutes)
- Freedom from a composite of SAE occurring within 7-days post-index ablation procedure as adjudicated by an independent CEC for relatedness to the procedure or device.
- Freedom from documented AF, AT and AFL episodes following the blanking period through 12-month follow-up post-ablation procedure in the absence of class I and III anti-arrhythmic drug therapy.
- Rate of acute procedural success, defined as confirmation of electrical isolation of PVs via assessment of entrance block at least 20 minutes following the last ablation around the respective PV.
- Rate of single procedure success defined as the rate of subjects treated with one single ablation procedure during study participation and with freedom from documented AF, AT and AFL* at 12 months.
- Rate of single procedure success defined as the rate of subjects treated with one single ablation procedure during study participation and with freedom from ALL primary effectiveness endpoint failure criteria.
- Rate of occurrence of electrically reconnected PVs following a 20-minute waiting period assessed by entrance block at index procedure.

- Accumulated changes in QOL using the AFEQT Questionnaire from baseline through 6 and 12 months following ablation procedure.
- Neurological changes measured using the NIH stroke scale between baseline and post-ablation (pre-discharge visit) and at 12 months post-ablation procedure.
- Total procedure time (minutes), defined as time of first assigned ablation catheter insertion into the vasculature to time of last procedural ablation catheter removed.
- Time to achieve initial PVI at index procedure (minutes), defined as time of delivery of first RF ablation with the assigned ablation catheter until confirmation of PVI via exit block following a 20-minute waiting period.
- Total treatment device time (minutes), defined as time of delivery of first RF ablation with the assigned ablation treatment catheter to removal of the treatment catheter.
- Total number of RF ablations per procedure.
- Total fluid infused through the assigned ablation catheter (mL).
- Total fluoroscopy time (minutes).
- Number of re-hospitalizations due to atrial fibrillation recurrence after blanking period.

* *Occurrence and/or ablation of cavotricuspid isthmus (CTI)-dependent AFL, as confirmed by entrainment maneuvers during EP testing at any time during this study is not a primary effectiveness failure because it is not considered an iatrogenic arrhythmia following a left atrial ablation procedure for AF.*

8.6. Sample Size Justification

With a randomization ratio of 1:1 and an estimated attrition rate of 7%, 240 subjects per treatment group (total N=480) should yield sufficient power for both the primary safety and primary effectiveness endpoints.

For primary safety, assuming a control composite SAE rate of 6.5%, 226 subjects per group yields 80% power to detect a non-inferiority margin of 6.5% between treatment groups at a one-sided significance level of 0.025. Similarly, assuming a control effectiveness rate of 65%, 229 subjects per group yields 80% power to detect a non-inferiority margin of -12.5% between treatment groups at a significance level of 0.025.

8.7. Statistical Analysis

Before database lock, the final SAP for clinical data will be prepared to provide full details of all planned analyses. The analyses presented here represent an outline of the intended methodology.

Analysis Populations

The following analysis populations are defined in this study:

- ITT Population: The Intention-to-Treat (ITT) population will be comprised of all randomized subjects regardless of whether they receive study treatment, with analyses conducted according to the randomized treatment assignment.

- Per Protocol Analysis Set: The Per Protocol analysis set will be a subset of the ITT Set and comprised of all subjects who did not have any major protocol deviations.
- Safety Analysis Population: In the unlikely case where a subject is randomized but the procedure is prematurely halted and no catheter is deployed, said catheter will e included in the ITT Set but excluded from the Safety Set since the subject was not exposed to the study device. The Safety Set will be comprised of all randomized subject in which treatment was at least attempted (assigned treatment catheter inserted into vasculature), with analyses conducted by actual treatment received.

General Considerations

Descriptive summary statistics for continuous variables will include the number of subjects, mean, standard deviation or standard error, median, minimum and maximum. Nominal categorical variables will be summarized using counts and percentages. Ordinal variables may be analyzed as if they were continuously scaled.

The study will be considered successful when the primary safety and effectiveness endpoints are met.

If primary effectiveness success is determined to be less than 52% for either the treatment arm or the control arm, the primary effectiveness endpoint will be difficult to interpret, and additional analyses will be necessary to explain the poor device performance.

Subject Disposition

The number and percentage of subjects who complete and discontinue as well as reasons for early discontinuation will be presented.

Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively. Treatment groups will be compared statistically to confirm that the randomization process generated two homogeneous groups prior to treatment.

Catheter Model Analysis

The final study data will include evaluations of the DiamondTemp Unidirectional and Bidirectional Catheters in aggregate as well as stratified by catheter model.

There will be a minimum of 30 subjects treated with the DiamondTemp Bidirectional Catheter.

8.8. Site Training

Technical training with the DiamondTemp Ablation System will be provided by the Sponsor. Training will be documented and will include a review of the investigational plan, study procedures, CRF completion, instructions for use (IFU) and all study compliance requirements.

9. SUBJECT SELECTION

9.1. Criteria for Eligibility

Subjects included in the DIAMOND-AF study should be selected from the general patient population indicated for or currently scheduled for catheter ablation of PAF. Investigators are responsible for screening all potential subjects and selecting those who meet all inclusion and none of the exclusion criteria for the study**.**

9.2. Study Inclusion Criteria

Candidates must meet ALL the following criteria to be enrolled in the DIAMOND-AF study:

1. Above eighteen (18) years of age or of legal age to give informed consent specific to state and national law.
2. Subjects with a history of symptomatic, paroxysmal atrial fibrillation (PAF) who have had ≥2 episodes of PAF reported within the 6 months prior to index ablation procedure with a physician note indicating recurrent, self-terminating AF.
3. At least one episode of PAF documented by electrocardiographic data within the 12 months prior to index ablation procedure.
4. Refractory to at least one Class I-IV AAD for treatment of PAF.
5. Suitable candidate for intra-cardiac mapping and ablation of arrhythmia.
6. Subject agrees to comply with study procedures and be available (geographically stable) for follow-up visits for at least 12 months after enrollment.
7. Subject is willing and able to provide written consent.

9.3. Study Exclusion Criteria

Candidates will be excluded from the DIAMOND-AF study if any of the following conditions apply within the following timeframes:

At time of enrollment and/or prior to procedure:

1. AF secondary to electrolyte imbalance, thyroid disease or reversible or non-cardiac cause.
2. LA diameter > 5.5 cm.
3. LVEF < 35%.
4. Currently NYHA Class III or IV or exhibits uncontrolled heart failure.
5. BMI > 40 kg/m^2.
6. LA ablation, septal closure device or mitral valve surgical procedure at any time prior to enrollment.
7. Presence of intramural thrombus, tumor or abnormality that precludes vascular access, catheter introduction or manipulation.
8. Coagulopathy, bleeding diathesis or suspected procoagulant state
9. Sepsis, active systemic infection or fever (>100.5^{o}F / 38^{o}C) within a week prior to the ablation procedure.

10. Significant restrictive or obstructive pulmonary disease or chronic respiratory condition.
11. Renal failure requiring dialysis or renal compromise that in the investigator's judgement would increase risk to the subject or deem the subject inappropriate to participate in the study.
12. Known allergies or intolerance to anticoagulant and antiplatelet therapies to be used in conjunction with the study or contrast sensitivity that cannot be adequately pre-treated prior to the ablation procedure.
13. Positive pregnancy test results for female subjects of childbearing potential or breast feeding.
14. Enrollment in a concurrent clinical study that in the judgement of the investigator would impact study outcomes.
15. Acute or chronic medical condition that in the judgment of the investigator would increase risk to the subject or deem the subject inappropriate to participate in the study.
16. Life expectancy < 12 months based on medical history or the medical judgement of the investigator.

Within 1 month of enrollment or just prior to procedure:

17. Documented LA thrombus upon imaging.
18. Creatinine >2.5mg/dl or creatinine clearance <30mL/min.

Within 2 months of enrollment:

19. Regularly (uninterrupted) prescribed amiodarone.

Within 3 months of enrollment:

20. Significant GI bleed.
21. MI, unstable angina, cardiac surgery or coronary intervention.

Within 6 months of enrollment:

22. CABG procedure.
23. ICD, CRT leads or pacemaker implant procedure.
24. Documented stroke, CVA, TIA or suspected neurological event.

Within 12 months of enrollment:

25. An episode of AF lasting >7 days in duration.

10. SUBJECT ACCOUNTABILITY

10.1. Point of Enrollment

All subjects will be considered enrolled following the assignment to a randomized treatment arm. Since full eligibility for the study may not be confirmed without pre-ablation procedure testing (e.g. echocardiography, pregnancy test, creatinine), consented subjects will count

towards the maximum enrollment ceiling once final eligibility is confirmed and they are randomized. Once randomized, a subject will be considered enrolled in the study.

10.2. Subject Status and Classification

The following classifications will be applied to all subjects:

- Screening Failure: A subject who has consented (signed ICF) but is found to not meet eligibility criteria through medical file review and/or screening procedures to confirm eligibility. Screening failures do not count against the maximum study enrollment ceiling and there are no follow-up requirements. If screening failure occurs after randomization but prior to insertion of the assigned treatment catheter, the screening failure will be documented.
- Intent-to-Treat: Includes all subjects who sign ICF, meet eligibility criteria and are randomized into one of the two study groups. These subjects will count against the maximum study enrollment ceiling.
- Treatment-Per-Protocol: A subject who is successfully treated per the study protocol with the assigned randomized treatment catheter. These subjects are followed in accordance with the follow-up schedule and are included in all analyses of safety and effectiveness.

The statistical analysis for each classification will be documented in the Statistical Analysis Plan (SAP).

10.3. Subject Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study or lost to follow-up) will be accounted for and documented. If a subject withdraws from the clinical study, the reason(s) will be documented. Reasons for withdrawal may include physician discretion, subject choice to withdraw consent, loss to follow-up or death. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment.

