Medtronic

Clinical Investigation Plan

Clinical Investigation Plan/Study Title	DIAMOND- AF II Study Study Title: A Prospective Clinical Evaluation of the DiamondTemp™ Ablation System for the Treatment of Persistent Atrial Fibrillation
Clinical Investigation Plan Identifier	MDT20012 (TP01071)
Study Product Name	DiamondTemp Ablation System
Sponsor/Local Sponsor	**Sponsor:** [redacted] Medtronic, Inc. [redacted]
Document Version	Version H
Version Date	06-Dec-2021

Confidentiality Statement

Investigator Statement and Signature Page

Study Product Name	DiamondTemp Ablation System
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I have read this Clinical Investigational Plan and agree to adhere to the requirements, and will make a reasonable effort to complete the study within the time designated. I will share this Clinical 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 Clinical 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), ISO14155:2020 (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. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the Clinical Investigation without the prior written consent of Medtronic.

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.

I agree to disclose if I was involved in an investigation or other research that was terminated, by providing an explanation of the circumstances that led to termination to the Sponsor.

Investigator's Signature:	
Investigator Role (select one)	☐ Principal Investigator ☐ Sub-Investigator
Investigator's Name:	
Institution:	
Date: (DD-MMM-YYYY)	

1. Table of Contents

2. Glossary

2.1 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
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
PeAF	Persistent 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

2.2 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.

<table>
<tr><td>Atrioesophageal fistula</td><td>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.</td></tr>
<tr><td>Attempt Subject</td><td>Refers to a subject who has been enrolled and has treatment catheter introduced but does not receive an ablation with the catheter per protocol.</td></tr>
<tr><td>Blanking Period</td><td>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 was treated with. Subjects can be prescribed antiarrhythmic drugs as determined necessary by the Investigator during blanking period.</td></tr>
<tr><td>Bleeding complication</td><td>Major bleed that requires a transfusion or results in a ≥ 20% fall in hematocrit.</td></tr>
<tr><td>Cardiac tamponade / perforation</td><td>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.</td></tr>
<tr><td>CHA_2DS_2-VASc score</td><td>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 CHADS2 score by inclusion of additional stroke risk modifier risk factors.
<table>
<tr><th colspan="2">Condition</th><th>Points</th></tr>
<tr><td>C</td><td>Congestive heart failure (or LV systolic dysfunction)</td><td>1</td></tr>
<tr><td>H</td><td>Hypertension (consistently > 140/90mmHg or treated)</td><td>1</td></tr>
<tr><td>A2</td><td>Age ≥ 75 years</td><td>2</td></tr>
<tr><td>D</td><td>Diabetes Mellitus</td><td>1</td></tr>
<tr><td>S2</td><td>Prior stroke or TIA or thromboembolism</td><td>2</td></tr>
<tr><td>V</td><td>Vascular disease (e.g. peripheral artery disease, MI, aortic plaque)</td><td>1</td></tr>
<tr><td>A</td><td>Age 65-74 years</td><td>1</td></tr>
<tr><td>Sc</td><td>Sex category (i.e. female sex)</td><td>1</td></tr>
</table></td></tr>
<tr><td>Char</td><td>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.</td></tr>
<tr><td>Congestive Heart Failure</td><td>Heart doesn’t pump properly and fluid builds up in arms, legs, ankles, feet, lungs, or an organ.</td></tr>
<tr><td>Coagulum</td><td>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.</td></tr>
<tr><td></td><td></td></tr>
</table>

Extended hospitalization	Extended hospital stay or re-hospitalization that is related to the procedure or device that is not: • a planned hospitalization for a pre-existing condition, or procedure required by the Clinical Investigational Plan (including repeat ablation procedure), without serious deterioration in health. • hospitalizations due to recurrent AF/AT/AFL or prolonged hospitalization during the 30 days following procedure to adjust anticoagulation or anti-arrhythmia regimen or to administer diuretic medication.
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.
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 (PeAF)	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.

Significant Pericardial Effusion	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.
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.

3. Synopsis

Title	DIAMOND-AF II
Clinical Study Type	Global, multi-center, prospective, single-arm, IDE Study
Product Name	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
Sponsor	**Sponsor:** [redacted] Medtronic, Inc. [redacted]

External Organizations	[redacted]
Indication under investigation	Current indication in the US: 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 RF generator and accessories (DiamondTemp catheter-to-RF generator cable, DiamondTemp GenConnect cable, DiamondTemp EGM cable,

	DiamondTemp irrigation pump, DiamondTemp irrigation tubing set) and compatible mapping system. Indication under investigation for the US and Canada: The DiamondTemp Catheter is indicated for use in cardiac electrophysiological mapping (stimulation and recording) and for treatment of drug refractory, symptomatic persistent 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. The indication under investigation is within the approved indication in Europe.
Investigation Purpose	The purpose of this study is to demonstrate the safety and effectiveness of the DiamondTemp Ablation System for the treatment of drug refractory, symptomatic persistent Atrial Fibrillation.
Product Status	The DiamondTemp™ Cardiac Ablation System (unidirectional and bidirectional catheters, the RF Generator, Irrigation Pump, and its accessories) (see **Figure 7**) is market-released in the US and will become investigational when used as indicated in the study in the US. The DiamondTemp System is market released and will be used within the approved indications in Europe, therefore, is not considered investigational for the intended patient population in Europe. The DiamondTemp Ablation components will be considered investigational in geographies (Canada) in which the product is not available commercially and will be labeled for exclusive use in Clinical Investigations.
Primary Safety Endpoint	The primary safety endpoint is defined as freedom from a composite of serious adverse events (SAEs) occurring within 7 days, procedure and/or device-related significant pericardial effusion that occurs within 30 days and severe or clinically symptomatic pulmonary vein stenosis and atrioesophageal fistula through 6-months of the 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 • Significant Pericardial Effusion

	• Stroke/CVA • Thromboembolism • Transient ischemic attack (TIA) • Vagal nerve injury • Vascular access complication
Primary Effectiveness Endpoint	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 previously failed AAD at a dose greater than the highest ineffective dose for AF 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 will include: • Freedom from a composite of SAE occurring within 30-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 during the effectiveness evaluation period lasting ≥30 seconds in duration by ECG monitoring. • Freedom from documented AF, AT and AFL* episodes during the effectiveness evaluation period 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 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.

	• 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. ** 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.*

Ancillary Endpoints	Ancillary endpoints to further characterize the performance of the DiamondTemp Ablation System will include:
	• Procedure characteristics:
	  ○ Total procedure time (minutes), defined as time of investigational catheter insertion into the vasculature to time of last procedural ablation catheter removed.
	  ○ Total treatment device time (minutes), defined as time of delivery of first RF ablation with investigational catheter to removal of the investigational catheter.
	  ○ Mean cumulative RF Time (minutes).
	  ○ Mean duration of RF ablations (seconds).
	  ○ Total fluid infused through the investigational catheter (mL).
	  ○ Total fluoroscopy time (minutes).
	• Number of re-hospitalizations due to Atrial Fibrillation recurrence during the effectiveness evaluation period.

Study Design	The DIAMOND-AF II Study is a prospective, multi-center trial being performed at centers in the United States, Canada and Europe. A maximum of 376subjects will be enrolled at up to 30 centers in the United States (US), Canada, and Europe. Approximately 50% of the data will be generated from sites within the US.
Inclusion/Exclusion Criteria	**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 documented symptomatic, persistent Atrial Fibrillation with 1) a physician's note documenting a continuous AF episode lasting longer than 7 days but less than 12 months AND 2) two electrocardiograms from any form of rhythm monitoring showing continuous AF taken at least 7 days apart OR a 24-hour Holter within 180 days of the ablation procedure showing continuous AF. 3. Refractory, intolerant or contraindicated to at least one Class I or III anti-arrhythmic (AAD) drug for treatment of Atrial Fibrillation. 4. Suitable candidate for intra-cardiac mapping and ablation of arrhythmia. 5. Subject agrees to comply with study procedures and be available (geographically stable) for follow-up visits for at least 12 months after enrollment. 6. Subject is willing and able to provide written consent. **Exclusion Criteria:** At time of enrollment and/or prior to procedure:

	1. Continuous AF >12 months (long-standing persistent AF). 2. Paroxysmal AF with longest episode <7 days. 3. AF secondary to electrolyte imbalance, thyroid disease or reversible or non-cardiac cause. 4. Rheumatic heart disease. 5. Severe mitral regurgitation. 6. Hypertrophic cardiomyopathy. 7. LA diameter >5.5 cm. 8. Left ventricular ejection fraction (LVEF) <40%. 9. Currently NYHA Class III or IV or exhibits uncontrolled heart failure. 10. Body Mass Index (BMI) >42 kg/m^2. 11. LA ablation, septal closure device or mitral valve surgical procedure at any time prior to enrollment. 12. Presence of intramural thrombus, tumor or abnormality that precludes vascular access, catheter introduction or manipulation. 13. Coagulopathy, bleeding diathesis or suspected procoagulant state. 14. Sepsis, active systemic infection or fever (>100.5° F / 38° C) within a week prior to the ablation procedure. 15. Significant restrictive or obstructive pulmonary disease or chronic respiratory condition. 16. 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. 17. 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. 18. Positive pregnancy test results for female subjects of childbearing potential or breast feeding. 19. Enrollment in a concurrent clinical study that in the judgement of the Investigator would impact study outcomes. 20. 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. 21. 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:*** 22. Documented LA thrombus upon imaging. 23. Creatinine >2.5mg/dl or creatinine clearance <30mL/min. ***Within 3 months of enrollment:*** 24. Significant gastrointestinal (GI) bleed. 25. Myocardial infarction (MI), unstable angina, cardiac surgery or coronary intervention. ***Within 6 months of enrollment:*** 26. Coronary artery bypass graft (CABG) procedure. 27. Implant procedure performed for ICD, CRT leads or pacemaker.

<table>
<tr><td></td><td>28. Documented stroke, CVA, TIA or suspected neurological event.</td></tr>
<tr><td>Study Procedures and Assessments</td><td>The initial focus of the ablation procedure is to create a series of radiofrequency (RF) lesions encircling the left and right PVs to achieve electrical pulmonary vein antrum isolation (PVI) from the rest of the left atrium (LA).

Physicians will be allowed to consider additional ablation strategies per their current standard ablation practice and within the recommendations of the protocol. All subjects will be considered enrolled following review and signature on informed consent. For full details of procedures performed per visit, please see “Study Procedures” section.

Follow-Up Visit Schedule:
<table>
<tr><th>Subject Visit Description</th><th>Timeframe / Visit Window</th></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>7 days Follow-Up (Phone)</td><td>7 ± 3 days</td></tr>
<tr><td>1 Month Follow-Up</td><td>30 ± 14 days</td></tr>
<tr><td>3 Month Follow-Up</td><td>90 ± 21 days</td></tr>
<tr><td>6 Month Follow-Up</td><td>180 ± 28 days</td></tr>
<tr><td>12 Month Follow-up</td><td>365 ± 45 days</td></tr>
<tr><td>Unscheduled Visits</td><td>As needed/necessary</td></tr>
<tr><td>Repeat Ablation Procedure</td><td>As needed/necessary</td></tr>
</table></td></tr>
<tr><td>Safety Assessments</td><td>All adverse events will be collected starting at the time of signing the Informed Consent Form (ICF) through the duration of the subject’s participation in the study. In addition, any device deficiency related to the DiamondTemp Ablation System and associated accessories should be reported.</td></tr>
<tr><td>Statistics</td><td>The primary safety and effectiveness endpoints will be analyzed using the Kaplan-Meier method. The study will be considered successful when both the primary safety and the primary effectiveness objectives are met.