All applicable case report forms up to the point of subject withdrawal must be completed. For subjects who are "lost-to-follow-up" the investigator/center should have at least three documented attempts to contact the subject prior to withdrawal from the study. No additional data may be collected after a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. All open adverse events should be closed or documented as chronic. Data collected up to the point of subject withdrawal may be used.

11. STUDY METHODS

11.1. Enrollment and Visit Schedule

Enrollment of subjects will occur at the clinical sites only after the appropriate local and national study approvals, "Approval to Enroll" documentation from the Sponsor and written informed consent from subjects have been obtained. **Table 7** summarizes the study follow-up and testing schedule:

Table 7. Follow up and Testing Schedule

Assessments/ Activities	Baseline Evaluation	Ablation Procedure	Blanking Period (Ablation procedure – 3 months post procedure)				Effectiveness Evaluation Period (3 months -12 months post procedure)		
			Pre-Discharge	7-Day Follow-Up (± 3 days)	1-Month Follow-Up (± 14 days)	Repeat Ablation Procedure	3-Month Follow-Up (±21 days)	6-Month Follow-up (± 28 days)	12-Month Follow-up (± 45 days)
Eligibility Screening	X								
Informed Consent	X								
Patient Demographics	X								
Medical History	X								
Physical Exam	X		X		X	X[A]	X	X	X
12-lead ECG		X	X		X	X[A]	X	X	X
TEE or TTE	X[B]								
TEE or ICE[G]		X[C]				X[C]			
Chest CT / MRI							X[F]	X[F]	X[F]
NIH Stroke Scale	X		X			X[A]			X
Procedural Data		X				X[A]			
Event Monitor Recording			X[D]	X[D]	X[D]		X[E]	X[E]	X[E]
24 hr. Holter Monitor								X	X
Cardiac Medication Changes	X	X	X	X	X	X[A]	X	X	X
Protocol Deviations	X	X	X	X	X	X[A]	X	X	X
Adverse Events	X	X	X	X	X	X[A]	X	X	X
AF Quality of Life Survey (AFEQT)	X					X[A]		X	X

[A] Only required if a repeat ablation procedure performed. 1 repeat ablation procedure is allowed during Blanking Period.

[B] TEE or TTE only required if subject does not have imaging data to determine LA diameter, LVEF for eligibility within 180d of ablation procedure

[C] TEE or ICE required pre-procedure to rule out LA thrombus if any of the following are met: CHA2DS2-VASc score is ≥ 2, if LA diameter ≥4.6 or if pre-procedure anticoagulation requirements are not met

[D] Event monitor recording only required if subject is experiencing symptoms during blanking period

[E] Following the blanking period (3-12 month following ablation), subjects are required to take two 1-minute event monitor recordings per month regardless of whether they are experiencing symptoms.

[F] Only required if subject presents with symptoms associated with PV stenosis

[G] ICE allowed for subjects who cannot undergo TEE

11.2. Screening Evaluation

Investigators and research staff at each site are responsible for conducting screening evaluations and obtaining subject medical history to identify subjects that meet eligibility requirements per the study inclusion and exclusion criteria. Sites should maintain a subject screening log to document subjects evaluated for enrollment into the study that did not consent. A reason for ineligibility or not providing consent should be provided. Subjects who meet general eligibility for consideration in the study will sign an informed consent and undergo a baseline evaluation.

11.3. Baseline Evaluation

After eligible subjects have signed an informed consent form and before the scheduled interventional procedure, subjects will undergo a baseline evaluation. This evaluation may be conducted up to 45 days prior to the interventional procedure or on the same day. The evaluation will include but is not limited to the following:

- Medical History and Physical Exam:
  - Subject Demographics
  - Limited Physical Assessment
    - Height and weight
    - Resting blood pressure
    - Resting heart rate
  - Medical History
    - History and documentation of PAF
    - NYHA score
    - CHA_2DS_2-VASc score
    - Cardiovascular or other medical history as it pertains to eligibility criteria
  - Medication History
    - Class I-IV AAD history, current doses and/or failure or intolerance
    - Other: cardiac, diuretic, and anticoagulation medications
- Baseline Tests
  - Transesophageal or transthoracic echocardiography (TEE or TTE)*
    - to determine LA diameter and % LVEF
  - Transesophageal or Intracardiac echocardiography (TEE or ICE for subjects who cannot undergo TEE)
    - Required within 48 hours of the ablation procedure to rule out LA thrombus in subjects that meet <u>any</u> one of the following criteria:
      - CHA_2DS_2-VASc score is ≥ 2
      - LA diameter ≥ 4.6 cm
      - Pre-procedure anticoagulation requirements are not met
  - Pregnancy test for women of child bearing potential
- Baseline Assessments

- NIH Stroke Scale administration**
- AF Quality of Life Survey (AFEQT Questionnaire version 1.0)

* *Only required if subject does not have imaging data within 180 days of procedure to determine LA diameter, LVEF for eligibility*

** *NIH Stroke Scale must be administered by staff certified to conduct assessment*

11.4. Pre-Ablation Testing and Requirements

- Echocardiogram (TEE or TTE) must be performed prior to ablation in the following instances:
  - To confirm LA diameter and LVEF
    - if not available within 180 days of the ablation procedure
- Echocardiogram (TEE) must be performed within 48 hours of the ablation procedure to rule out LA thrombus* in subjects that meet the following criteria:
  - Not currently and adequately anticoagulated for 3 weeks or longer
    - If subject is on an oral anticoagulant (OAC) they should be taking it regularly for 21 days prior to ablation
    - If a subject is on warfarin prior to ablation, they should have a therapeutic International Normalized Ratio (INR) > 2
  - CHA_2DS_2-VASc score is ≥2
  - LA diameter ≥4.6 cm

**ICE may be considered to rule out LA thrombus in subjects contraindicated for TEE*

If a thrombus is observed on echo, the subject no longer meets eligibility criteria. The subject can be anticoagulated for 30 days until confirmation is received that the clot has resolved but if the clot persists, the subject will not meet eligibility for the study.

- Discontinuation of AADs prior to the procedure is left to the discretion and practice of the investigator and investigational site best practices. AADs should be maintained at current failed dose.
  - Regular amiodarone use must be discontinued 2 months prior to the ablation procedure and not restarted after the ablation procedure.
- Performance of the ablation procedure on uninterrupted anti-coagulation therapy (e.g. warfarin or OACs) is strongly recommended.
  - For subjects anticoagulated with a OAC prior to AF catheter ablation, it is reasonable to hold one to two doses of the OAC prior to AF ablation with re-initiation post-ablation.
- Women of child bearing potential will be required to verify entrance criteria prior to procedure by providing documentation of a negative pregnancy test conducted within 7 days prior to enrollment.

11.5. Ablation Procedure

Pre-procedural Preparation

Subjects that meet the eligibility and pre-ablation requirements will be prepped for the ablation procedure with the ablation system to which they are randomized.

The procedures will follow standard hospital practice but should, at a minimum, include the following:

1. Prep and sedate subject per institutional standard practice.
    a. Method of sedation will be recorded (i.e. conscious sedation or general anesthesia).
    b. Placement of an esophageal temperature probe to guide energy delivery on the posterior wall is strongly recommended.
        i. An esophageal temperature increase of 1 – 2 °C from baseline or a recorded temperature of 39 – 40 °C should trigger interruption of RF energy delivery. Care should be taken to ensure that the esophageal temperature probe is aligned as close as possible with the position of the ablation catheter during ablation to avoid a false impression of safety.
        ii. Deviation of the esophageal temperature probe is allowed if standard practice at the institution.
    c. Place Ensite Velocity or Precision patches on subject per IFU.
    d. Place commercially available Dispersive Indifferent Electrode (DIP) patch.
2. Gain vascular access per lab protocol via the femoral veins and/or right or left internal jugular or subclavian veins by insertion of sheaths.
3. Any commercially available 8.5F, fixed or steerable, sheath may be used.
    a. A steerable sheath is recommended to be used with the DiamondTemp Ablation Catheter.
4. Aspirate and flush sheaths with heparinized saline to remove air prior to introduction into the body and catheter insertion.
    a. Sheaths (fixed or steerable) should be continuously infused with heparinized saline at 1-2ml/min throughout the procedure.
5. Complete a single or double transseptal puncture to access the LA.
6. A heparin loading dose should be administered just prior to transseptal puncture (recommended) or immediately following. A standard heparin infusion through catheter and sheaths should be given to maintain anticoagulation and activated clotting times (ACT) ≥300 seconds throughout the ablation procedure.
    a. ACT must be ≥300 seconds prior to first ablation.
    b. ACT levels should be checked every 20-30 minutes during the ablation procedure.
    c. If ACT is <300 seconds during ablation procedure, more heparin should be administered.
7. Insert and place multi-electrode diagnostic catheters under fluoroscopic guidance.

a. Placement of intracardiac catheters will be per standard lab practice but must include a coronary sinus (CS) catheter and a multi-electrode circular catheter for PV mapping and verification of PV isolation and entrance block.

8. Create a 3D anatomical map of the left atrium and location of the PVs with a multielectrode catheter using Ensite Velocity or Precision system.
   a. RF applications and location will be added to the map during the procedure.
9. A pre-ablation EGM/12 lead ECG documenting the subject's rhythm at the beginning of the procedure will be collected.
10. All peri-procedural AEs must be recorded on the AE CRF and reported to the Sponsor. All device issues, malfunction or deficiencies with the investigational or control devices must be reported on the Device Deficiency CRF. The use of a replacement (back-up) device should be indicated on the Procedure CRF.

TactiCath Quartz Contact Force Ablation Catheter Set-up

The TactiCath Quartz Contact Force Ablation Catheter and TactiSys Quartz Equipment hardware should be prepped and deployed following the operator's manual, IFUs and physician training. General recommended ablation parameters taken directly from the TactiCath IFU are listed in **Table 8.** Please refer to the TactiCath Quartz Catheter IFU for more information.

Table 8. TactiCath Recommended RF Application Parameters

General recommendations:

	Atrial ablation
Recommended power range	10 W to 30 W*
Contact Force	Target 20 g with a minimum of 10 g[1,2]
Temperature monitoring	37 to 50 °C**
Irrigation flow rate during RF application	17 to 30 ml/min

* Power levels exceeding 30 Watts may be used when transmural lesions cannot be achieved at lower energy levels. For power settings > 30 Watts, the recommended irrigation flow rate is 30 ml/min.

Warning: Application of higher power is associated with a higher likelihood of audible steam pop occurrence. High power should only be used in special circumstances and only when good contact force cannot be achieved.

Warning: Contact force in excess of 70 g may not improve the characteristics of lesion formation and may increase the risk for perforation during manipulation of the catheter.

** The temperature displayed on the generator does not represent tissue temperature or electrode tissue interface temperature.

Additional recommendation:

For isthmus dependent flutter ablation, power applications exceeding 30 Watts and up to 50 Watts maximum should only be used if conduction block cannot be achieved at lower power levels.

DiamondTemp Ablation System Set-up

EPIX DiamondTemp Ablation System and Catheter should be prepped and deployed following the respective user manuals, IFUs and physician training. The recommended Generator and Irrigation Pump settings are listed in **Table 9**.

Table 9. Recommended DiamondTemp RF Generator and Irrigation Pump Settings

RF Generator Settings	
Operational Mode	Temperature Control
Maximum Temperature Set Point	60°Celcius
Maximum Power Setting	50 Watts
Ablation Duration	45 seconds
Irrigation Pump Settings	
High Irrigation Flow Rate (during ablation)	8 mL/min
Low Irrigation Flow Rate (minimum continuous flow rate)	2 mL/min

When using the DiamondTemp Catheter, the change in the high-resolution EGM will be used to guide the termination of the RF delivery. After EGM amplitude attenuation is reached, RF delivery is to be stopped three (3) to five (5) seconds after EGM amplitude attenuation is reached. The point of significant EGM attenuation is defined as the time when there are no more changes in the EGM amplitude and/or there is a 75 to 80% reduction in EGM amplitude.

Investigators are recommended to not ablate for greater than 45 seconds without moving the tip of the investigational ablation catheter.

In the event of a generator cutoff (impedance, temperature) or if a steam pop is observed, the catheter must be withdrawn and the tip electrode observed for the presence of char or coagulum formation. The tip should be cleaned, if necessary, before RF current is reapplied. Purge the catheter prior to insertion into the subject.

Pulmonary Vein Electrical Mapping

The electrical activity of the PVs must be mapped prior to ablation. The investigator may determine the order in which the PVs are mapped and if PV angiography is necessary to facilitate vein access.

To perform the electrical PV mapping, each vein should have a diagnostic catheter inserted to document the presence of PV potentials. Documentation of the PV electrical mapping (PV potentials or lack thereof) is required for each vein. If the mapping catheter is successfully positioned in the vein but no PV potentials are present, ablation of the PV is not recommended. Pre-ablation mapping determines which veins are clinically relevant for appropriate declaration of acute procedural success. If the investigator determines it is not clinically relevant to perform ablation of a PV, the rationale must be noted prior to starting the ablation.

Index Ablation Procedure

The primary focus of the ablation procedure will be to create a series of point-by-point RF lesions encircling the left and right PVs to achieve PVI (electrical isolation of PVs from the LA).

Investigators may use their preferred approach to obtain PVI such as antral or WACA targeting PVs segmentally or PV pairs ipsilaterally. A circumferential approach applying RF application 1-2 cm outside of the PV ostium to prevent PV stenosis is recommended. Targeting non-PV foci and complex fractionated electrograms is not recommended in this investigation. If the investigator identifies additional focal or macro-reentrant atrial sites to be clinically relevant to AF and requires ablation, the ablation location will be documented.

The order in which PVs are isolated is up to the investigator's discretion. While isolating the right superior PV, high-voltage pacing may be used before each RF application to check for phrenic nerve stimulation. Ablation should be avoided in areas of phrenic nerve capture as to not cause injury to the phrenic nerve. While ablating on the posterior wall in proximity to the esophagus it is highly recommended that investigators use an esophageal temperature probe during RF ablation procedures to monitor esophageal temperature and help guide energy delivery. An esophageal temperature increase of 1-2°C from baseline or a recorded temperature of 39°C–40°C should trigger interruption of RF energy delivery[26]. Care should be taken to ensure that the esophageal temperature probe is aligned as close as possible with the position of the ablation catheter during ablation to avoid a false impression of safety. Additionally, each ablation on the posterior LA wall needs to consider the duration, power and temperature (investigational catheter only) settings while in proximity to other structures that could potentially be injured, such as the esophagus. Moving a catheter after shorter durations of RF application, reducing the power (W) and/or temperature set point to 50 or 55 ^{o}C (investigational system only) is encouraged but is left to the discretion of the investigator.

Procedural recommendations

- PVI must be confirmed and documented by entrance block of potentials into the PV a minimum of 20 minutes following the last RF application in each PV or PV pair to monitor for PV reconnection.
- Adenosine and/or isoproterenol may be administered 20 minutes following PVI to detect for the presence of dormant PV conduction.
    - Administration of isoproterenol for the sole purpose to identify non-PV triggers is allowed but not recommended.
- Exit block testing is not required, but if performed, exit block must be demonstrated for the PVI to be considered successful. If conduction resumes in any of the PVs, additional RF application can be applied until PVI is achieved. If additional ablation is performed following reconnection of PV, PVI must be reconfirmed at a minimum of 20 minutes following last ablation in the respective PV or PV pair.
- Empiric targeting of complex fractionated electrogram, rotors, ganglionated plexi or performing left atrial mitral isthmus or roof lines are not recommended.

- Spontaneously-occurring atrial arrhythmias that present during the procedure are allowed to be ablated at the investigator's discretion.
    - CTI-dependent (typical) flutter is also allowed if the subject has a known history of typical flutter.
- Cardioversions do not signify procedural failures and are not adverse events. A post-ablation EGM/12 lead ECG documenting the subject's rhythm at the end of the procedure will be collected.

All procedure logistical data, ablation parameters, procedural outcomes, adverse events, fluids administered from both catheter and non-catheter sources (i.e., steerable sheath, etc.) and medications administered will be recorded and reported throughout the procedure. Prophylactic administration of intravenous diuretics during or after the procedure is allowed and will not be considered an adverse event. All ablation catheters must be removed from the subject and inspected for char and coagulum formation if there is a generator cutoff (impedance or temperature) as well as each time a steam pop is observed.

Ablation data collected during the procedure will include but may not be limited to:

- Catheter lot/serial number(s) used
- Temperature set point
- Power set point
- Total number of RF applications for PVI
- Total number of RF applications during the procedure
- Total RF time during the procedure
- ACT levels and times taken
- Location of additional ablations performed and number of RF applications per location
- Total fluid infused from the ablation catheter
- Presence of char or coagulum formation and incidence(s) of steam pops
- Procedure and fluoroscopy times
- EP recording system gain and filter settings for the ablation distal recording channel and manufacturer

If at any time during the ablation procedure the investigator is unable to continue the ablation with the investigational or control catheter (other than when ablating an RA flutter line), the investigator may consider the case a procedural failure and complete the case with a device determined best for the subject. The point at which failure was determined as well as the rationale must be documented.

After removal from the subject, the investigational or control catheter should be inspected, and if any abnormalities such as char or coagulum formation are noted on the catheter, it must be documented. All adverse experiences with the investigational device during the ablation procedure must be promptly reported to the Sponsor and documented on the CRF.

Post-Procedure

All sheaths will be removed immediately after ablation and hemostasis will be achieved either by direct pressure or the use of a commercially-available closure device. Investigators may use protamine to reverse the intravenous heparin used during the procedure.

Subjects must be anticoagulated for a minimum of 60 days post index ablation procedure. It is up to the investigator's discretion which drug is best suited for the subject. If anticoagulation was discontinued prior to and during the ablation procedure, anticoagulation should be resumed within 24 hours post-procedure to achieve a therapeutic anticoagulation level. It is recommended that investigators follow the anticoagulation guidelines set forth in the 2017 HRS Expert Consensus Statement on Catheter and Surgical Ablation of AF [26], regardless of the apparent success or failure of the AF ablation procedure. Additionally, the Investigator's decision regarding continuation of systemic anticoagulation more than 60 days post ablation should be based on the subject's stroke risk profile (e.g CHA_2DS_2-VASc score ≥2 in men and ≥3 in women, prior stroke or TIA and/or age ≥75 years) and not on the perceived success or failure of the ablation procedure.

If AADs are restarted following the ablation procedure, it is recommended to maintain subjects on a drug regimen for a duration of 2 to 4 weeks to address symptoms or early recurrences of AF, AFL or AT during the post-ablation healing and stabilization phase.

If AADs are restarted for clinical reasons during the blanking period but not later than the 3-month follow-up visit, it is recommended that subjects are maintained under the same AAD regimen throughout the effectiveness period (12-month follow-up). During the effectiveness evaluation period, physicians may discontinue an AAD, but may not add a new class or substitute an AAD.

11.6 Pre-Discharge Follow-Up Visit

Prior to being discharged from the hospital, subjects will complete a pre-discharge visit. The evaluation while in the hospital will include but is not limited to the following:

- Complete Physical Exam to assess for procedure related complications per investigational center's standard of care including but not limited to:
  - Vital signs (blood pressure, heart rate, respiration rate, temperature) will be obtained
  - Cardiovascular and pulmonary examination
  - Standard neurological assessment
  - Catheter insertion sites (both groins) will be assessed
- Assess the subject for any adverse events following ablation procedure
- Perform a 12-lead ECG
  - Report presence or absence of atrial fibrillation or other supraventricular tachycardias
- NIH Stroke Scale Evaluation follow-up

- Provide subjects with cardiac event monitor and operating instructions
- Record medication changes since ablation procedure
  - Cardiac, AAD, diuretic, or anticoagulation

Subjects will be discharged from the hospital when stable, per the investigator's discretion.