Descriptive summary statistics for continuous variables will include the number of subjects, mean, standard deviation, median, quartiles and range. Nominal categorical variables will be summarized using counts and percentages. Ordinal variables may be analyzed as if they were continuously scaled.</td></tr>
</table>

4. Introduction

4.1 Background- 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] [4] [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] [7] [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] Episodes of AF that are continuous and sustained beyond 7 days but less than 12 months are classified as persistent AF (PeAF) according to the most recent 2017 HRS/EHRA Consensus Statement. Long-standing persistent AF is defined as continuous AF of greater than 12 months duration. [10]

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. [11] [12]

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. [13]

4.1.1 Prior Clinical Evidence for RF Ablation to Treat Persistent AF

Catheter ablation is commonly performed for persistent AF (PeAF), but few high quality randomized controlled trials (RCTs) exist. [17] Multiple RF catheters have been approved for the treatment of paroxysmal Atrial Fibrillation, but to date there are no RF catheters approved in the United States specifically for the treatment of PeAF.

Following the approval of RF catheters for PAF, companies are now seeking approval for PeAF. Biosense-Webster is currently enrolling subjects in the PRECEPT study (NCT#02817776) to demonstrate safety and effectiveness of the THERMOCOOL SMARTTOUCH® SF Catheter in the treatment of drug refractory, symptomatic persistent Atrial Fibrillation.

The optimal RF lesion set to treat PeAF is a controversial topic, but as demonstrated in a large RCT study, STAR-AF II (NCT#01203748), it was shown that PVI only may be as effective as other additional ablation strategies. STAR-AF II randomly assigned 589 participants with PeAF in a 1:4:4 ratio to a) ablation with PVI only (67 patients), b) PVI plus ablation of electrograms (egm) showing complex fractionated activity (263 patients) or c) PVI plus additional linear ablation across the atrial roof and mitral isthmus (259 patients) [18]. While there was a greater percentage of patients with no recurrent PeAF at 18 months in the PVI only group (59% vs. 49% and 46%, for the PVI plus complex fractionated egm or linear ablation, respectively) the study found that there was no reduction in the freedom from PeAF based on study ablation strategies.

The DiamondTemp Ablation System was being evaluated in the DIAMOND-AF Study for the treatment of drug refractory, symptomatic paroxysmal Atrial Fibrillation (NCT#03334630). DIAMOND-AF was a global, multi-center, randomized clinical study to evaluate the DiamondTemp System in 480 subjects with paroxysmal Atrial Fibrillation. The DIAMOND-AF study enrollment was completed in 2018.

The Sponsor is initiating a study to pursue a US indication to demonstrate the safety and effectiveness of the DiamondTemp Ablation System for the treatment of persistent AF. The study will focus on PVI being the “cornerstone” of PeAF ablation but will allow physicians to consider additional ablation strategies per their standard ablation practice and within the recommendations of the protocol.

The DiamondTemp Ablation System is designed to give operators direct measures of lesion creation (i.e. tissue - tip interface temperatures and local electrograms recordings that attenuate during ablation and lesion formation). 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 the catheter-tissue interface temperature at a pre-defined set point optimal for creating an effective lesion. These features may prove to be beneficial in creating safe and effective RF ablation for the treatment of PeAF.

4.1.2 Summary Of First-In-Human Clinical Study (TRAC-AF)

Epix Therapeutics conducted a multi-center First-In-Human clinical study, TRAC-AF, 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 TempeRAture-Controlled and Contact Sensing RF Ablation Clinical Trial for Atrial Fibrillation, NCT#02821351) study was a prospective, multi-center, single-arm feasibility study initiated in 2016 and conducted at four European investigational sites.

Enrollment was conducted in two phases. Phase 1 included enrollment of 38 subjects from January through March of 2016; 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 12-month follow-up visits and are now exited from the study.

All primary study endpoints have been met through 30 days follow up. Assessments of primary safety events resulted in two (2) SAEs (2.9%) through the 7-day safety endpoint and three (3) SAEs (4.3%) through the 30-day safety endpoint. The primary effectiveness endpoint of acute procedural success was achieved in 100% of subjects. Freedom from AF at 12 months post-procedure was 72.5%.

4.1.3 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] [10] Subjects received ablation using the investigational device which required electrical isolation of all clinically relevant pulmonary veins.

4.1.4 TRAC-AF Investigational Device

The TRAC-AF investigational device was the DiamondTemp Ablation System. The investigational device was used with a commonly available EP recording system, cardiac stimulator and mapping device, the St. Jude EnSite Velocity or Precision Cardiac Mapping System. There were no control devices in the study.

4.1.5 TRAC-AF Clinical Endpoints

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 Ablation System was assessed by evaluating the nature and frequency of SAEs and SADEs at 30 days post-procedure.

Primary Effectiveness Endpoint: The effectiveness of the DiamondTemp Ablation 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 Ablation 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.

4.1.6 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.
5. Active gastrointestinal bleeding
6. Active infection or fever (>100.5 ◦F/38 ◦C)
7. Sepsis
8. Cardiac surgery within the past two months.
9. 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)
10. Severe uncontrolled systemic hypertension (systolic pressure > 240 mm Hg within the last 30 days)
11. Documented anaphylaxis during previous exposure to angiographic contrast media
12. Uncontrolled congestive heart failure (NYHA1 Class III or IV)
13. Unstable angina or acute myocardial infarction within the past three months
14. Bleeding, clotting disorders, or known thrombosis
15. Severe Peripheral vascular disease
16. Uncontrolled diabetes
17. Heart valve replacement
18. Mitral clip (E-valve)
19. Women who are of childbearing potential who are currently pregnant or not willing to use contraception for the duration of the study
20. Active participation in another investigational protocol currently or the last 30 days
21. Unable or unwilling to take anti-coagulants
22. Unwilling or unable to comply with any protocol or follow up requirements

4.1.7 Study Results

Study Accountability and Disposition

Study enrollment in TRAC-AF 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. 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	**N (%)**
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	**N (%)**
Hepatic Disease	9 (12.9)
Pulmonary disease	17 (24.3)
Other Relevant Cardiac Diseases	**N (%)**
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 PVs supported by the EnSite Velocity or Precision to collect electrical map of the atrium and assist the navigation of the DiamondTemp Catheter 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, 51% of subjects) or confirming PVI after a minimum of 20 minutes (n=34, 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 (4.3%) 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 Ablation System was 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.

4.1.8 Conclusion from Clinical Study

The objective of the TRAC-AF First-In-Human study was to substantiate the safety and effectiveness of the DiamondTemp Ablation System to ablate cardiac tissue in patients with paroxysmal Atrial Fibrillation. The study endpoints achieved the efficacy performance goal demonstrating 100% effectiveness by confirming PVI in all subjects treated as intended under the study protocol. Freedom from AF 12 months post-procedure was 72.5%. The safety profile demonstrated in the study indicates the DiamondTemp Ablation System can be used safely in cardiac ablation procedures in the defined 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 the subjects treated with the DiamondTemp Ablation 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. [10]

4.2 Purpose

The purpose of this study is to demonstrate the safety and effectiveness of the DiamondTemp Ablation System for the treatment of drug refractory, symptomatic persistent Atrial Fibrillation.

5. Endpoints

5.1 Primary Safety Endpoint

The primary safety endpoint is defined as freedom from a composite of serious adverse events (SAEs) occurring within 7 days, procedure and/or device-related significant pericardial effusion that occurs within 30 days and severe or clinically symptomatic pulmonary vein stenosis and atrioesophageal fistula 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 [10]
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.
Significant Pericardial Effusion	Results in hemodynamic compromise, requires elective or urgent pericardiocentesis or results in a 1-cm or more pericardial effusion as documented by echocardiography.
Stroke/CVA	Stroke Diagnostic Criteria:

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 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 or anti-arrhythmia regimen or to administer diuretic medication are not considered part of the combined primary safety endpoint.

5.2 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 previously failed AAD at a dose greater than the highest ineffective dose for AF 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.*

5.3 Secondary Endpoints

Secondary endpoints to characterize the performance of the DiamondTemp Ablation System will include:

- Freedom from a composite of SAE occurring within 30-days post-index ablation procedure as adjudicated by an independent CEC for relatedness to the procedure or device.
- Freedom from documented AF, AFL* or AT episodes during the effectiveness evaluation period lasting ≥30 seconds in duration by ECG monitoring.
- Freedom from documented AF, AT and AFL episodes during the effectiveness evaluation period 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 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.
- 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.

** 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.*

5.4 Ancillary Endpoints

Ancillary endpoints to further characterize the performance of the DiamondTemp Ablation System will include:

- Procedure characteristics
  - Total procedure time (minutes), defined as time of investigational catheter insertion into the vasculature to time of last procedural ablation catheter removed.
  - Total treatment device time (minutes), defined as time of delivery of first RF ablation with the investigational catheter to removal of the treatment catheter.
  - Mean cumulative RF Time (minutes).
  - Mean duration of RF ablations (seconds).
  - Total fluid infused through the investigational catheter (mL).
  - Total fluoroscopy time (minutes).
- Number of re-hospitalizations due to Atrial Fibrillation recurrence during the effectiveness evaluation period.

6. Study Design

The DIAMOND-AF II Study is a prospective, non-randomized (single-group assignment) 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 patients with persistent Atrial Fibrillation.

This study will enroll up to 376 subjects diagnosed with persistent AF 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 expected that one investigational ablation catheter, and appropriate accessory components will be used for each enrollment. It is anticipated that approximately 50% of the subjects will be enrolled at centers within the United States, with enrollment anticipated to be completed in 2022. The maximum number of enrollments per site will be identified within each sites Clinical Trial Agreement (CTA), but should not exceed 20%. There is no minimum requirement for enrollment at each site.

6.1 Duration

It is the intent of the protocol that all subjects will be followed for a minimum of 12 months post procedure. 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.

6.2 Rationale

The DIAMOND-AF II study is a pivotal clinical study designed to demonstrate that the DiamondTemp Ablation system is safe and effective. Justification of design is both based on a clinical evaluation and aligned with risk assessment results. See Section 4 for further background information and evaluation of clinical data. See Section 6 for further background on the study design.

6.3 Study Oversight

6.3.1 Steering Committee

The DIAMOND-AF II Steering Committee is comprised of senior clinical, medical and regulatory members of the Sponsor, as well as international physician investigator advisors. 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, the Sponsor remains responsible for all decisions related to any such requests in line with approved study agreements.

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7. Product Description

7.1 General- Product Classification, Code, Regulation

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

7.2 Investigational Device Description

The Medtronic DiamondTemp Ablation components will be considered investigational in geographies in which the product is not available commercially (Canada) and will be labeled for exclusive use in Clinical Investigations. The DiamondTemp ablation system [redacted] are market-released in the US and Europe. Investigational centers in the US will utilize the commercially released DiamondTemp Ablation Catheters, [redacted] (and future commercially released generators), [redacted] and its accessories (see Table 7) for the remainder of this study. The DiamondTemp system will be used within the approved indications in Europe, therefore is not considered investigational for the intended patient population in Europe.

Any changes made to these devices during this investigation will be subject to IDE Modification Reporting Requirements, as applicable. Any changes to devices that require an update to the CIP will be addressed in a CIP amendment.

Instructions for use for all devices used in this study are provided in their respective manuals. Labeling language requirements will be consistent with local regulations.

The DiamondTemp Ablation System investigational device is shown in Table 7.