11.7 Seven Day Follow-up Phone Call

All subjects must be evaluated seven days (7 ± 3 days) post ablation procedure. The follow-up will be conducted over the phone and the following evaluation will be completed:

- Adverse Event Assessment
  - Ask the subject if there have experienced any new adverse events since discharge from the hospital and inquire about resolution of any previously reported event(s)
- Medication changes
  - Ask subject if there have been any changes in their regularly prescribed medications (cardiac, AAD, diuretic, or anticoagulation)
- Review event monitor data for recordings made due to symptomatic episodes of arrhythmias since the last follow-up

11.8 One Month Follow-Up Visit

All subjects must be evaluated at one month (30 ± 14 days) after the index ablation procedure. During the follow up, the following will be performed:

- Perform a complete physical exam with vital signs and 12-lead ECG
- Assess the subject for any new adverse events and inquire about resolution of any previously reported events(s).
- Record any medication changes
- Review event monitor data for recordings made due to symptomatic episodes of arrhythmias since the last follow-up
  - If there has been an early recurrence of AF, investigator should schedule a visit so he/she can evaluate subject to determine if a repeat ablation procedure can be scheduled before the end of the 90-day blanking period.

11.9 Repeat Ablation Procedure (if applicable)

It is expected that some subjects will have early recurrences of atrial arrhythmias (e.g. AF, AT, AFL) within the blanking period (90 days following the ablation procedure)[18]. Investigators may perform one repeat ablation procedure in subjects with highly symptomatic or multiple early recurrences of atrial arrhythmias that cannot be controlled with antiarrhythmic therapy [26, 28]. Subjects with documented early recurrence during the blanking period are not being considered a primary effectiveness failure.

The repeat ablation procedure must be performed with the originally assigned investigational or control catheter. Prior to the repeat ablation procedure, subjects must meet the pre-ablation requirements described in Section 11.4 and repeat baseline NIH Stroke Scale and

QOL survey. Investigators must follow all procedural requirements defined in Section 11.5 for the repeat ablation procedure. During the repeat procedure, the presence or absence of PV electrical reconnection will be recorded. In addition, the location of reconnection will be noted.

The blanking period and follow-up visit schedule will not restart following the repeat ablation procedure. Subjects that receive a repeat ablation procedure will undergo a repeat ablation pre-discharge visit.

11.10 Three Month Follow-Up Visit

All subjects must be evaluated three-months (90 ± 21 days) following the index ablation procedure. During this follow-up visit, the following will be performed:

- Perform a limited physical exam (weight, resting heart rate, and blood pressure).
- Assess the subject for any new adverse events and inquire about resolution of any previously reported events(s).
  - Subjects who have experienced symptoms or adverse events suggestive of PV stenosis are required to receive a chest CT or MRI scan to rule out PV stenosis.
- Perform a 12-lead ECG
  - Report the absence or presence of atrial fibrillation or other atrial tachyarrhythmia.
- Record any medication changes
- Review event monitor data from the 2 required monthly recordings to ensure compliance, assess whether or not there has been a recurrence of AF, AT, or AFL since last visit or if there were symptoms associated with the episodes of arrhythmias since the last follow-up.

11.11 Six Month Follow-Up Visit

All subjects must be evaluated six-months (180 ± 28 days) following the index ablation procedure. During this follow-up visit, the following will be performed:

- Perform a limited physical exam (weight, resting heart rate, and blood pressure).
- Assess the subject for any new adverse events and inquire about resolution of any previously reported events(s).
  - Subjects who have experienced symptoms or adverse events suggestive of PV stenosis are required to receive a chest CT or MRI scan to rule out PV stenosis.
- Perform a 12-lead ECG
  - Report the absence or presence of atrial fibrillation or other atrial tachyarrhythmia.
- Record any medication changes
- Review event monitor data for recordings made due to symptomatic episodes of arrhythmias (if applicable) since the last follow-up and the event monitor data from the two (2) required monthly recordings.

- Subjects will be provided a 24-hour Holter monitor
    - Subjects will be given instructions for set-up and return to the core lab
- Administer a follow-up AFEQT Questionnaire (QOL)

11.12 Twelve Month Follow-Up Visit

All subjects must be evaluated twelve-months (365 ± 45 days) following the index ablation procedure. During this follow-up visit, the following will be performed:

- Perform a limited physical exam (weight, resting heart rate, and blood pressure).
- Assess the subject for any new adverse events and inquire about resolution of any previously reported events(s).
    - Subjects who have experienced symptoms or adverse events suggestive of PV stenosis are required to receive a chest CT or MRI scan to rule out PV stenosis.
- Perform a 12-lead ECG
    - Report the absence or presence of atrial fibrillation or other atrial tachyarrhythmia.
- Record any medication changes
- Review event monitor data for recordings made due to symptomatic episodes of arrhythmias (if applicable) since the last follow-up and the event monitor data from the two (2) required monthly recordings.
- Subjects will be provided a 24-hour Holter monitor
    - Subjects will be given instructions for set-up and return to the core lab
- Administer a follow-up QOL assessment (AFEQT Questionnaire)
- Administer a follow-up NIH Stroke Scale assessment

- To evaluate the success of subject blinding, ask subject if they think they were in the 1. Investigational group 2. Control group or 3. Didn't Know

11.13 Unscheduled Visits

Unscheduled visits may occur at any time during the study for the assessment of for example, possible adverse events and/or medication changes. Each unscheduled visit will be documented in a CRF.

11.14 Subject Lost to Follow-Up

The investigator will attempt to contact a subject at least three times prior to designating them as lost-to-follow-up subjects; two of these attempts should include attempting to contact subject via registered mail. The investigator will document the date and type of attempted communication, and will complete the Study Completion Form when a subject is lost to follow-up.

11.15 Extended Follow-up Period (if applicable)

Dependent on the safety and efficacy data collected in this study, it is possible that extended surveillance of subjects will be requested by a Regulatory Authority, including the FDA resulting in an extended follow-up period of up to three (3) years. If extended follow-up is requested, subjects would be re-consented and followed per standard of care for their Institution with continued adverse event collection and reporting. The information collected during these regular follow-up visits would be reported via the EDC system or equivalent and the decision to extend follow-up would be documented in a letter communicated at a minimum to the Investigators, IRB/EC and regulatory authorities as necessary. CEC review of clinical event information and DSMB oversight, if applicable would continue to occur as specified in the CEC/DSMB charter.

11.16 Study Completion

It is the intent of the protocol that all subjects will be followed for a minimum of 12 months post procedure. Documentation of study completion will be required for all subjects, independent of the point at which they complete the study (including screening failure, early withdrawal or loss to follow-up as applicable).

12. STUDY CONDUCT

12.1. Statement of Compliance

This study will be conducted in accordance with the ethical principles stated in the latest Declaration of Helsinki, ISO 14155: 2011 and FDA 21 CFR parts 50, 54, 56, 812. The study will not begin until appropriate national and local approvals have been obtained, as appropriate. Any additional requirements imposed by the IRB/EC or regulatory authority will be followed where appropriate.

12.2. Regulatory Considerations

The clinical investigational plan, subject informed consent and associated documents will be reviewed by the relevant Ethics Committee (EC)/Institutional Review Board (IRB) and appropriate agencies prior to any subject enrollment. The study will not start without the written approval of the IRB/EC and, where needed, the FDA and/or Competent Authority (CA) approval, and after the completion of any other local regulation requirements.

12.3. Investigator Responsibilities

The Principal Investigator of an investigational center is responsible for ensuring that the study is conducted in accordance with all Clinical Study Agreements, the clinical investigational plan and applicable regulations in FDA 21 CFR part 812, as well as any prevailing local and/or country laws and/or regulations, whichever affords the greater protection of the subject's rights, safety and welfare. In addition, Investigators are responsible for:

- Ensuring that an IRB/EC reviews and approves Clinical Investigational Plan
- Maintaining adequate and accurate records related to:
  - Subject eligibility

- Subject Informed Consent form
- Study related subject source data as described in clinical investigational plan
- Case report forms
- Device accountability log
- Staff delegation of authority and training logs

- Ensuring that conducting the study will not give rise to conflicts of interest
- Informing the Sponsor in writing of the reason(s) for any withdrawal of any IRB/EC approval.
- Ceasing the enrollment of subjects immediately in the event of the withdrawal of any IRB/EC approval.
- Ensuring that no subjects will be enrolled, without prior, written Approval to Enroll from the Sponsor.
- Agreeing to use their best efforts to satisfactorily complete the planned work and comply with accepted GCP.
- Ensuring that informed consent is obtained appropriately and that the conditions of informed consent are complied with.
- Ensuring the appropriate completion of all CRFs (paper and/or EDC) with the understanding that certain records and reports may be submitted to regulatory agencies by the Sponsor to support regulatory submissions.
- Supporting a monitor/auditor (as applicable) in their activities.
- Informing the Sponsor of all adverse events and adverse device effects in a timely manner and informing the IRB/EC of any serious adverse device effects as applicable.

12.4. Confidentiality and Data Protection

Health data will be recorded and forwarded to the sponsor of the study, and where needed, to participating IRB/EC and the FDA/CA for evaluation as required. Information obtained in this study that can be identified with the subject's identification will remain confidential. Any data that may be published in scientific journals will not reveal the identity of the study participants.

12.5. Insurance

As the Sponsor of this clinical investigation, EPIX will provide proof and type of insurance coverage for subjects in the study, upon request or where required by local/country regulations.