Table 7: DiamondTemp Ablation System Investigational Device:

Product Name	Model Number		Geography Status at Study Start	Manufacturer
[redacted]	EU/US: [redacted]	CAN: [redacted]	CAN: Investigational EU: CE Marked US: FDA approved*	Medtronic Sunnyvale- EPIX Therapeutics
DiamondTemp Unidirectional Catheters, Large Curve	EU/US: [redacted]	CAN: [redacted]		
DiamondTemp Bidirectional Catheters, Small Curve	EU/US: [redacted]	CAN: [redacted]	CAN: Investigational EU: CE Marked US: FDA approved*	Medtronic Sunnyvale- EPIX Therapeutics

DiamondTemp Bidirectional Catheters, Large Curve	EU/US: [redacted]	CAN: [redacted]		
DiamondTemp RF Generator	[redacted]		CAN: Investigational EU: CE Marked US: FDA approved*	Medtronic Sunnyvale- EPIX Therapeutics
DiamondTemp Irrigation Pump	[redacted]		CAN: Investigational EU: CE Marked US: FDA approved*	Medtronic Sunnyvale- EPIX Therapeutics
DiamondTemp Tubing Set	[redacted]		CAN: Investigational EU: CE Marked US: FDA approved*	Medtronic Sunnyvale- EPIX Therapeutics
DiamondTemp Catheter-to-RFG Cable	[redacted]		CAN: Investigational EU: CE Marked US: FDA approved*	Medtronic Sunnyvale- EPIX Therapeutics
DiamondTemp GenConnect Cable	[redacted]		CAN: Investigational EU: CE Marked US: FDA approved *	Medtronic Sunnyvale- EPIX Therapeutics
DiamondTemp Generator Connection Box E	[redacted]		CAN : Not applicable EU: CE Marked US: FDA approved*	Plexus Manufacturing Sdn.Bhd., [redacted]
DiamondTemp EGM Cable	[redacted]		CAN : Not applicable EU: CE Marked US: FDA approved*	BMED/CEA Medical, [redacted]

* Investigational when used for DAF-II Study

The DiamondTemp Ablation System can be used with compatible mapping systems [redacted] 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 Ablation System:

- The DiamondTemp Ablation System allows for cardiac mapping, pacing and ablation when connected to the 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.
- 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 and lot number and will be tracked for dispositioning throughout the study. For the DiamondTemp Catheter, Generator and Irrigation Pump, 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 serial number and/or lot number and model number.

7.2.1 DiamondTemp Ablation Catheter

The DiamondTemp Catheter is an 8Fr catheter designed to be used with an 8.5Fr sheath (7.5Fr tip), sterile, single use, externally-irrigated cardiac ablation catheter, 110 cm in length, designed to deliver radiofrequency (RF) energy at the composite tip for mapping and cardiac ablation. The DiamondTemp Catheter is available with either unidirectional (Figure 2a) or bidirectional (Figure 2b) steering. The distal tip and ring electrodes are designed to record electrocardiogram (ECG) signals for mapping and to deliver stimulus for pacing. RF delivery from the composite catheter tip is similar to commercially available, externally-irrigated catheters.

Figure 2a. DiamondTemp Ablation Catheter, Unidirectional

Figure 2b. DiamondTemp Ablation Catheter, Bidirectional

7.2.2 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 such as temperature, power and impedance curves resulting during RF delivery.

Figure 3. DiamondTemp RF Generator, Front Panel Display

7.2.3 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 Generator or Irrigation Pump.

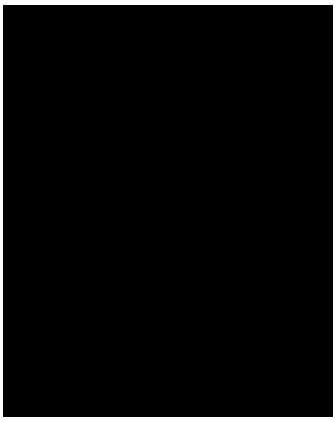

Figure 4. DiamondTemp Irrigation Pump

7.2.4 DiamondTemp Tubing Set

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

7.2.5 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

7.2.6 DiamondTemp 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.

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. 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 6. DiamondTemp Catheter-to-RFG Cable

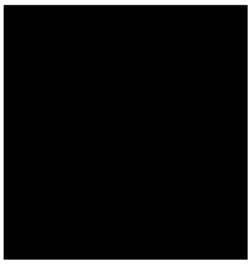

Figure 7. DiamondTemp GenConnect Cable

7.2.7 DiamondTemp EGM Cable [redacted] - For US and EU only

The Medtronic DiamondTemp EGM cable [redacted] is 3 meters (m) long and has 4 connectors. The one end of the cable (1 in Figure 8) has a male, 9-pin connector that will connect with the DiamondTemp RF Generator and the other end of the cable (2 in **Figure 8**) has male, 2.0 mm shrouded pin connectors (x4) that will connect with the hospital's compatible EP recording system (**Figure 8).** The DiamondTemp EGM Cable is provided non-sterile.

Figure 8: DiamondTemp 4-Lead EGM Cable

7.2.8. DiamondTemp Generator Connection Box E [redacted] - For US and EU only

The Medtronic DiamondTemp Generator Connection Box E [redacted] is a signal filtration device used to connect the DiamondTemp ablation catheter and DiamondTemp RF generator to the [redacted] cardiac mapping and navigation system (**Figure 9**). The box transmits intracardiac signals from the catheter electrodes to a compatible 3D mapping and navigation system without any signal distortion or interference by the generator.

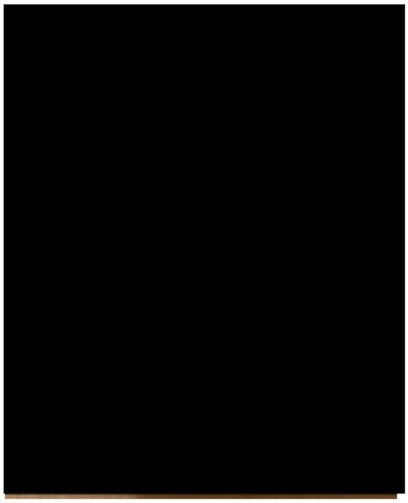

Figure 9: DiamondTemp Generator Connection Box E

7.2.9 Mapping System and EP Recording System Compatibility

The DiamondTemp Ablation System is used with compatible mapping systems [redacted] and commonly available EP recording systems and cardiac stimulators.

7.3 Product Use

Instructions for use of the devices used in this study, as well as test equipment used and exposure to bodily fluid, are provided in their respective manuals and Investigator Brochure. No human and/or animal tissues or their derivatives are found within the study product.

7.4 Product Training Materials

Technical training with the DiamondTemp Ablation System will be provided by the Sponsor. Training will be documented and will include a review of the Clinical Investigational Plan, study procedures, CRF completion, Instructions for Use, and all study compliance requirements.

7.5 Product Storage

Investigational product, once received at the study site, must be stored in a secure location at the study site. 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. It is the responsibility of the investigator to correctly handle, store, and track the investigational products maintained at the study site. Investigational products will be used only in the clinical study according to the CIP.

7.6 Product Return

All potentially defective devices should be returned to Medtronic Sunnyvale EPIX for analysis when permissible by local laws and regulations. Returns will be facilitated by Medtronic field personnel.

DiamondTemp Ablation System components and accessories are to be returned to Medtronic Sunnyvale EPIX by each study site as described below:
If no device deficiency, devices can be destroyed/disposed according to local laws and regulations.
Unused investigational devices should be returned as described in the notes below:

- [redacted]

Note: For DiamondTemp Ablation system accessories shipped to sites as investigational, unopened or expired accessories are required to be returned to Medtronic Sunnyvale EPIX. For accessories only considered investigational upon opening per the CIP there is no requirement to return unopened product to Medtronic Sunnyvale EPIX.

7.7 Product 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 Principal Investigator or his/her authorized representative is responsible to keep records documenting the receipt and tracking of the investigational device at their site. A form will be provided to the site that will log the received by date, received by name, model/lot/serial numbers, and expiration dates as applicable for each device. [redacted]

8. Study Site Requirements

8.1 Investigator/Investigation Site Selection

All Investigators managing the subject's Atrial Fibrillation must be qualified practitioners and experienced in the diagnosis and treatment of subjects with Atrial Fibrillation. All physicians must be experienced and/or trained in the handling of DiamondTemp Ablation System.

The role of the Principal Investigator is to implement and manage the day-to-day conduct of the Clinical Investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the Clinical Investigation.

The Principal Investigator shall:

- Be qualified by education, training, and experience to assume responsibility for the proper conduct of the Clinical Investigation (in accordance with the applicable requirements).

- Be experienced in the field of application and training in the use DiamondTemp Ablation System.
- Disclose potential conflicts of interest, including financial, that interfere with the conduct of the Clinical Investigation or interpretation of results.
- Be able to demonstrate that the proposed investigational study site:
  - Has the required number of eligible subjects needed within the recruitment period.
  - Has one or more qualified investigators, a qualified investigational study site team and adequate facilities for the foreseen duration of the Clinical Investigation.

8.2 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 and ISO14155:2020, 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.
- PI shall be able to demonstrate that the proposed investigation site has an investigation site team that is: qualified by education, training and experience to assume responsibility for the proper conduct of the Clinical Investigation in accordance with this standard and the applicable national regulations.
- PI is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The PI may delegate tasks to qualified members of the investigation site team but retains responsibility for the Clinical Investigation. This also applies when activities are outsourced to an external organization by the PI in which case, he/she shall implement procedures to ensure the integrity of all tasks performed and any data generated by this external organization.

- 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.
- 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.

8.3 Study Site Activation

A Site Activation Letter is an official letter confirming that an Investigative site can begin enrolling subjects in the Clinical Investigation. Prior to sending a site the letter, Study Management will verify the Investigative site and Investigator have completed the following: (1) Protocol Training; (2) Device Training; (3) Site Initiation ctivities , (4) signed Clinical Study Agreement, (4) appropriate national, international, and Regulatory approvals are received, including an approved Informed Consent Form and (5) a Site Activation Checklist has been completed.

Once all documents are complete and training has been conducted, Study Management will send the Investigator a Site Activation Letter to verify that they may begin treating and enrolling subjects in the Clinical Investigation.

8.4 Role of Sponsor Representative

In addition to performing monitoring and auditing activities, Sponsor representatives may provide support at the study site as required for the study under supervision of the Principal Investigator, including:

- Study training relevant and pertinent to the involvement of personnel conducting study activities and Investigator responsibilities.
- Technical support at all visits, but no CRF data entry shall be performed by Sponsor personnel.

In addition, for this study, sponsor representatives may be authorized by the Principal Investigator to perform the following significant trial related duties:

- Support study Investigators in performing the study ablation procedure.
- Support data collection during the ablation procedure.

Any data collection completed by Medtronic personnel will be clearly identified as such.

9. Selection of Subjects

9.1 Study Population

Subjects included in the DIAMOND-AF II study should be selected from the general patient population indicated for or currently scheduled for catheter ablation of persistent AF.

9.2 Subject Enrollment

Subjects who meet general eligibility for consideration in the study will sign an informed consent and undergo a baseline evaluation. All subjects will be considered enrolled following review and signature

on informed consent. The date the subject signed the IC, and the process for which signature was obtained, must be documented in the subject's medical records. Investigators are responsible for ensuring that subjects meet all of the inclusion criteria and none of the exclusion criteria. Institutional Review Board or Ethics Committee approval of the DIAMOND-AF II protocol and informed consent form must be obtained prior to enrolling subjects in the study.
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.

9.3 Inclusion Criteria

Candidates must meet ALL the following criteria to be enrolled in the DIAMOND-AF II 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 documented symptomatic, persistent Atrial Fibrillation with 1) a physician's note documenting a continuous AF episode lasting longer than 7 days but less than 12 months AND 2) two electrocardiograms from any form of rhythm monitoring showing continuous AF taken at least 7 days apart OR a 24-hour Holter within 180 days of the ablation procedure showing continuous AF.
3. Refractory, intolerant or contraindicated to at least one Class I or III AAD for treatment of Atrial Fibrillation.
4. Suitable candidate for intra-cardiac mapping and ablation of arrhythmia.
5. Subject agrees to comply with study procedures and be available (geographically stable) for follow-up visits for at least 12 months after enrollment.
6. Subject is willing and able to provide written consent.

9.4 Exclusion Criteria

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

At time of enrollment and/or prior to procedure:

1. Continuous AF >12 months (long-standing persistent AF).
2. Paroxysmal AF with longest episode <7 days.
3. AF secondary to electrolyte imbalance, thyroid disease or reversible or non-cardiac cause.
4. Rheumatic heart disease.
5. Severe mitral regurgitation.
6. Hypertrophic cardiomyopathy.
7. LA diameter >5.5 cm.
8. Left ventricular ejection fraction (LVEF) <40%.
9. Currently NYHA Class III or IV or exhibits uncontrolled heart failure.
10. BMI >42 kg/m^2.
11. LA ablation, septal closure device or mitral valve surgical procedure at any time prior to enrollment.
12. Presence of intramural thrombus, tumor or abnormality that precludes vascular access, catheter introduction or manipulation.
13. Coagulopathy, bleeding diathesis or suspected procoagulant state.