12.6. Protocol Amendments

Changes to this study that affect the safety or welfare of the subject, scope of the investigation or scientific integrity of the data will require an amendment to the investigational plan. Amendments to the investigational plan may be initiated by EPIX or at the request of an Investigator. A formal amendment cannot be initiated by an Investigator or clinical site staff without the approval of EPIX.

Protocol amendments must be submitted and subsequently approved by the site IRB/EC and CA and FDA, if applicable.

EPIX may make certain administrative changes to the protocol without prior approval of the IRB/EC. EPIX will notify all investigative sites of such changes to ensure the study continues to be conducted consistently across all sites.

12.7. Adverse Event Reporting

All AEs observed by the Investigator or staff during a physical or laboratory examination, interventional procedure or mentioned by the subject, either spontaneously or upon questioning, will be recorded on an AE case report form. All AEs will be documented with the date of occurrence, relatedness to device or procedure, severity, action taken, resolution and any pertinent additional information. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution.

All adverse events (AE) will be monitored from the time of signed ICF through the twelve-month follow-up visit. **Table 10** details AE classification, definitions and reporting timelines.

Table 10. Adverse Event Classification, Definitions and Reporting Timelines

Event Classification	Definition	Reporting Timeline
Adverse Event (AE)	Any untoward and unintended medical occurrence experienced by a clinical study subject. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a Sponsor's investigational system or the control system, whether it is related to the product or not.	Study staff must complete an AE CRF for each AE that occurs per subject throughout the duration of the study. AE CRF will be completed in a timely manner.
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device	Study staff must complete an AE and device deficiency CRF within 2 business days after the event for each subject through the duration of the study.
Serious Adverse Event (SAE)	AE that: • Led to death, • Led to serious deterioration in the health of the subject, that either resulted in: o a life-threatening illness or injury, or o a permanent impairment of a body structure or a body function, or o in-patient or prolonged hospitalization of existing hospitalization, or o medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function	Study staff must complete an AE CRF within 2 business days after becoming aware of an SAE for each subject through the duration of the study. Study staff must provide all relevant / supporting source information (de-identified) in a timely manner when documentation becomes available. SAE or SADE will be reported to IRB/EC or FDA/CA per local/regional regulations.

	• Led to fetal distress, fetal death, or a congenital abnormality or birth defect.	
Serious Adverse Device Effect (SADE)	ADE that has resulted in any of the consequences characteristic of the above-mentioned SAE.	Study staff must complete an AE and device deficiency CRF within 2 business days after becoming aware of an SAE for each subject through the duration of the study.
Unanticipated Adverse Device Effect (UADE)	Any SAE or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or risk analysis plan, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.	Study staff must complete and AE and device deficiency CRF within 1 business day of becoming aware of the event and report to IRB/EC or FDA/CA per local/regional regulations.

Adverse events will be recorded, reported and followed for all subjects for the duration of their participation in the study regardless of whether they are in the investigational or control cohort. The Principal Investigator is responsible for informing the IRB/EC, and regulatory authorities of UADE(s) and SAE(s) as required by local/regional regulations.

Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without serious deterioration in health, is not considered as part of the primary composite safety endpoint. Additionally, underlying diseases/ pre-existing conditions will not be reported as an AE unless there has been a substantial increase in the severity or frequency of the problem which has not been attributed to natural history during the investigation. To this extent, hospitalizations due to recurrent AF / AFL or prolonged hospitalization following procedure to adjust anticoagulation regimen or to administer diuretic medication are not considered AEs for this study.

Device-Related Adverse Event

An AE is considered to be device-related (ADE) when, in the opinion of the Investigator, the clinical event has an association in time and/or proximity with the use of the investigational device such that it is reasonable and likely that the investigational device directly caused or contributed to the AE. A device-related adverse event that impacts or potentially impacts a primary and/or secondary safety endpoint will be reviewed and adjudicated by the independent CEC. ADEs include any AE resulting from insufficient or inadequate IFU, deployment, operation, or malfunction of the investigational medical device, as well as, from intentional misuse of the device.

Procedure-Related Adverse Event

An AE is considered to be procedure-related when, in the opinion of the Investigator, it is reasonable to believe that the event is associated with the ablation procedure and is not specific to the investigational device used and that other products, surgical techniques, or

medications required specifically for the procedure are likely to have caused or contributed to the event. A procedure-related adverse event that impacts or potentially impacts a primary and/or secondary safety endpoint will be reviewed and adjudicated by the independent CEC.

12.8. Device Deficiency Reporting

A device deficiency is defined as any inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, misuse or use errors and inadequate labeling.

Device deficiencies related to the investigational ablation systems may occur in the absence of any associated AE and must be completely documented on a CRF.

Device deficiencies related to the DiamondTemp Ablation System and associated accessories should be reported to the Sponsor within two (2) business days and returned to the sponsor for analysis as expeditiously as possible. Instructions for returning the clinical device(s) will be provided to investigational sites by the Sponsor. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record. If a device deficiency is associated with an AE that specific event would be recorded as an AE.

Device deficiencies related to the control system will be handled per the hospital standard complaint handling procedure.

Note: Any Device Deficiency that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered reportable and should be notified to EPIX.

12.9. Protocol Deviations

The Investigator is not allowed to deviate from the protocol without prior approval by Sponsor and prior review and documented approval from the governing IRB/EC.

Under emergency circumstances, deviations from the clinical investigation plan to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the IRB/EC.

Reports of any deviation from the clinical investigational plan as per above emergency circumstances will be reported to the Sponsor and to the IRB/EC as soon as possible after detection, but no later than twenty-four (24) hours from the time of the deviation.

Deviations must be documented on the appropriate protocol deviation CRF.

Any report of withdrawal of IRB/EC approval will be submitted to the Sponsor within five (5) working days.

If a Clinical Monitor becomes aware that an Investigator is not complying with the signed Investigator's Agreement, the Investigational Plan, the requirements of ISO 14155 or other applicable regulations, or any conditions of approval imposed by the reviewing IRB/EC Committee, Sponsor will immediately either secure compliance or discontinue shipments of the device to the Investigator and terminate the Investigator's participation in the

investigation. The Investigator will be required to return all investigational components to Sponsor, unless this action would jeopardize the rights, safety or welfare of a subject.

Protocol deviations will be analyzed by Sponsor for the impact to the overall integrity of the study. Input from the statistician and/or the Data Safety Monitoring Board (DSMB) may be obtained to determine if the deviation warrants disqualifying the Investigator.

Disqualification is warranted when an investigator has repeatedly or deliberately violated governing regulations or has repeatedly or deliberately submitted false information in any report. Where protocol deviations occur, which do not warrant disqualification from a study, Sponsor will implement appropriate corrective and preventive actions, including repeat training as deemed necessary.

12.10 Investigational Device Accountability

No device supplies will be shipped to the Investigator until IRB/EC and regulatory authority (CA and/or FDA) approval has been achieved in writing and each Investigator has supplied Sponsor with copies of the IRB/EC approval document and the approved informed consent form to be used.

The investigational devices are to be used only in this clinical investigation and according to this protocol and the IFU. The devices for use in this study must be stored in a secure area. The secure area will have restricted access and the study devices will be kept separate from other medical devices. The study devices will only be handled by trained personnel and will not be supplied to any individual not involved in the investigation. The study devices will be inventoried at regular intervals during the study and all unused or expired devices will be returned to the Sponsor when study enrollment is closed.

The Principal Investigator or his/her authorized representative is responsible to keep records documenting the receipt, use, return and disposal of the investigational devices. A form will be provided to the site that will log the device model, lot number or serial number and date received by the site. As the devices are used, the site will record the subject study identification number and date of procedure for each device. A space will be provided for recording returned product and the reason for the return.

12.11. Documentation

Source documents may include a subject's medical record, hospital charts, clinic charts, the Investigator's study files, questionnaires and the results of diagnostic tests such as laboratory tests, electrocardiograms, CT angiograms, MR angiograms, echocardiograms and such. The Investigator's copy of the CRFs serves as part of the Investigator's record of a subject's study-related data.

The following information should be included in the subject's medical record:

- Name and contact information
- The study title (DIAMOND-AF Study), study number, and Sponsor name (Epix Therapeutics or EPIX)
- Date the subject was informed about the study, that he/she had sufficient opportunity to ask questions and he/she was informed regarding alternative treatments

- The subject was allowed adequate time to consider participation prior to signing the consent form
- A statement that written informed consent was obtained
- Date of enrolment into the clinical study and the subject ID number
- Date of procedure, procedural type, and device lot number
- Visit dates
- Cardiac medications
- Occurrence of any adverse events
- Date subject exited the study, and a notation as to whether the subject completed the study or discontinued, with the corresponding reason.

The Investigator is responsible for ensuring that data are properly recorded in each subject's source data, CRFs and related documents and ensuring timely transfer of data to the CRF. The Investigator who signs the Protocol Signature Page should sign the CRFs requiring signatures to ensure that the observations and findings are recorded correctly and completely. Source data from baseline until 12-month follow-up, respectively, must be transferred to the CRF. All CRFs will be reviewed for completeness, accuracy and clarity. Queries for missing or unclear data will be made as necessary and must be answered within 10 business days.

12.12. Record Retention

The Investigator will maintain, at the investigative site, in original format, all essential study documents and source documents that support the data collected on the study subjects in compliance to ICH/GCP guidelines. Documents will be retained for at least two (2) years after the last approval of a marking application or until at least two (2) years have elapsed after the formal discontinuation of the clinical trial of the device. Documents may be retained longer by agreement with the Sponsor or in compliance with other local regulations. The Investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. Sponsor requires to be notified in writing if the Investigator intends to leave the hospital so that both parties can be assured a new responsible person is appointed in the hospital responsible for maintaining these essential documents.

13. POTENTIAL RISKS AND BENEFITS

13.1. Anticipated Adverse Events

There are potential or anticipated risks associated with the use of the DiamondTemp Ablation System. The handling characteristics and principles of operation of the DiamondTemp System are like conventional RF ablation systems and it is anticipated that the rate of catheter/system related complications in this study will be similar to those reported from ablation procedures used with commercially approved ablation systems.