14. Sepsis, active systemic infection or fever (>100.5°F / 38°C) within a week prior to the ablation procedure.
15. Significant restrictive or obstructive pulmonary disease or chronic respiratory condition.
16. 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.
17. 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.
18. Positive pregnancy test results for female subjects of childbearing potential or breast feeding.
19. Enrollment in a concurrent clinical study that in the judgement of the Investigator would impact study outcomes.
20. 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.
21. 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:

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

Within 3 months of enrollment:

24. Significant gastrointestinal (GI) bleed.
25. Myocardial infarction, unstable angina, cardiac surgery or coronary intervention.

Within 6 months of enrollment:

26. Coronary artery bypass graft (CABG) procedure.
27. ICD, CRT leads or pacemaker implant procedure.
28. Documented stroke, CVA, TIA or suspected neurological event.

10. Study Procedures

Prior to performing study related procedures, all sites must have Ethics Committee (EC) and associated regulatory authority approval if applicable (e.g., Competent Authority approval) as well as documentation from the Sponsor of site readiness. Site personnel training will be completed prior to participation in this clinical study. In addition, all participating site staff must be trained on their respective aspects of the study and must be delegated by the Principal Investigator to perform study related activities. Study materials will be provided to site staff after site readiness.

Sponsor personnel may provide technical support, including completion of a Sponsor Technical Support List , during the ablation procedure.

10.1 Schedule of Events

Schedule of Events is outlined in Table 8 below.

10.2 Data Collection

Clinical data is collected at designated time points throughout the study. Data will be collected using an electronic data management system for clinical studies. Data will be stored in a secure, password-protected database.

Data will be reviewed using programmed and manual data checks. Data queries will be made available to study sites for resolution. Study management reports may be generated by the sponsor (or delegate) to monitor data quality and study progress. At the end of the study, the data will be locked and retained by the sponsor. Data collection requirements are summarized in Table 8.

Table 8: Follow up and Data Collection 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 ICEG		X[C]				X[C]			
Chest CT / MRI							X[F]	X[F]	X[F]
NIH Stroke Scale	X		X		X				X
Procedural Data		X				X[A]			
Symptomatic Event Monitor Recording			X[D]	X[D]	X[D]		X[D]	X[D]	X[D]
Scheduled Event Monitoring Recording							X[E]	X[E]	X[E]
24 hr. Holter Monitor							X	X	X
Cardiac Medication Changes	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[H]	X	X	X
Device Deficiency		X				X			
AF Quality of Life Survey (AFEQT)	X							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: CHA_2DS_2-VASc score is ⩾ 2, if LA diameter ⩾4.6 cm or if pre-procedure anticoagulation requirements are not met.
D Event monitor recording if subject is experiencing symptoms during blanking period as well as outside of scheduled recordings during the effectiveness evaluation 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. A symptomatic event monitored during the effectiveness evaluation period may count toward a scheduled monthly recording.
F Only required if subject presents with symptoms associated with PV stenosis.
G ICE allowed for subjects who cannot undergo TEE.
H Adverse Events for recurrent AF are not required to be collected for Repeat Ablation Procedures.

10.3 Scheduled Follow-up Visit Windows

After receiving notice of successful ablation procedure, the Sponsor will provide the target dates and windows for each visit to the study site. Should a subject miss a visit or the visit fall outside the pre-specified window, a protocol deviation must be reported, and the original follow-up schedule maintained for subsequent visits.

Data analyses include follow-up visits, regardless of whether the visit occurs within the window, where applicable. Therefore, a late visit is preferred over a missed visit but must be accompanied by a deviation report. Follow-up visit windows are listed in Table 8 and are based on days post-ablation.

Table 9: Follow up Visit Windows:

Subject Visit Description	Timeframe / Visit Window
Enrollment and Screening Visit(s)	Within 60 days of ablation procedure
Ablation Procedure (Index)	Day 0; follow-up visit windows determined by ablation procedure completion date
Pre-Discharge	Prior to discharge from hospital following ablation procedure
7 days Follow-Up (Phone)	7 ± 3 days
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	As needed/necessary

10.4 Subject Screening

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 prior to insertion of the investigational catheter.
- Intent-to-Treat: Includes all subjects who sign ICF and attempt the study treatment.
- Modified Intent-to-Treat: Includes all subjects who sign ICF, meet eligibility criteria, and attempt the study treatment.
- Treatment-Per-Protocol: Includes all subjects who sign ICF, meet eligibility criteria, and attempt the study treatment, without any major protocol deviations.

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

10.4.1 Subject Consent

An Informed Consent Form (ICF) is used to protect the rights and welfare of subjects in a Clinical Investigation. Informed consent (IC) is defined as a legally effective documented confirmation of a subject's (or their legally authorized/designated representative or guardian, only applicable for US & Canada) voluntary agreement to participate in a particular study after information has been given and explained to the subject on all aspects of the study that are relevant to the subject's decision to participate. This process includes obtaining an Informed Consent Form (ICF), and an Authorization to Use and Disclose Personal Health Information that has been approved by the study site's EC and signed and dated by the subject (or their legally authorized/designated representative or guardian). A subject may only consent after information has been given and explained to the subject on all aspects of the Clinical Investigation that are relevant to the subject's decision to participate. IC may be given by the legally authorized/designated representative only if a subject is unable to make the decision to participate in a Clinical Investigation. In such cases, the subject shall also be informed about the Clinical Investigation within his/her ability to understand.

Prior to enrolling subjects, the IC and the Authorization to Use and Disclose Personal Health Information form must be approved by the EC. The document(s) must be controlled (i.e. versioned and/or dated) to ensure it is clear which version(s) were approved by the EC. Any adaptation of the sample IC must be reviewed and approved by the Sponsor and the EC reviewing the application prior to enrolling subjects.

The Investigator must notify the subject (or their legally-authorized/designated representative or guardian) of any significant new findings about the study that become available during the course of the study which are pertinent to the safety and well-being of the subject, as this could impact a subject's

willingness to participate in the study. If relevant, consent may be requested from subjects to confirm their continued participation.

Prior to initiation of any study-specific procedures, IC must be obtained from the subject (or their legally authorized/designated representative or guardian). Likewise, privacy or health information protection regulation may require subjects to sign additional forms to authorize study sites to submit subject information to the study sponsor. The IC process must be conducted by the Principal Investigator or an authorized designee, and the ICF and an Authorization to Use and Disclose Personal Health Information form must be given to the subject (or their legally authorized/designated representative or guardian) in a language he/she is able to read and understand. The process of IC must be conducted without using coercion or undue improper influence on or inducement of the subject to participate by the Investigator or other study site personnel. The IC process shall not waive or appear to waive subject's legal right. The language used shall be as non-technical as possible and must be understandable to the subject and the impartial witness, where applicable.

The subject must have ample time and opportunity to read and understand the ICF, to inquire about details of the study, and to decide whether or not to participate in the study. All questions about the study should be answered to the satisfaction of the subject.

When the subject decides to participate in the study, the ICF must be signed and personally dated by the subject and Investigator or authorized designee, as required by the ICF, and ensured by the Principal Investigator or his/her authorized designee.

A copy of the ICF and the Authorization to Use and Disclose Personal Health Information, signed and dated as required by law, must be provided to the subject and his/her authorized designee.

If the ICF is obtained the same day the subject begins participating in study-related procedures, it must be documented in the subject's case history that consent was obtained prior to participation in any study-related procedures. It is best practice for the IC process to be documented in the subject's case history, regardless of circumstance.

In the event the subject cannot read and/or write, witnessed (impartial witness) IC will be allowed, provided detailed documentation of the process is recorded in the subject's case history and the witness signs and dates the IC. The IC should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated consent to participate in the study.

In the event the subject or legally designated representative cannot read and/or write, the IC process shall be obtained through a supervised oral process. An independent and impartial witness must be present during this process. The IC and any other information must be read aloud to the prospective subject or his/her legally designated representative. Whenever possible, either the subject or his/her legally designated representative shall sign and personally date the informed consent form. The witness signs and personally dates the IC attesting that the information was accurately explained and that informed consent was freely given.

The template IC will be provided under separate cover. The original of the signed ICF must be filed in the hospital/clinical chart and/or with the subject's study documents.

The ICF and Authorization to Use and Disclose Personal Health Information must be available for monitoring and auditing. Any Sponsor personnel who support the study procedure must be able to review the subject's signed and dated ICF and verify its completeness prior to proceeding with the procedure. In the event the Sponsor field personnel identify IC as being incomplete, the study procedure will not be allowed to occur until the consent of the subject can be adequately and appropriately obtained.

10.5 Enrollment and Baseline

When a patient signs and dates the consent form, he/she is considered a subject enrolled in the study. A log of all subjects enrolled in the study should be maintained.

The following evaluations will be performed after consent, unless previously performed as part of routine clinical evaluations within the specified windows:

Within 6 months prior to the procedure:

- Transesophageal or transthoracic echocardiography (TEE or TTE)
  - to determine LA diameter and % LVEF

Following Consent but prior to the interventional procedure date

- Assessment of all factors specified for evaluation in Inclusion and Exclusion criteria
- Medical History
- Physical Exam
- Review cardiovascular medication history
  - Concomitant antiarrhythmic medication and anticoagulation
- Review of arrhythmia symptoms, occurrences, history
- NIH Stroke Scale
  - Administered by staff member certified to conduct assessment
- AF Quality of Life Survey (AFEQT Questionnaire version 1.0)

Within 7 days prior to the procedure

- Pregnancy Screen
  - Women of child bearing potential will be required to have documentation of a negative pregnancy test conducted within 7 days prior to the study procedure.

Within 48 hours prior to the procedure:

- TEE or ICE (for subjects who cannot undergo TEE)
  - to rule out LA thrombus in subjects that meet any one of the following criteria:
    - CHA_2DS_2-VASc score is ≥2
    - LA diameter ≥4.6 cm
    - Pre-procedure anticoagulation requirements are not met
  - 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

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 and must be withdrawn.

10.6 Procedure

The majority of procedures and assessments will be performed per routine practice at participating institutions. However, some protocol requirements may not align with a sites routine practice. The protocol required scheduled follow up cadence may not align with or be more frequent than routine practice at some participating sites.

10.6.1 Pre-Ablation Requirements

- Anti-arrhythmic drugs (AADs)
  - Discontinuation of AADs prior to the procedure is left to the discretion and practice of the Investigator and investigational site best practices.
  - Amiodarone use must be discontinued at least 7-14 days prior to the ablation procedure and not restarted after the ablation procedure.
- Anti-coagulation therapy
  - Performance of the ablation procedure on uninterrupted anti-coagulation therapy (e.g. warfarin or NOACs) is strongly recommended.
  - For subjects anticoagulated with a NOAC prior to AF catheter ablation, it is reasonable to hold one to two doses of the NOAC prior to AF ablation with re-initiation post-ablation.
- Pregnancy screen
  - 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 study procedure.
  -

10.6.2 Ablation Procedure

Pre-procedural Preparation

- Subjects that meet the eligibility and pre-ablation requirements will be prepped for the ablation procedure. The procedures will follow standard hospital practice but should, at a minimum, include the following:
  - Prep and sedate subject per institutional standard practice.
    - Method of sedation will be recorded (i.e. conscious sedation or general anesthesia).
    - Placement of an esophageal temperature probe to guide energy delivery on the posterior wall is strongly recommended.
      - 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.
- Deviation of the esophageal temperature probe is allowed if standard practice at the institution.

- Place Ensite Velocity or Precision patches on subject per IFU.
- Place commercially available dispersive indifferent electrode (DIP) patch on subject.

- Gain vascular access per lab protocol via the femoral veins and/or right or left internal jugular or subclavian veins by insertion of sheaths.
- Any commercially available 8.5F, fixed or steerable, sheath may be used.
  - A steerable sheath is recommended to be used with the DiamondTemp Ablation Catheter.
- Aspirate and flush sheaths with heparinized saline to remove air prior to introduction into the body and catheter insertion.
  - Sheaths (fixed or steerable) should be continuously infused with heparinized saline at 1-2ml/min throughout the procedure.
- Complete a single or double transseptal puncture to access the LA.
- 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.
  - ACT must be ≥250 seconds prior to first ablation and should be maintained at >300 seconds throughout the procedure.
  - ACT levels should be checked every 20-30 minutes during the ablation procedure.
  - If ACT is <300 seconds during ablation procedure, more heparin should be administered.
- Insert and place multi-electrode diagnostic catheters under fluoroscopic guidance.
  - Placement of intracardiac catheters will be per standard lab practice but must include a coronary sinus (CS) catheter and a multi-electrode catheter for PV mapping and verification of PV isolation and entrance block.
- Create a 3D anatomical map of the left atrium and location of the PVs with a multi-electrode catheter using Ensite Velocity or Precision system.
  - RF applications and location will be added to the map during the procedure per site standard practice.
- A pre-ablation EGM/12 lead ECG documenting the subject's rhythm at the beginning of the procedure will be collected.
- 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 devices must be reported on the Device Deficiency CRF. The use of a replacement (back-up) device should be indicated on the Procedure CRF.

DiamondTemp Ablation System Set-up

The DiamondTemp Ablation System 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 10.

Table 10. Recommended DiamondTemp RF Generator and Irrigation Pump Settings

RF Generator Settings	
Operational Mode	Temperature Control
Maximum Temperature Set Point	60° Celsius
Maximum Power Setting	50 Watts
Maximum Ablation Duration in one location	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 30 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 re-applied. Purge the catheter prior to re-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.

Index Ablation Procedure

The primary focus of the ablation procedure for PeAF will be to create a series of 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.

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 [10]. 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 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 of the initial PVI in each PV or PV pair to monitor for PV reconnection.
- Adenosine may be administered following PVI to detect for the presence of dormant PV conduction.
- Administration of isoproterenol to identify non-PV triggers is allowed.
- 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.
- Empiric targeting of rotors, ganglionated plexi or performing ablation on posterior wall or LA roof is allowed and will be documented.
- Spontaneously-occurring atrial arrhythmias that present during the procedure are allowed to be ablated at the Investigator's discretion. CTI-dependent (typical) Atrial Flutter is also allowed if the subject has a known history of typical Atrial Flutter.
- Investigator's may also perform a CTI line prophylactically if it is their standard practice.
- Investigators are discouraged from ablating the mitral lines unless there is a specific flutter that has to be ablated.
- 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 catheter 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:

a. Catheter lot/serial number(s) used
b. Temperature set point
c. Power set point
d. Total number of RF applications for PVI
e. Total number of RF applications for non-PVI targets

f. Total RF time during the procedure
g. Total number of ablations total
h. Total fluid infused from the ablation catheter
i. Presence of char or coagulum formation and incidence(s) of steam pops
j. Procedure and fluoroscopy times

If at any time during the ablation procedure the Investigator is unable to continue the ablation with the investigational 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 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 Anticoagulation

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 [10], 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 (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.

Post-Procedure AADs

- 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 escalate an AAD.

10.6.3 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:
  a. Vital signs (blood pressure, heart rate, respiration rate, temperature) will be obtained.
  b. Cardiovascular and pulmonary examination.
  c. Standard neurological assessment.
  d. Assessment of catheter insertion sites (both sides of the groin).
- Assess the subject for any adverse events following ablation procedure.
- Perform a 12-lead ECG.
  a. 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.
  a. Cardiac, AAD, diuretic, or anticoagulation.

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

10.7 Scheduled Follow-up Visits

10.7.1 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.

10.7.2 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.
  - Cardiovascular and pulmonary examination.
  - Standard neurological assessment.
  - Assessment of catheter insertion sites (both sides of the groin) .
- Administer a follow-up NIH Stroke Scale assessment.
- 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.

10.7.3 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). [19] Investigators may perform repeat ablation procedure in subjects with highly symptomatic or multiple early recurrences of atrial arrhythmias that cannot be controlled with antiarrhythmic therapy. [10] [20] Subjects with documented early recurrence during the blanking period are not being considered a primary effectiveness failure.

The repeat ablation procedure during the blanking period must be performed with the investigational catheter. Prior to the repeat ablation procedure, subjects must meet the pre-ablation requirements described in this protocol. Investigators must follow all procedural requirements defined in this protocol 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. Each Repeat Ablation Procedure and discharge will be documented in a CRF. Adverse Events for recurrent AF are not required to be collected for Repeat Ablation Procedures.

Commercial devices are allowed for use during a Repeat Ablation Procedure that is performed after the Blanking Period (~90 days post index ablation procedure), and will also be documented in a CRF.

10.7.4 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 for recordings made due to symptomatic episodes of arrhythmias (if applicable).
- Instruct subject to record twice-monthly 1-minute recordings as well as symptomatic events.
- Subjects will be instructed on how to use the event monitor to capture 24-hour Holter reading and the data will be transmitted remotely to the Corelab.

10.7.5 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 instructed on how to use the event monitor to capture 24-hour Holter reading and the data will be transmitted remotely to the Corelab.
- Administer a follow-up AFEQT Questionnaire (QOL).

10.7.6 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 instructed on how to use the event monitor to capture 24-hour Holter reading and the data will be transmitted remotely to the Corelab.
- Administer a follow-up QOL assessment (AFEQT Questionnaire).
- Administer a follow-up NIH Stroke Scale assessment.

10.7.7 Alternative Methods for Follow-Up Visits

Alternative methods of data collection may be necessary in the case of extenuating circumstances, such as a global pandemic, when subjects are prohibited from coming into the office for required assessments. These are listed below as “alternative processes used only during extenuating circumstances”. Data unable to be collected remotely or via an alternative method should be collected at the next possible in-person visit.

In the event a subject is unable to return for an in-office follow-up visit, the alternative methods of obtaining follow-up assessments include virtual visit and/or phone visit. The study assessments which may not be feasible to be completed via the alternative methods are listed below:

1. Virtual Visit, i.e. inclusive of video with study subject.

The following assessments may not be (fully) completed with a virtual visit:

- Physical examination (limited review per physician discretion).
- Chest CT or MRI scan to rule out PV stenosis*:
  - Make every effort to schedule in-person imaging as soon as possible.
  - When possible, the subjects could be referred to a local imaging center for assessment. Local imaging technicians would require study training and delegation prior to assessment.
- NIH Stroke Scale assessment (limited review per physician discretion).

2. Phone Visit, i.e. no video with the subject.

The following assessments may not be (fully) completed with a phone visit:

- Physical examination (limited review per physician discretion).
- Chest CT or MRI scan to rule out PV stenosis*:
  - Make every effort to schedule in-person imaging as soon as possible.
  - When possible, the subjects could be referred to a local imaging center for assessment. Local imaging technicians would require study training and delegation prior to assessment.
- NIH Stroke Scale assessment.

* 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.

10.7.8 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.

10.8 Protocol Deviations

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. The use of waivers for deviating from the Clinical Investigation Plan is prohibited, going forward the study will be executed under Medtronic procedures.
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 or Medtronic Representative becomes aware that an Investigator is not complying with the signed Investigator's Agreement, the Clinical Investigational Plan, the requirements of ISO14155:2020 or other applicable regulations, or any conditions of approval imposed by the reviewing IRB/EC Committee, the 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 the Sponsor, unless this action would jeopardize the rights, safety or welfare of a subject.

Protocol deviations will be analyzed by the 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, the Sponsor will implement appropriate corrective and preventive actions, including repeat training as deemed necessary.

10.9 Subject Exit, Withdrawal or Discontinuation

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, lost to follow-up or death, etc. 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. At the time of study exit, all adverse events with an outcome of ongoing must be reviewed by the Investigator to determine a final status of the event. Data collected up to the point of subject withdrawal may be used.

10.10 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). Subjects will be followed by standard of care after Clinical Investigation has been completed.

10.11 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. When subjects are lost to follow-up the Investigator will make efforts to confirm the vital status of the subject. If allowed per local regulations, a person identified by the subject is informed of the possibility to be contacted by the principal investigator regarding how to reach the subject and the subject's health status and a civil register may be contacted by the principal investigator to inquire about the subject's whereabouts.

11. Risks and Benefits

11.1 Potential Risks

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 Ablation System are similar to 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. A risk analysis for the DIAMOND-AF II has been performed in accordance with ISO 14971, and will ensure that the level of risk is acceptable throughout the duration of the study.

Specific risks are outlined in the system labeling and Investigator Brochure, 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.

11.2 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 any findings of risk that would be considered intolerable to the subject or user. The potential risks associated with any ablation procedure include standard surgical risks such as 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 system allows for the measurement of tissue interface 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.

Risks associated with the DIAMOND-AF II 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 the Sponsor with data and information as required by this protocol.

Additionally, extensive in vitro bench and in vivo animal studies have been successfully performed with the DiamondTemp Ablation System. Design verification and validation testing has been completed. Lot release testing is performed for all components of the system. 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, the Sponsor has determined that the benefits of the system 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.

11.3 Potential 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 persistent Atrial Fibrillation.

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 Ablation 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 and c) utilize a low irrigation flow rate for all power output up to 50 Watts.

11.4 Risk-Benefit Rationale

The Risk-Benefit Rationale is provided within the current Investigator Brochure, and all subsequent versions.

12. Adverse Events and Device Deficiencies

12.1 Adverse Events

For the purposes of the study, all Adverse Events (AEs) will be collected starting at the time of signing the Informed Consent Form through the duration of the subject's participation in the study. This includes 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.

12.2 Device Deficiency

Device deficiency (DD) information will be collected throughout the study and reported to the Sponsor, as per Table 13.

Device deficiencies related to the investigational ablation system 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 DD is associated with an AE that specific event would be recorded as an AE. Refer to table 13 for Device Deficiency Reporting requirements.

Note: Any Device Deficiency that might have led to a SADE 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 the Sponsor.

12.3 Definitions/Classifications

Where the definition indicates "device", it refers to any device used in the study. This might be any component of the system under investigation, or any market released component or accessory of the system. Adverse Events (AE) will be classified according to the definitions below.

Table 11: Adverse Event and Device Deficiency Definitions

Term	Definition
Adverse Event (AE)	Untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved. NOTE 3: For users or other persons, this definition is restricted to events related to the of investigational medical devices or comparators. (ISO14155:2020, 3.2)
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device. NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. NOTE 3: This includes 'comparator' if the comparator is a medical device. (ISO14155:2020, 3.1)
Device Deficiency (DD)	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance. NOTE 1: Device deficiencies include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. NOTE2: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO14155:2020, 3.19)

Relatedness	
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.
Seriousness	
Serious Adverse Event (SAE)	<u>Adverse event that led to any of the following:</u> a) death, b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic disease, or 3) in-patient or prolonged hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment. NOTE 1: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a SAE. (ISO14155:2020, 3.45)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO14155:2020, 3.44)

Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety 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 a nature, severity, or degree of incidence in the Clinical Investigational Plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. NOTE 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in risk assessment. (ISO14155:2020, 3.51)
Serious Health Threat	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. NOTE 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals. (ISO14155:2020, 3.46)

12.4 Reporting of Adverse Events

Reporting of AEs to the Sponsor will occur on an AE CRF, including AE description, AE start date, seriousness, treatment, relatedness to the device and procedure and AE outcome. Each AE must be recorded on a separate AE CRF.

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/AT/AFL or prolonged hospitalization following procedure to adjust anticoagulation regimen or to administer diuretic medication are not considered AEs for this study. Adverse Events for recurrent AF are not required to be collected for Repeat Ablation Procedures.

For any changes in status of a previously reported adverse event (i.e. change in treatment, outcome, relatedness), an update to the original AE must be provided. All AEs must be followed until the AE has resolved, the subject exits the study or until study closure, whichever occurs first.

In the event that a subject is exited from the study prior to study closure, all efforts should be made to continue following the subject until all "ongoing" procedure or device related AEs are resolved. At the time of study exit, all AEs with an outcome of "ongoing" must be reviewed and updates provided as applicable.