Specific risks are outlined in the system labeling, but in summary the possible risks for catheterization and RF ablation are, but are not limited to the following:

1. Access site complications, including:
    a. Arteriovenous fistula

   b. Ecchymosis
   c. Hematoma
   d. Hemorrhage or aneurysm
   e. Infection
   f. Pain
   g. Surgical correction involving loss of limb
   h. Thrombosis
2. Sequelae of fluoroscopic exposure, including:
   a. Possible cancer risk
   b. Risk of birth defect
   c. Harm to fetus
   d. Skin burns
3. Direct cardiac damage, including:
   a. Cardiac tamponade / perforation resulting in pericardial effusion
   b. Catheter entrapment within heart or blood vessels, leading to damaged heart wall, valves, chordae tendineae or blood vessels, possibly requiring surgical correction or involving loss of function
   c. Congestive heart failure
   d. Damage to cardiac conduction system
   e. Pulmonary vein stenosis
   f. Endocarditis
   g. Myocardial infarction
   h. Pericarditis resulting in pericardial effusion
   i. Persistence of an atrial septal defect (resulting from the transseptal puncture)
   j. Stiff left atrial syndrome
   k. Valve damage due to catheter entrapment
4. Other intrathoracic collateral effects, including:
   a. Atrioesophageal fistula
   b. Damage to trachea, bronchi or pulmonary tissue
   c. Damage to great vessels
   d. Esophageal injury
   e. Phrenic nerve injury
   f. Vagal nerve injury
5. Embolic phenomena including:
   a. Coronary artery embolism with or without myocardial infarction
   b. Gas embolism from procedural error or equipment malfunction with embolic phenomenon
   c. Infarction of other tissues

d. Obstruction of vasculature leading to limbs causing the need for surgical interventions, loss of a limb, or loss of organ function
e. Pulmonary embolism
f. Paradoxical embolism through patent foramen ovale
g. Stroke or TIA

6. Arrhythmias including:
   a. New arrhythmias occur
   b. Worsening of existing arrhythmia
   c. Creation of a partial or complete conduction block, with or without the implantation of a temporary or permanent pacemaker
7. The general sequelae of catheterization including:
   a. Pulmonary edema
   b. Skin burns
   c. Hypotension
   d. Sepsis
   e. Pneumothorax
   f. Myocardial infarction
   g. Cardiac arrest
   h. Death
8. Medication side effects, especially:
   a. Heparin administration: including bleeding, thrombosis, changes in circulating blood elements and skin necrosis
   b. Ionic and nonionic radiopaque contrast medium, major complications: life-threatening reactions including: cardiovascular collapse, severe respiratory difficulty, nervous system dysfunction, convulsions, coma and cardio-respiratory arrest
   c. Ionic and nonionic radiopaque contrast medium, minor complications: allergic reactions including: nausea, vomiting, facial flush, feeling of body warmth, dermal manifestations of urticaria with or without pruritus, erythema and maculopapular rash, dry mouth, allergic glossitis, sweating, conjunctival symptoms, facial, peripheral and angio-neurotic edema
   d. Anesthetic reactions: including respiratory difficulties, sedation induced apnea, pneumonia, low blood pressure, cardiac arrest (death) and nausea and/or vomiting.

13.2. Risk Minimization

A comprehensive functional risk analysis was performed to quantify the risks associated with the use of the DiamondTemp Ablation System. This functional risk analysis evaluated the potential interfaces of the DiamondTemp Ablation System with the subject and/or user and listed the potential harms and potential causes. The associated probability of each cause was estimated and risk control measures were considered and implemented to further reduce the potential for all risks.

The completed risk analyses of the DiamondTemp Ablation System identified all known potential risks to the subject and user. All risks were categorized in the negligible or marginal categories. Since all identified risks were low or moderate, the design is determined to be safe for human use. The risk analysis did not result in findings of any risk that would be considered intolerable. The potential risks associated with any ablation procedure include standard surgical risks for example: infection, electrical shock, perforation, tamponade, skin burns and complications associated with use of ancillary devices, drugs, and anesthetic. The DiamondTemp Ablation System does not create new risks nor does it increase procedural risks as compared with other ablation systems for electrophysiology procedures. The risks associated with the use of the DiamondTemp Ablation System have been identified and evaluated, controls have been put in place to adequately mitigate risks, and a system is implemented that monitors the effectiveness of the risk controls and provides a process to implement corrective and preventive actions

The DiamondTemp Ablation System is similar in design to existing commercial ablation systems and intends to provide an equivalent functionality to existing irrigated electrophysiology ablation catheter/systems on the market. Additionally, technology integrated within the catheter allows to measure interface tissue temperature and the RF generator can be set to automatically adjust the power to achieve a desired interface tissue temperature. The DiamondTemp Ablation System does not introduce any new or additional safety risks beyond those associated with similar cardiovascular and ablation procedures. Further, the system is also capable of assessing the extent of contact between the ablation electrode and the cardiac tissue ensuring good energy to transfer to the therapy location. This study is intended to evaluate the safety and performance effectiveness of the DiamondTemp Ablation System for the treatment of atrial arrhythmias.

Risks associated with the DIAMOND-AF Study can be minimized through appropriate training of Investigators and research staff, compliance to this protocol, adherence to inclusion / exclusion criteria and by promptly supplying Epix Therapeutics with data and information required by this protocol.

Additionally, extensive *in vitro* bench and *in vivo* animal studies have been successfully performed with the DiamondTemp Ablation System. Verification and lot release testing for all components of the system will be completed. The associated risks proposed in this study are similar to risks posed by other interventional, electrophysiological cardiac procedures.

Based upon the risk analysis conducted to assess the DiamondTemp Ablation System, EPIX has determined that the benefits of the device can outweigh the risks if used in the appropriate patient population by a physician trained in the use of electrophysiology procedures. As a primary treatment for cardiac arrhythmias, the DiamondTemp Ablation System is determined to be safe for human use.

13.3. Benefits

Participants in this research study may or may not receive benefits from participation in this study as compared to standard of care treatment of PAF.

Based on bench and clinical testing with the DiamondTemp Ablation System it is expected that the subjects enrolled in this study will experience similar benefits as those of the currently available commercial systems.

Subjects included in this research study may benefit from closer evaluation of their atrial fibrillation via more frequent office follow-ups, cardiac event monitoring and from having diagnostic non-invasive and invasive evaluation of their cardiac anatomy in the event of previously undiagnosed cardiac abnormalities. There is potential that subjects may have their AF eliminated or AF burden reduced resulting in a better quality of life and reduced need for medication.

Additionally, there may be a benefit to the subjects enrolled in this study through improved therapy delivery. The DiamondTemp system was designed to provide investigators with additional information to a) monitor real-time tissue interface temperatures b) automatically adjust output power to a temperature set point based on the composite temperature c) utilize a low irrigation flow rate for all power output up to 50 Watts.

14. MONITORING

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. Monitoring will occur in line with the Study Monitoring Plan.

14.1. Study Monitor

Study Monitors assigned to the DIAMOND-AF study will be responsible for reviewing the device accountability documentation and subject data as collected on CRFs or via an EDC system. The monitor will ensure that the clinical protocol has been approved by the IRB/EC and will assure ongoing compliance with clinical protocol.

The Investigator/institution guarantees direct access to original source documents by Sponsor personnel, their designees, and appropriate regulatory authorities.

14.2. Monitoring Procedures

Monitoring visits to the clinical sites will be made periodically to ensure that Investigators and their staff understand and accept their defined responsibilities, assess compliance with current GCP guidelines, evaluate clinical trial progress, assess the continued acceptability of the clinical site facilities, assess compliance with the investigational plan, and verify the accuracy of data recorded on CRFs or via an EDC system to source documentation.

The Sponsor Monitor or its designated representative will be allowed to visit the clinical site and have direct access to all study records throughout the duration of the study. The Monitor will review all source data and compare them to the data documented in the case report forms, in addition to performing a review of the Regulatory Binder and conducting device accountability. Subject safety will be ensured by noting that consent was properly documented, the investigational plan was followed and that AEs were reported and followed-up as appropriate.

The Investigator and/or institution will provide direct access to source data/documents for trial-related monitoring, audits, IRB/EC review and regulatory inspection.

It is important that the Investigator and relevant study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

Additionally, telephone and/or e-mail contact will be conducted on a regular basis with the Investigator and the site staff to ensure that the protocol is being followed and to address any issues that may occur during the trial.

If a deficiency is noted during the trial the Clinical Monitor is required to bring this to the attention of EPIX Clinical Affairs Management to discuss the situation and (if required) to secure compliance.

The study Monitor will evaluate and summarize the results of each clinical site visit in written reports, identifying any repeated data problems with any Investigator and specifying recommendations for resolution of noted deficiencies.

As required by IDE regulations, the conduct and monitoring of the clinical investigation will be conducted in accordance with the Sponsor's approved monitoring plan.

14.3. ECG Core Lab

A designated CRO, HeartcoR Solutions, LLC (Algonquin, IL) will provide centers and/or subjects with instructions and training on the use of an event monitors that serves as a hand-held event recorder for short duration recordings and can be worn as a 24 hr. Holter. Subjects will be provided with an event monitor prior to discharge from the hospital and instructed to collect 1-minute ECG recordings with their event monitor if they experience AF symptoms throughout the study. Additionally, subjects will be required to collect 1-minute ECG recordings with their event monitor two times per month starting at the end of the 3-month blanking period to the 12-month follow up visit.

The event monitors will be configured to automatically transmit recordings securely and wirelessly to the core lab. All events will be analyzed by the core lab to determine if symptoms are associated with arrhythmia recurrence. The core lab will be blinded to subject treatment assignment. The company will identify the subject's transmitted rhythm and send reports to the investigational center within 72 hours. If there is discordance between the core labs rhythm analysis in the report and the investigator, a third-party cardiologist will be used for final rhythm determination. All event monitors should be returned to the Core Lab after a subject completes the study.