Upon Sponsor receipt of an AE, a Sponsor representative will review the AE for completeness and accuracy and when necessary will request clarification and/or additional information from the Investigator. The Sponsor will utilize MedDRA, the Medical Dictionary for Regulatory Activities, to assign a MedDRA term for each AE based on the information provided by the Investigator.

For emergency contact regarding a UADE, USADE, SAE and/or SADE, contact a study representative immediately (refer to the study contact list provided in the study site's study documents binder/Investigator site file or refer to the Sponsor contact information provided on the title page).

Adverse Events will be classified according to the standard definitions in Table 13 and the responsibilities outlined below in Table 12:

Table 12: Adverse Event Classification Responsibilities

What is classified?	Who classifies?	Classification Parameters
Relatedness	Investigator	Procedure related; device related
	Sponsor	Procedure related; device related
Seriousness	Investigator	SAE, Device Deficiency with SADE potential
	Sponsor	SAE, UADE/USADE, Device Deficiency with SADE potential
Diagnosis	Investigator	Based on presenting signs and symptoms and other supporting data
	Sponsor	MedDRA term assigned based on the data provided by Investigator
Cause of Death	Investigator	Cardiac, Non-Cardiac, Unknown

12.4.1 Adverse Event and Device Deficiency Reporting Requirements

Regulatory reporting of AEs and DDs will be completed according to local regulatory requirements. Refer to Table 13 for a list of required Investigator and Sponsor reporting requirements and timeframes. It is the responsibility of both to abide by any additional AE reporting requirements stipulated by the IRB/EC responsible for oversight of the study.

For AEs that require immediate reporting, initial reporting may be done by contacting the study sponsor per the sponsor contact information provided in this document.

Table 13: Adverse Event Reporting Timelines to Sponsor

Event Classification	Reporting Timeline to Sponsor
Adverse Event (AE)	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. AE's will be reported to IRB/EC or FDA/CA per local/regional regulations.
Adverse Device Effect (ADE)	Study staff must complete an AE CRF within 2 business days after the event for each subject through the duration of the study. ADE's will be reported to IRB/EC or FDA/CA per local/regional regulations.
Serious Adverse Event (SAE)	Study staff must complete an AE CRF within 2 business days after becoming aware of a 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 will be reported to IRB/EC or FDA/CA per local/regional regulations.
Serious Adverse Device Effect (SADE)	Study staff must complete an AE CRF within 2 business days after becoming aware of an SADE for each subject through the duration of the study. SADE's will be reported to IRB/EC or FDA/CA per local/regional regulations.
Device Deficiencies (DD)	Study staff must complete a DD CRF within 2 business days after becoming aware of a DD for each subject through the duration of the study. DD's will be reported to IRB/EC or FDA/CA per local/regional regulations.
Unanticipated Adverse Device Effect and Unanticipated Serious Adverse Device Effect (UADE)/(USADE)	Study staff must complete an AE CRF within 1 business day of becoming aware of the event and report to IRB/EC or FDA/CA per local/regional regulations. UADE or USADE's will be reported 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. The PI is responsible for informing the IRB/EC, and regulatory authorities of UADE(s) and SAE(s) as required by local/regional regulations.

12.5 Subject Death

All subject deaths must be reported by the Investigator to the Sponsor on a Death CRF and an AE CRF (AE with outcome of death) as soon as possible after the Investigator first learns of the death. In case of death, there should be only one AE with the outcome of death. Local laws and procedures must be followed where applicable.

In summary, the following data will be collected:

- Death CRF
- Corresponding Adverse Event CRF
- Date of death
- Detailed description of death
- Cause of death

- Relatedness to device and procedure
- In addition, the following source may be collected:
  - Death summary/hospital records (if available and allowed by state/local law)
  - Autopsy report (if available and allowed by state/local law)
  - Death certificate (if available and allowed by state/local law)

12.6 Product Complaint Reporting

In geographies where devices are market-released, product complaint reporting is applicable. This includes when an AE is related to a market-released device during the study. The reporting of product complaints is not part of the clinical study and should be done in addition to the Adverse Event and Device Deficiency reporting requirements. Refer to local regulations for reporting requirements.
Product Complaint: Any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a medical device that has been placed on the market.

It is the responsibility of the Investigator to report all product complaint(s) associated with a medical device distributed by the Sponsor, regardless whether they are related to intended use, misuse or abuse of the product. Reporting must be done immediately and via the regular channels for market-released products.

The reporting of product complaints by the clinical team must be done according to the local Standard Operating Procedures. The Sponsor will notify the regulatory authorities (e.g. FDA) as applicable for the following incidents immediately upon learning of them:

- Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or instructions for use which led or might have led to the death or serious deterioration in the state of health of a patient, user, or other person.
- Any technical or medical reason resulting in withdrawal of a device from the market by the manufacturer.
- A serious deterioration in the state of heath includes:
  - Life-threatening illness or injury.
  - Permanent impairment of a body function or permanent damage to a body structure.
  - A condition necessitating medical or surgical intervention to prevent permanent impairment of a body function or permanent damage to a body structure.

13. Data Review Committees

13.1 Data Safety Monitoring Board

The purpose of the Data Safety Monitoring Board (DSMB) is to conduct 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 the Sponsor and they will not be a participating DIAMOND-AF II Investigator.

The DSMB will be responsible to communicate any safety concerns, scientific concerns or other perceived concerns to the Sponsor 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 suggested changes for the conduct of the trial. The Sponsor 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.

13.2 Clinical Events Committee

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

13.3 CRO/Core Lab(s)

A designated contract research organization (CRO) 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 24 hour Holter monitors.

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 blanking period to the 12-month follow up visit. Recordings made due to symptomatic episodes during the effectiveness evaluation period may count towards the scheduled, required monthly recordings.

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 arrhythmia recurrence. 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 Lab's 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.

Subjects will be provided instructions on how to collect a 24 hour Holter reading with the event monitor provided for event monitoring during the 3, 6 and 12 months post-ablation procedure follow-up visit windows.

The Core Lab will 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. Statistical Design and Methods

Before database lock, a Statistical Analysis Plan (SAP) will be prepared to provide full details of all planned analyses. The analyses presented here represent an outline of the intended methodology. Any change to the data analysis methods described in the Clinical Investigation Plan will require an amendment only if it changes a principal feature of the CIP. Any other change to the data analysis methods described in the CIP, and the justification for making the change, will be described in the clinical study report.

14.1 Analysis Populations

Three analysis populations are defined in this study:

- The Intent-to-Treat (ITT) population will be comprised of all subjects who sign ICF and attempt study treatment (i.e. catheter inserted into vasculature).
- The modified ITT (mITT) population will be a subset of the ITT population and comprised of all ITT subjects who meet eligibility criteria.
- The Per-Protocol population will be a subset of the mITT population and comprised of all mITT subjects who do not have any major protocol violations (i.e. eligibility criteria violations, or ablation treatment with a non-study catheter for the index procedure or during blanking period).

14.2 General Aspects of Analysis

The DIAMOND-AF II study will be considered successful when both the primary safety objective and the primary effectiveness objective are met. For each objective, the sample size ensures a power of at least 80% for a one-sided hypothesis test with alpha level of 0.025.

The main analysis of the study objectives will be based on the modified Intent-to-Treat (mITT) population, which includes all subjects who sign informed consent, meet eligibility criteria, and attempt study treatment (i.e. catheter inserted into vasculature). Additionally, sensitivity analyses for the primary objectives will be conducted on the Per-Protocol population, which includes all mITT subjects who do not have any major protocol violations (i.e., eligibility criteria violations, or ablation treatment with a non-study catheter), and the ITT population, which includes all subjects who sign informed consent and attempt study treatment.

The main analysis will include data from all contributing geographies. A poolability analysis will be performed by stratifying analysis of the primary objectives by geographical region and reporting results separately for each region. Similarly, poolability by age and gender will be assessed.

The subjects' baseline characteristics will be summarized for the mITT population with standard descriptive summary statistics, including counts and percentages for categorical variables, and mean, standard deviation, median, quartiles and range for continuous variables. Ordinal variables may be analyzed as if they were continuously scaled. Treatment characteristics and safety data will be summarized for the mITT population.

For the ITT population, subject disposition will be illustrated in a study flow diagram, and subject attrition will be identified and summarized. Subject visits will be tabulated and compliance to visit schedule will be summarized for the mITT population.

For each of the objectives the available data will be summarized. The main analysis of the study objectives will be based on available data and missing data will not be imputed. For the primary safety and effectiveness objectives, a tipping point analysis will be performed to assess the potential impact of missing data.

14.3 Analysis Execution

A final clinical study report for the DIAMOND-AF II study will be prepared once all data collection has ended and all subjects have completed the 12-month follow-up visit or have been exited. The final clinical study report will be written within six (6) months of the database closure at the end of the study. Analyses will include all primary, secondary, and ancillary objectives. The final report will be signed by the global coordinating Investigator and provided to all study Investigators.

14.4 Primary Objective(s)

14.4.1 Primary Safety Objective

Primary Safety Objective

To demonstrate that the primary safety event rate associated with the Diamond-Temp ablation system is lower than the pre-specified Objective Performance Criterion (OPC).

Hypothesis

H_0: $P \geqslant P_0$

H_1: $P < P_0$

where P_0 = 11.5% (Safety OPC), and lower event rates are better.

Endpoint definition and derivation

The primary safety endpoint is defined as freedom from a composite of serious adverse events (SAEs) occurring within 7 days, procedure and/or device-related significant pericardial effusion that occurs within 30 days, and severe or clinically symptomatic pulmonary vein stenosis and atrioesophageal fistula 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
- Significant Pericardial Effusion
- Stroke / CVA
- Thromboembolism
- Transient ischemic attack (TIA)
- Vagal nerve injury
- Vascular access complications

Performance Requirements

The null hypothesis will be rejected if the one-sided 97.5% upper confidence bound is lower than 11.5%.

Rationale for Performance Criteria

This performance goal was derived from a point estimate of 7% and a margin of indifference of 4.5%. This point estimate value was determined from a review of the FDA publicly available information combined with the published literature for all FDA approved medical device trials for Atrial Fibrillation treatment[1] and some other studies[2] on ablation treatment for Atrial Fibrillation. Based on the Sponsor's best estimations, the overall rates of SAEs reported in these studies ranged from 4.9% to 14.6%, while most IDE approved randomized trials were designed to allow for 8% to 10% non-inferiority margins.

Analysis Methods

The primary safety event rate will be analyzed using the Kaplan-Meier method. The components of the SAE composite endpoint will also be summarized to show the number and percentage of subjects meeting each component.

Determination of Subjects/Data for Analysis

The main analysis of the primary safety objective will be based on the mITT population, which includes all subjects who sign informed consent, meet eligibility criteria and attempt study treatment (i.e. catheter inserted into vasculature). Additionally, sensitivity analysis for the primary safety objective will be conducted on the Per-Protocol population, which includes all mITT subjects who do not have any major protocol violations (i.e., eligibility criteria violations, or ablation treatment with a non-study catheter), and the ITT population, which includes all subjects who sign informed consent and attempt study treatment.

[1] Reddy, et al. "Results of the TOCCASTAR Study," Circulation. Aug. 10, 2015. DOI 10.1161 CirculationAHA 114.014092
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[2] Squara, et al. Europace (2015) 17, 718-724.
Kuck, Karl-Heinz, et al. NEJM 374;23, June 9, 2016, 2235-2245.
Chen, Yi-He et al. Europace (2017) 19, 784-794

14.4.2 Primary Effectiveness Objective

Primary Effectiveness Objective

To demonstrate that the primary effectiveness rate associated with the Diamond-Temp ablation system is higher than the pre-specified Objective Performance Criterion (OPC).

Hypothesis

H_0: $P \leqslant P_0$

H_1: $P > P_0$

where P_0 = 40% (Effectiveness OPC), and higher effectiveness rates are better.

Endpoint definition and derivation

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 $\geqslant$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 previously failed anti-arrhythmic drug (AAD) at a dose greater than the highest ineffective dose for AF 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.*

Performance Requirements

The null hypothesis will be rejected if the one-sided 97.5% lower confidence bound is greater than 40%.