At 6 and 12 months post-ablation procedure, the event monitor will be configured to take a 24-hr continuous reading (like a Holter monitor) supplied by the core lab.

The ECG core lab will also review, analyze and report on all event and Holter recordings as well as the 12-lead ECGs taken at the 3, 6 and 12-month follow-up visits.

14.4. Data Safety Monitoring Board

The purpose of the DSMB committee is to complete unbiased review of all safety data in comparison to the established criteria in order to determine if the rate of SAEs is acceptable, to evaluate interim data analysis results, to provide related advice on study management and progress, and to make any recommendations regarding the study protocol. Members of the DSMB will be comprised of three (3) voting individuals with relevant expertise for the study

and a biostatistician, they will not be employees or shareholders of EPIX and they will not be a participating DIAMOND-AF Investigator.

The DSMB will be responsible to communicate any safety, scientific concerns, or other perceived concerns to EPIX or designee as soon as possible. The DSMB will provide, after each scheduled meeting, written recommendation regarding the continuation of the trial, early stopping, or any suggested changes for the conduct of the trial. EPIX is responsible for informing the IRB/EC and regulatory authorities, as applicable, if the DSMB has advised them of any major safety concerns and has recommended the study be stopped or if they have made any recommendations to alter the study. DSMB decisions are final and non-negotiable by the sites.

14.5. Clinical Events Committee

The purpose of the CEC is to complete unbiased reviews and classification of serious adverse events and deaths reported by clinical study investigators. The CEC will consist of physicians who are not participating Investigators in the DIAMOND-AF Study and who do not have any significant investment in Sponsor's or any of their entities. The three (3) voting members will also serve on the CEC to provide an independent unbiased review and adjudication of clinical events throughout the trial will not also be DSMB members. A complete description of CEC and DSMB responsibilities, qualifications, members and operating principles will be outlined in a combined charter.

14.6. Steering Committee

The DIAMOND-AF Steering Committee is comprised of senior clinical, medical and regulatory members of EPIX, as well as international physician investigator advisors and the study statistician. The role of the Steering Committee is to provide oversight of the clinical study regarding the design, submission and conduct of the study. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission; however, EPIX remains responsible for all decisions related to any such requests in line with approved study agreements.

15. SUSPENSION OR TERMINATION

15.1. Premature Termination of the Study

EPIX reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

Possible reasons for premature study termination include, but are not limited to, the following.

- The occurrence of UADEs that present a significant or unreasonable risk to subjects enrolled in the study;
- A decision on the part of Epix Therapeutics to suspend or discontinue development of the device.

15.2. Termination of Participation

Any investigator or IRB/ EC involved in the DIAMOND-AF study may discontinue participation in the study or withdrawal approval of the study, respectively, with suitable written notice to Epix Therapeutics Investigators, associated IRBs/ECs, and regulatory authorities, as applicable.

Requirements for Documentation and Subject Follow-up

In the event of premature study termination by the Sponsor, a written statement as to why the premature termination has occurred will be provided to all participating centers by EPIX. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an IRB or EC terminates participation in the study, participating investigators, associated IRBs/ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by EPIX.

In the event an investigator terminates participation in the study, study responsibility will be transferred to a co-investigator when possible or another authorized clinical Investigator. In the event there are no opportunities to transfer investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by EPIX.

The investigator must return all documents and investigational product to EPIX, unless this action would jeopardize the rights, safety, or welfare of the subjects.

Criteria for Suspending/Terminating a Study Center

EPIX reserves the right to stop the inclusion of subjects at a study center at any time if no subjects have been enrolled for a period beyond 3 months after the site has been granted Approval to Enroll or if the center has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of investigator participation, all study-related devices and equipment, as applicable, will be returned to EPIX unless this action would jeopardize the rights, safety or well-being of the subjects. The IRB/EC and regulatory authorities, as applicable, will be notified. All subjects enrolled in the study at the center will continue to be followed per protocol-defined follow-up. The Principal Investigator at the center must make provision for these follow-up visits unless EPIX notifies the investigational center otherwise.

16. PUBLICATION AND REPORTING POLICY

Epix Therapeutics is committed to the publication and dissemination of clinical study results, regardless of study outcomes. Any publication or presentation relating to the DIAMOND-AF Study will require that ACT's role as a sponsor or financial supporter is included.

The final clinical study report of the conclusions of this study will be written within six (6) months of the closing of the database at the end of the study. The report will be signed by the global study principal investigators and provided to all study investigators. The study protocol will be registered at www.clinicaltrials.gov before the inclusion of any study subjects.

17. REIMBURSEMENT AND COMPENSATION FOR SUBJECTS

Travel and other expenses incurred by subjects because of participation in the study may be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

18. ABBREVIATIONS AND DEFINITIONS

18.1. Table of Definitions

Term	Definition
ACT	ACT is a test that is used to monitor the effectiveness of the administration of Heparin through measuring activated clotting time (ACT)
Asymptomatic AF, AT or AFL	Also known as silent AF or silent atrial tachycardia (e.g. AT, AFL). Defined as an opportune diagnosis of AF, AT, and/or AFL with electrocardiographic data; specifically, subject's event monitor, 24 hr. Holter monitor or 12 lead ECG at clinic visit.
Atrioesophageal fistula	Creation of direct communication between the left atrium and esophagus as documented by esophageal erosion combined with evidence of a fistulous connection to the atrium (e.g. air emboli, an embolic event or direct observation at the time of surgical repair). A CT or MRI scan is recommended to document event.
Attempt Subject	Refers to a subject who has been enrolled and has treatment catheter introduced but does not receive an ablation with the treatment or control catheter per protocol.
Blanking Period	The ~ 90-day period between ablation procedure and the 3-month follow-up visit. During the blanking period, a repeat ablation can be performed with the same treatment catheter subject originally randomized to and was treated with. Subjects can be prescribed antiarrhythmic drugs as determined necessary by the investigator during blanking period.
Bleeding complication	Major bleed that requires a transfusion or results in a $\geq$ 20% fall in hematocrit
Cardiac tamponade / perforation	Significant pericardial effusion with hemodynamic compromise that requires elective or urgent pericardiocentesis or results in a 1-cm or more pericardial effusion as documented by echocardiography.
CHA_2DS_2-VASc score	Clinical prediction rules for estimating stroke risk in patients with non-rheumatic AF. The rule gives a better risk stratification of low-risk patients than $CHADS_2$ score by inclusion of additional stroke risk modifier risk factors.

	Condition		Points
	C	Congestive heart failure (or LV systolic dysfunction)	1
	H	Hypertension (consistently > 140/90mmHg or treated)	1
	A2	Age ≥ 75 years	2
	D	Diabetes Mellitus	1
	S2	Prior stroke or TIA or thromboembolism	2
	V	Vascular disease (e.g. peripheral artery disease, MI, aortic plaque)	1
	A	Age 65-74 years	1
	Sc	Sex category (i.e. female sex)	1
Char	The remains of solid biomass originating from intracavity blood or myocardium that has formed as proteins in the blood are denatured by excessive heating that present as friable material observed on the catheter after RF ablation.		
Congestive Heart Failure	Heart doesn't pump properly and fluid builds up in arms, legs, ankles, feet, lungs, or an organ.		
Coagulum	The remains of solid biomass originating from intracavity blood or myocardium that has formed as proteins in the blood are denatured by excessive heating that present as adherent material observed on the catheter after RF ablation.		
Death	Cardiovascular related death post ablation		
Effectiveness Evaluation Period	The period between subject's 3-month follow-up visit and 12-month follow-up visit during which the primary effectiveness endpoint will be assessed.		
Enrolled Subject	All subjects who sign ICF and are randomized to a treatment arm.		
Heart block	Damage to the heart's electrical system that controls heart rhythm.		
Hemoptysis	Coughing up blood		
Femoral (groin) hematoma	Bleeding at the catheter insertion site that causes swelling or a pocket of blood. May need to be drained or require additional procedure.		

Long Standing Persistent AF	Long-standing persistent AF is defined as continuous AF of greater than 12 months duration.
Myocardial infarction	MI as it relates to AF ablation resulting in the presence of any one of the following criteria: • ECG changes indicative of new ischemia that persist for > 1 hour • development of new pathological Q waves on an ECG • imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Paroxysmal Atrial Fibrillation (PAF)	Recurrent atrial fibrillation that last ≥ 30 seconds and terminates spontaneously within 7 days.
Pericardial effusion	Accumulation of blood between heart and lining of the heart (pericardium). It is not uncommon to observe "trace" pericardial effusion following AF ablation. Trace effusion that does not need intervention is not considered a serious AE.
Persistent Atrial Fibrillation	Recurrent atrial fibrillation that lasts ≥ 7 days and does not terminate spontaneously
Self-Limiting Pericarditis	Pleuritic chest discomfort with or without pericardial rub and ECG changes and did not require additional hospitalization. Generally, not an SAE.
Serious Pericarditis	Pericarditis resulting in an effusion that leads to hemodynamic compromise, requires pericardiocentesis, prolongs hospitalization > 48 hours or persists for more than 30 days following procedure.
Source Data	Original records (or certified copies) of clinical findings, information, observations, or other activities in an investigation necessary for the reconstruction and evaluation of the clinical study.
Source Document	Printed or electronic document containing source data like hospital charts / records, lab notes, device accountability records, radiographs, signed procedural worksheets, records kept at the investigation site, and at the laboratories involved in the clinical study.
Phrenic nerve paralysis	Absence of phrenic nerve function assessed by a sniff test that persists > 7 days. A phrenic nerve paralysis is considered to be permanent when it is documented to be present ≥ 12 months following ablation.
Pulmonary edema	Pulmonary alveolar fluid accumulation accompanied by typical symptoms (dyspnea), physical findings (rales, hypoxemia),