Rationale for Performance Criteria

The performance goal was derived based on the minimum 12-month success rate for persistent AF recommended in the 2017 HRS Expert Consensus Statement on Catheter and Surgical Ablation of AF.

Analysis Methods

The primary effectiveness rate will be analyzed using the Kaplan-Meier method. The components of the effectiveness composite endpoint will also be summarized to show the number and percentage of subjects meeting each component.

Determination of Subjects/Data for Analysis

The main analysis of the primary effectiveness objective will be based on the mITT population, which includes all subjects who sign informed consent, meet eligibility criteria and attempt study treatment (i.e. catheter inserted into vasculature). Additionally, sensitivity analysis for the primary effectiveness objective will be conducted on the Per-Protocol population, which includes all mITT subjects who do not have any major protocol violations (i.e., eligibility criteria violations, or ablation treatment with a non-study catheter), and the ITT population, which includes all subjects who sign informed consent and attempt study treatment.

14.5 Secondary Objective(s)

The secondary objectives will further characterize the performance of the DiamondTemp Ablation System. All secondary endpoints will be analyzed using descriptive statistics.

14.5.1 Secondary Objective #1

Objective

To estimate the freedom from a composite of SAE occurring within 30-days post-index ablation procedure as adjudicated by an independent CEC for relatedness to the procedure or device.

Endpoint Definition and derivation

The SAE composite endpoint is comprised of the same types of events as defined for the primary safety endpoint but occurring within 30 days post index ablation.

Analysis Methods

This secondary endpoint will be analyzed using the Kaplan-Meier method. The components of the SAE composite endpoint will also be summarized to show the number and percentage of subjects meeting each component.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

14.5.2 Secondary Objective #2

Objective

To estimate the freedom from documented AF/AFL/AT episodes during the effectiveness evaluation period lasting ⩾30 seconds in duration by ECG monitoring.

Endpoint Definition and derivation

A subject is considered a failure for this endpoint if he/she has any documented AF/AFL/AT episode ⩾ 30 seconds by ECG monitoring during the effectiveness evaluation period.

Analysis Methods

This secondary endpoint will be analyzed using the Kaplan-Meier method.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

14.5.3 Secondary Objective #3

Objective

To estimate the freedom from documented AF/AFL/AT episodes during the effectiveness evaluation period in the absence of class I and III anti-arrhythmic drug therapy.

Endpoint Definition and derivation

A subject is considered a failure for this endpoint if he/she has any documented AF/AFL/AT episode and/or uses any class I/III AAD during the effectiveness evaluation period.

Analysis Methods

This secondary endpoint will be analyzed using the Kaplan-Meier method.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

14.5.4 Secondary Objective #4

Objective

To estimate the rate of acute procedural success.

Endpoint Definition and derivation

An acute procedural success is defined as confirmation of electrical isolation of PVs at least 20 minutes following the last ablation around the respective PV.

Analysis Methods

This secondary endpoint will be analyzed using the Binomial method.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis. The analysis will be based on index ablation procedures only.

14.5.5 Secondary Objective #5

Objective

To estimate the rate of single procedure success with freedom from AF/AFL/AT recurrence.

Endpoint Definition and derivation

A subject is considered a single procedure success if he/she is treated with one single ablation procedure during study participation and free from documented AF/AFL/AT episode at 12 months post index ablation.

Analysis Methods

This secondary endpoint will be analyzed using the Kaplan-Meier method.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

14.5.6 Secondary Objective #6

Objective

To estimate the rate of single procedure success with freedom from all primary effectiveness failure criteria.

Endpoint Definition and derivation

A subject is considered a single procedure success if he/she is treated with one single ablation procedure during study participation and free from all primary effectiveness failure criteria at 12 months post index ablation.

Analysis Methods

This secondary endpoint will be analyzed using the Kaplan-Meier method.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

14.5.7 Secondary Objective #7

Objective

To evaluate changes in QOL using the AFEQT Questionnaire.

Endpoint Definition and derivation

Subject's QOL is measured using the AFEQT Questionnaire at baseline, 6-month visit and 12-month visit. The QOL change from baseline to 6 months, as well as change from baseline to 12 months will be calculated for each subject.

Analysis Methods

This secondary endpoint will be analyzed using descriptive statistics.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

14.5.8 Secondary Objective #8

Objective

To evaluate neurological changes measured using the NIH stroke scale.

Endpoint Definition and derivation

Subject's neurological function is measured using the NIH stroke scale at baseline, pre-discharge visit and 12-month visit. The neurological change from baseline to pre-discharge, as well as change from baseline to 12 months will be calculated for each subject.

Analysis Methods

This secondary endpoint will be analyzed using descriptive statistics.

Determination of Subjects/Data for Analysis
All subjects in the mITT population will be included in the analysis.

14.6 Ancillary Objective(s)

The ancillary endpoints will further characterize the performance of the DiamondTemp Ablation System. All ancillary endpoints will be analyzed using descriptive statistics.

14.6.1 Ancillary Objective #1

Objective
To characterize procedural characteristics.

Endpoint Definition and derivation
The following procedure characteristics will be summarized for all index ablation procedures:

- Total procedure time (minutes), defined as time of investigational catheter insertion into the vasculature to time of last ablation catheter removal.
- Total treatment device time (minutes), defined as time of delivery of first RF ablation with the investigational catheter to removal of the catheter.
- Mean cumulative RF Time (minutes).
- Mean duration of RF ablations (seconds).
- Total fluid infused through the investigational catheter (mL).
- Total fluoroscopy time (minutes).

Analysis Methods
This ancillary endpoint will be analyzed using descriptive statistics.

Determination of Subjects/Data for Analysis
All subjects in the mITT population will be included in the analysis. The analysis will be based on index ablation procedures only.

14.6.2 Ancillary Objective #2

Objective
To characterize the number of re-hospitalizations due to Atrial Fibrillation recurrence during the effectiveness evaluation period.

Endpoint Definition and derivation
The number of re-hospitalizations due to Atrial Fibrillation recurrence during the effectiveness evaluation period will be calculated for each subject.

Analysis Methods
This ancillary endpoint will be analyzed using descriptive statistics.

Determination of Subjects/Data for Analysis

All subjects in the mITT population will be included in the analysis.

14.7 Sample Size Determination

For the primary safety objective, a sample size of 269 achieves 81% power to detect a difference of at least -4.5% against an OPC of 11.5% using a one-sided alpha level of 0.025.

For the primary effectiveness objective, a sample size of 274 yields 86% power to detect a difference of 9% against an OPC of 40% using a one-sided alpha level of 0.025.

Assuming a drop-out rate of 12%, as well as accounting for eligibility/screen failures, the enrollment goal of up to 376 subjects should be sufficient.

14.8 Minimization of Bias

Investigational site selection, subject selection, subject treatment, and evaluation of study data are potential sources of bias. Methods incorporated in the study design to minimize potential bias include (but are not limited to):

- Subjects will undergo a rigorous screening to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to enrollment.
- Demographics and medical history will be collected at baseline in order to later assess possible characteristics that may influence study endpoints.
- Investigators and investigational sites will undergo site evaluation or qualification process based on pre-determined criteria prior to being invited to participate in the study.
- All investigational site personnel and sponsor/delegate personnel will be trained on their respective aspects of the study using standardized training materials.
- All study clinicians will be trained on and required to follow the Clinical Investigation Plan.
- Monitoring visits will be conducted to verify case report forms (CRF) against source data and adherence to the Clinical Investigation Plan.
- An independent Clinical Events Committee will be utilized to regularly review and adjudicate reported adverse events and deaths.
- A Core Laboratory will be used to characterize atrial arrhythmia data obtained by Holter monitor and ECG.

15. Ethics

15.1 Statement(s) of Compliance

This study will be conducted in compliance with international ethical and scientific quality standards, known as GCP. GCP includes review and approval by an independent EC before initiating a study, continuing review of an ongoing study by an EC, and obtaining and documenting the freely given informed consent of a subject before initiating the study.

The DIAMOND- AF II study was designed to reflect the GCP principles outlined in ISO14155:2020 and other international clinical requirements outlined below. These include the protection of the rights, safety and well-being of human subjects, controls to ensure the scientific conduct and credibility of the

Clinical Investigation and the definition of responsibilities of the sponsor and Investigators. In accordance with ISO14155:2020, the sponsor shall avoid improper influence on, or inducement of, the subject, monitor, any Investigator(s) or other parties participating in, or contributing to, the Clinical Investigation. All Investigators shall avoid improper influence on or inducement of the subject, sponsor, monitor, other Investigator(s) or other parties participating in or contributing to the Clinical Investigation. AE and DD handling in the DIAMOND-AF II study is ISO14155:2020 compliant for all participating geographies. The study will comply with ISO 14155:2020 upon site activation on CIP version H, with noted exceptions outlined throughout the CIP and applicable study documents.

The principles of the Declaration of Helsinki (DoH) have been implemented through the IC process, EC approval, study training, clinical trial registration, pre-clinical testing, risk-benefit assessment and publication policy.
Ultimately, all study sites in all geographies will follow and comply with:

- Principles of DoH
- 21 CFR Part 11 (Electronic Records, Electronic Signatures)
- 21 CFR Part 54 (Financial Disclosure by Clinical Investigators)
- The CTA
- The procedures described within this Clinical Investigational Plan
- Local EC Requirements

In addition to the regulatory requirements outlined above, the study will be conducted according to federal, national and local laws, regulations, standards, and requirements of the countries/geographies where the study is being conducted. These include but are not limited to:

- In the United States, the study will be conducted under an FDA IDE in compliance with 21 CFR Parts:
  - 50: Protection of Human Subjects
  - 54: Financial Disclosure by Clinical Investigators
  - 56: IRBs
  - 812: IDEs
  - ISO14155:2020 exception for US; all activation related requirements will be conducted/collected in separate parts with exception of a formal SIV/visit report
- In Canada, SOR/98-282, Section 59-88 will be followed and Mandatory Problem Reporting 59(1), 59(2), 60 (1).
- In Europe the study will be conducted in compliance with the AIMDD 90/385/EEC or MDD 93/42/EEC> EU MDR, and DoH version 2013.

The study will be publicly registered prior to in accordance with the 2007 FDAAA and DoH on http://clinicaltrials.gov (PL 110-85, section 810(a)). In addition, the study may be registered in local regulatory databases where required by local law.

Approval of the Clinical Investigational Plan (CIP) and CIP amendments is required from the following groups prior to any study procedures at a study site:

- The Sponsor
- Principal Investigators (where required by local law/regulations)
- Geography-specific regulatory authorities (if regulatory approval is required)

- An independent medical EC or IRB.

Similarly, approval of subsequent revisions to the CIP is required at each study site from the above mentioned groups prior to implementation of the revised CIP at the study site.

16. Study Administration

16.1 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.

16.1.1 Study Monitor

Study monitors assigned to the DIAMOND-AF II 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.

16.1.2 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 Clinical 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 source data per the Study Monitoring Plan 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 Clinical 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 monitor is required to bring this to the attention of the Sponsors' Study 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.

16.2 Data Management

Data will be collected using an electronic data management system for studies. CRF data will be stored in a secure, password-protected database which will be backed up. Data will be reviewed using programmed and manual data checks. Study management reports may be generated to monitor data quality and study progress. At the end of the study, the data will be frozen and will be retained indefinitely by the Sponsor.

Procedures in the Clinical Investigational Plan (CIP) require source documentation. Source documentation will be maintained at the study site. Source documents, which may include but is not limited to, worksheets, subject medical records, and interrogation files, and must be created and maintained by the investigational study site team.