	radiologic findings, and response to diuretic therapy and requiring hospitalization.
Screen Failure	A subject who has consented (signed ICF) but is found to not meet eligibility criteria through medical file review and/or screening procedures to confirm eligibility.
Steam pop	Excessive tissue temperatures over ~100°C that may result in an audible pop. The pop is a sudden release or explosion due to the vaporization of interstitial fluid in myocardium. This may produce biotraumas and tissue disruption that is usually clinically benign but may cause rupture of thin-walled structures with subsequent pericardial tamponade, usually requiring emergency pericardiocentesis, and/or surgical repair.
Stroke post-ablation	Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax that persists for >24 hours as determined by the consulting neurologist and subsequent neuroimaging procedure (MRI or CT scan or cerebral angiography).
Symptomatic AF, AT or AFL	Symptoms associated with AF, AT or AFL that were experienced by the subject, made them seek medical attention, and were concurrent with a documented episode by ECG, event monitor and/or Holter monitor. Symptoms may have included palpitations, irregular pulse (i.e. rapid, racing, pounding, fluttering, bradycardic), dizziness, weakness, chest discomfort, and breathlessness.
Thromboembolism	Occurrence of deep vein thrombosis or pulmonary embolism post ablation
Thrombus	An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing vascular obstruction at the point of its formation.
Transient ischemic attack (TIA) post-ablation	Rapid onset of new focal neurological deficit with immediate symptom resolution (usually 1 to 2 hours), always within 24 hours as determined by consulting neurologist and neuroimaging without tissue injury.
Vagal nerve injury	Esophageal dysmotility or gastroparesis requiring or prolonging hospitalization following an ablation procedure
Vascular access complications	Resulting in development of a hematoma, an AV fistula or a pseudoaneurysm that requires intervention, such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.

Vasospasm	Sudden narrowing of artery that usually relaxes with medication or by waiting a short period of time (minutes).
Wide Area Circumferential Ablation (WACA)	The location of PVI has moved more proximally, from the PV ostium to the antral insertion of the PV, several centimeters proximal to the PV ostium. This is called "wide area circumferential ablation" or WACA, and is also known as PV antral isolation. Technique has several advantages: 1) decreases risk of PV stenosis 2) eliminates proximal antral AF triggers 3) modification of nerve bundles that innervate the atria and contribute to AF maintenance may also be ablated.

18.2. Table of Abbreviations

Abbreviation	Definition
AAD	Anti-arrhythmic drugs
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Quality of Life Survey
AFL	Atrial Flutter
AT	Atrial Tachycardia
BMI	Body Mass Index
CA	Competent Authority
CABG	Coronary artery bypass graft
CEC	Clinical Events Committee
CF	Contact Force
CFAE	Complex fractionated atrial electrogram
CS	Coronary Sinus
CT	Computed Tomography
CTI	Cavotricuspid Isthmus
DIP	Dispersive Indifferent Patch
DSMB	Data Safety Monitoring Board
EC	Ethics Committee (see IRB for US)
ECG	Electrocardiogram
EDC	Electronic Data Capture
EGM	Electrogram
EP	Electrophysiologist
EPIX	Epix Therapeutics
EU	European Union
F	French size
FDA	US Food and Drug Administration
GCP	Good Clinical Practice
ICE	Intracardiac Echocardiography
ICF	Informed Consent Form
IFU	Instructions for Use
IRB	Institutional Review Board
IU	International Unit
IV	Intra-venous
LA	Left Atrium
LVEF	Left Ventricular Ejection Fraction
MACE	Major Adverse Cardiovascular Event
MRI	Magnetic Resonance Imaging
NYHA	New York Heart Association
PAF	Paroxysmal Atrial Fibrillation

PI	Principal Investigator
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QOL	Quality of Life
RF	Radiofrequency
RFCA	Radiofrequency catheter ablation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEE	Transesophageal echocardiography
TIA	Transient Ischemic Attack
TTE	Transthoracic echocardiography
TTM	Trans-telephonic Monitor
UADE	Unanticipated Adverse Device Effect
US	United States
W	Watts
WACA	Wide area circumferential ablation

19. BIBLIOGRAPHY

1. Feinberg, W.M., et al., *Prevalence, age distribution, and gender of patients with atrial fibrillation. Analysis and implications.* Arch Intern Med, 1995. **155**(5): p. 469-73.
2. Go, A.S., et al., *Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study.* JAMA, 2001. **285**(18): p. 2370-5.
3. Krahn, A.D., et al., *The natural history of atrial fibrillation: incidence, risk factors, and prognosis in the Manitoba Follow-Up Study.* Am J Med, 1995. **98**(5): p. 476-84.
4. Wann, L.S., et al., *2011 ACCF/AHA/HRS focused update on the management of patients with atrial fibrillation (update on Dabigatran): a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines.* Circulation, 2011. **123**(10): p. 1144-50.
5. Friberg, J., et al., *Rising rates of hospital admissions for atrial fibrillation.* Epidemiology, 2003. **14**(6): p. 666-72.
6. Hamer, M.E., et al., *Quality-of-life assessment in patients with paroxysmal atrial fibrillation or paroxysmal supraventricular tachycardia.* Am J Cardiol, 1994. **74**(8): p. 826-9.
7. Dorian, P. and I. Mangat, *Quality of life variables in the selection of rate versus rhythm control in patients with atrial fibrillation: observations from the Canadian Trial of Atrial Fibrillation.* Card Electrophysiol Rev, 2003. **7**(3): p. 276-9.
8. Singh, S.N., et al., *Quality of life and exercise performance in patients in sinus rhythm versus persistent atrial fibrillation: a Veterans Affairs Cooperative Studies Program Substudy.* J Am Coll Cardiol, 2006. **48**(4): p. 721-30.
9. Fuster, V., et al., *2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines.* Circulation, 2011. **123**(10): p. e269-367.
10. Nattel, S., *Cardiac Electrophysiology: From Cell to Bedside*. 2004: Saunders.
11. Allessie, M.A., et al., *Pathophysiology and prevention of atrial fibrillation.* Circulation, 2001. **103**(5): p. 769-77.
12. Haissaguerre, M., et al., *Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins.* N Engl J Med, 1998. **339**(10): p. 659-66.
13. Fuster, V., et al., *ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society.* Circulation, 2006. **114**(7): p. e257-354.

14. Calkins, H., et al., *2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: recommendations for patient selection, procedural techniques, patient management and follow-up, definitions, endpoints, and research trial design.* Europace, 2012. **14**(4): p. 528-606.

15. Neuzil, P., et al., *Electrical reconnection after pulmonary vein isolation is contingent on contact force during initial treatment: results from the EFFICAS I study.* Circ Arrhythm Electrophysiol, 2013. **6**(2): p. 327-33.

16. Afzal, M.R., et al., *Use of Contact Force Sensing Technology During Radiofrequency Ablation Reduces Recurrence of Atrial Fibrillation: A Systematic Review and Meta-Analysis.* Heart Rhythm, 2015.

17. Packer, D.L., et al., *Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial.* J Am Coll Cardiol, 2013. **61**(16): p. 1713-23.

18. Wilber, D.J., *Comparison of Antiarrhythmic Drug Therapy and Radiofrequency Catheter Ablation in Patients With Paroxysmal Atrial Fibrillation A Randomized Controlled Trial.* Journal Americal Medical Assosiation, 2010. **303**(4): p. 333-340.

19. Yokoyama, K., et al., *Novel contact force sensor incorporated in irrigated radiofrequency ablation catheter predicts lesion size and incidence of steam pop and thrombus.* Circ Arrhythm Electrophysiol, 2008. **1**(5): p. 354-62.

20. Kuck, K.H., et al., *A novel radiofrequency ablation catheter using contact force sensing: Toccata study.* Heart Rhythm, 2012. **9**(1): p. 18-23.

21. Ikeda, A., et al., *Relationship between catheter contact force and radiofrequency lesion size and incidence of steam pop in the beating canine heart: electrogram amplitude, impedance, and electrode temperature are poor predictors of electrode-tissue contact force and lesion size.* Circ Arrhythm Electrophysiol, 2014. **7**(6): p. 1174-80.

22. Nakagawa, H., et al., *Locations of high contact force during left atrial mapping in atrial fibrillation patients: electrogram amplitude and impedance are poor predictors of electrode-tissue contact force for ablation of atrial fibrillation.* Circ Arrhythm Electrophysiol, 2013. **6**(4): p. 746-53.

23. Nakagawa, H. and W.M. Jackman, *The Role Of Contact Force In Atrial Fibrillation Ablation.* J Atr Fibrillation, 2014. **7**(1): p. 1027.

24. Natale, A., et al., *Paroxysmal AF catheter ablation with a contact force sensing catheter: results of the prospective, multicenter SMART-AF trial.* J Am Coll Cardiol, 2014. **64**(7): p. 647-56.

25. Reddy, V.Y., et al., *Randomized, Controlled Trial of the Safety and Effectiveness of a Contact Force-Sensing Irrigated Catheter for Ablation of Paroxysmal Atrial Fibrillation: Results of the TactiCath Contact Force Ablation Catheter Study for Atrial Fibrillation (TOCCASTAR) Study.* Circulation, 2015. **132**(10): p. 907-15.

26. Calkins, H., et al., *2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.* Heart Rhythm, 2017.

27. Doherty, J.U., et al., *2017 ACC Expert Consensus Decision Pathway for Periprocedural Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation: A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force.* J Am Coll Cardiol, 2017. **69**(7): p. 871-898.

28. Liang, J., et al., *Early recurrence of atrial arrhythmias following pulmonary vein antral isolation: Timing and frequency of early recurrences predicts long-term ablation success.* Heart Rhythm, 2015. **12** (12): p. 2461-2468.