Data management is performed by ARA Data Manager on an ongoing basis as data is entered by the Site and is marked as monitored. Since data will be entered and edited only by the Sites, no Self-Evident Corrections will be performed by ARA. If misspelled items are found during review, the Monitor for the Site will be notified. ARA will conduct ongoing review of query output and resolutions and provide feedback to the Sponsor as appropriate. During data review, ARA will discuss potential data issues with the Sponsor and/or a Monitor as needed to determine if data queries are warranted. Data queries entered by the Monitor are the responsibility of the Monitor to close or re-query as necessary. Those data queries entered by ARA Data Manager are generally the responsibility of ARA Data Manager to close or re-query as necessary; however, the Monitor can close an ARA Data Manager query when source data verification is required. If any query comments or responses require DM input, DM may also close those queries. Verification, validation and securing of electronic clinical data systems is the responsibility of the ARA Data Manager.

The Principal Investigator for each Site will be asked to electronically sign the eCRFs for each subject after the subject completes the study and the subject's data has been monitored, reviewed and reconciled, and there are no outstanding queries. Once signatures are complete, all forms will be locked, and all users will be changed to read-only, therefore removing the ability of the Site to change data and respond to queries. Once all the database lock activities are completed, the Sponsor will give approval to lock the database. The data reported on the eCRFs shall be derived from source documents and be consistent with these source documents, and any discrepancies shall be explained in writing.

The Investigator will clearly mark clinical records to indicate that the subject is enrolled in this Clinical Investigation. All records and other information about subjects participating in this study will be treated as confidential.

Data is transferred and processed in compliance with HIPPA in the US and in compliance with the European privacy legislation, as required by the General Data Protection Regulation (GDPR).

16.3 Direct Access to Source Data/Documents

The Sponsor may conduct audits at participating study sites. The purpose of an audit is to verify the performance of the monitoring process and the study conduct, independently of the personnel directly involved in the study. RAs, such as the FDA, may also perform inspections at participating study sites. The Investigator and/or institution shall permit the Sponsor, IRB/ECs and RAs direct access to source data and documents during monitoring, audits and regulatory inspections.

16.4 Confidentiality

All information and data sent to parties involved in study conduct concerning subjects or their participation in this study will be considered confidential. Study sites will assign a unique SID to each subject. Records of the subject/SID relationship will be maintained by the study site. The SID number is to be recorded on all study documents to link them to the subject's medical records at the study site. Confidentiality of data will be observed by all parties involved at all times throughout the Clinical Investigation. All data shall be secured against unauthorized access. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data. In the US, "Protected Health Information" (PHI) will be maintained in compliance with HIPAA. To maintain confidentiality, the subject's name or any other PHI should not be recorded on any study document other than the Informed Consent Form. This scenario will be covered in the Informed Consent. In the event a subject's name/PHI is included for any reason, it will be redacted as applicable. In the event of inability to redact the identification (e.g., digital media), it will be handled in a confidential manner by the authorized personnel. Data relating to the study might be made available to third parties (for example in case of an audit performed by RA), provided the data are treated as confidential and that the subject's privacy is guaranteed. No identifiable subject information will be published.

16.5 Liability/Warranty/Insurance Information

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

The Sponsor maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a clinical study insurance statement/certificate will be provided to the EC.

16.5.1 Insurance (Canada)

Medtronic Canada ULC of Canada Ltd. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate general liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific

insurance coverage. If required, a General Liability insurance statement/certificate will be provided to the IRB/EC.

16.5.2 Insurance (Europe, Middle East, Africa)

Medtronic Bakken Research Site B.V. is a wholly owned subsidiary of Medtronic, which as the parent company of such entity maintains appropriate clinical study liability insurance coverage as required under applicable laws and regulations and will comply with applicable local law and custom concerning specific insurance coverage. If required, a Clinical Trial insurance statement/certificate will be provided to the IRB/EC.

16.6 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.

16.7 CIP 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 Clinical Investigational Plan (CIP). Amendments to the Clinical Investigational Plan may be initiated by the Sponsor or at the request of an Investigator. A formal amendment cannot be initiated by an Investigator or clinical site staff without the approval of the Sponsor.

Protocol amendments must be submitted and subsequently approved by the site IRB/EC and Geography-specific regulatory authorities (if regulatory approval is required).

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

16.8 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. The 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.

The Sponsor will retain the study records according to the Sponsor's corporate policy and record retention schedule. The Sponsor's records and reports will be maintained in a password-protected document management system, and paper documents (where applicable) will be stored in secured file cabinets during the course of this study. After closure of the study, the Sponsor will archive records and reports per the Sponsor's standards and applicable regulations.

16.8.1 Investigator Records

The Investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the Investigator) or Subject Study Binder. CRFs must be maintained and signed electronically within the electronic data capture system during the study. The following records are subject to inspection and must be retained for a period of two years (or longer as local law or hospital administration requires) after product approval or the date on which the investigation is terminated, or the date that the records are no longer required for purposes of supporting a pre-market approval application.

- All correspondence between the IRB/EC, sponsor, monitor, Regulatory Agencies and the Investigator that pertains to the investigation, including required reports.
- Subject's case history records, including:
  - Signed and dated Informed Consent Form (In U.S. and Canada, signed by subject. In Europe, Middle East, Africa, signed by subject and Investigator).
  - Observations of AEs/ADEs/DDs
  - Medical history
  - Procedure and follow-up data
  - Documentation of the dates and rationale for any deviation from the protocol
- Financial disclosure
- Subject screening log& ID log.
- Normal value(s)/range(s) for clinical laboratory test (if applicable).
- Device Disposition Logs containing Model and serial numbers of devices delivered to the study site, subject IDs of the subjects with ablation, received dates of devices, used dates, , returned-to-sponsor dates and reasons, initials of all persons who received, used or disposed each device, and method of disposal/destruction.
- All approved versions of the CIP, IC, and IBs/Report of Prior Investigation Summary
- Signed and dated Clinical Trial Agreement (CTA).
- Curriculum Vitae (CV) of Principal Investigators and key members of investigation study site team (as required by applicable regulations.
- Documentation of delegated tasks.
- IRB/EC approval documentation. Written information that the Investigator or other study staff, when member of the IRB/EC, did not participate in the approval process. Approval documentation must include the IRB/ECs composition, where required per local law.
- RA notification, correspondence and approval, where required per local law.
- Study training records for study site staff.
- Insurance certificates (Europe, Middle East, Africa, India, Australia, New Zealand, Greater China, Latin America and only).
- Any other records that FDA and local regulatory agencies require to be maintained.
- Final Study Report including the statistical analysis.

16.8.2 Subject Source Documents

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:

1. Name and contact information.
2. The study title (DIAMOND-AF II study), study number, and sponsor name (Medtronic/Epix Therapeutics).
3. 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.
4. The subject was allowed adequate time to consider participation prior to signing the consent form.
5. A statement that written informed consent was obtained.
6. Date of enrollment into the clinical study and the subject ID number.
7. Date of procedure, procedural type, and device lot number.
8. Visit dates.
9. Cardiac medications.
10. Occurrence of any adverse events.
11. 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 type and location of source documents should be documented. The Investigator who signs Investigator Statement 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.

17. Reporting Requirements

17.1 Investigator Reports

The Investigator is responsible for the preparation (review and signature) and submission to the sponsor of all case report forms, adverse events and adverse device effects (reported per the country-specific collection requirements), device deficiencies, deaths, and any deviations from the Clinical Investigation Plan. If any action is taken by an IRB/EC with respect to this study, copies of all pertinent documentation must be forwarded to the Sponsor in a timely manner. Reports are subject to inspection and to the retention requirements as described above for Investigator records.

Safety data Investigator reporting requirements are listed in Section 12.4. The Investigator shall prepare and submit in a complete, accurate and timely manner the reports listed in this section.

Table 14: Investigator reports applicable for all geographies per Sponsor requirements

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC Approval	Sponsor and Relevant Authorities	The Investigator must report a withdrawal of approval by the reviewing IRB/EC of the Investigator's part of the investigation within 5 working days.
Study Deviations	Sponsor and IRB/EC	Any deviation from the Clinical Investigational Plan shall be recorded together with the explanation of the deviation. Notice of deviations from the CIP to protect the life or physical well-being of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations.
Final Report	IRBs/ECs and Relevant Authorities	This report must be submitted per local requirements.

Table 15: Additional Investigator reports applicable to the United States per FDA regulations

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC Approval (either suspension or termination)	Sponsor	The Investigator must report a withdrawal of approval by the reviewing IRB/EC of the Investigator's part of the investigation within 5 working days. (21 CFR 812.150(a)(2))
Progress Report	Sponsor and IRB/EC	The Investigator must submit this report to the sponsor and IRB/EC at regular intervals, but in no event less than yearly intervals. (21 CFR 812.150 (a)(3)).
Study Deviations	Sponsor and IRB/EC	Notice of deviations from the CIP to protect the life or physical wellbeing of a subject in an emergency shall be given as soon as possible, but no later than 5 working days after the emergency occurred. Except in such emergency, prior approval is required for changes in the plan or deviations. If the deviation may affect the scientific soundness of the plan or the rights, safety and welfare of the subjects, the deviation must be approved by the Sponsor, the IRB/EC, and the FDA/applicable RA. If the deviation does not affect these issues then only the Sponsor must approve it. (21 CFR 812.150(a)(4))
Failure to Obtain IC Prior to Investigational Device Use	Sponsor and IRBs/ECs	If an Investigator uses a device without obtaining IC, the Investigator shall report such use within 5 working days after device use. (21 CFR 812.150(a)(5))
Final Report	Sponsor IRBs/ECs Relevant Authorities	This report must be submitted within 6 months of study completion or termination of the investigation or completion or termination of the Investigator's part of the investigation. (21 CFR 812.150(a)(6))
Other	IRB/EC and FDA	An Investigator shall, upon request by a reviewing IRB/EC, FDA or any other RA, provide accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(a)(7))

Table 16: Investigator reports applicable to Europe, Middle East and Africa per ISO14155:2020

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC Approval	Sponsor	Report if required by local law.
Progress Report	Sponsor and IRB/EC	Provide if required by local law or IRB/EC.
Study Deviations	Sponsor, Competent Authority and IRB/EC	Any deviation from the CIP shall be recorded together with an explanation for the deviation. Deviations shall be reported to the sponsor who is responsible for analyzing them and assessing their significance. Note: When relevant, ethics committees, CAs or the appropriate RAs should be informed. (ISO14155:2020)
Failure to Obtain IC	Sponsor and IRBs/ECs	ICF shall be obtained in writing and documented before a subject is enrolled into the Clinical Investigation. (ISO14155:2020)

17.2 Sponsor Reports

The Sponsor shall prepare and submit the following complete, accurate, and timely reports listed in the tables below (by geography). In addition to the reports listed below, the Sponsor shall, upon request of the reviewing EC, RA or FDA, provide accurate, complete and current information about any aspect of the investigation. Safety data Sponsor reporting requirements are listed in section 11.4.

Table 17: Sponsor reports for the United States

Report	Submit to	Description/Constraints
Withdrawal of IRB/EC Approval	Investigators, IRB/EC, FDA, and Relevant Authorities	Notification within five working days. (21 CFR 812.150(b)(2))
Withdrawal of FDA Approval	Investigators, IRB/EC, and Relevant Authorities	Notification within five working days. (21 CFR 812.150(b)(3))
Progress Reports/ Investigator List	IRB/EC and FDA	Progress Reports/Investigator List will be submitted at least annually, and will include a current list of the names and addresses of all Investigators participating in the investigation. (21 CFR 812.150(b)(4)(5), 812.36(f)
Recall and Device Disposition	Investigators, Head of Institution, IRB/EC, Relevant Authorities, and FDA	Notification within 30 working days and will include the reasons for any request that an Investigator return, repair, or otherwise dispose of any devices. (21 CFR 812.150(b)(6))

Report	Submit to	Description/Constraints
Final Report	Investigators, IRB/EC, Regulatory Authorities upon request, and FDA	The Sponsor will notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted to the FDA, Investigators, and IRBs/ECs within six months after completion or termination of this clinical study. (21 CFR 812.150(b)(7))
Failure to Obtain Informed Consent	FDA	Investigator's report will be submitted to FDA within five working days of notification. (21 CFR 812.150(b)(8))
Study Deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate Clinical Investigator(s), are reported on the CRFs and the final report of the Clinical Investigation. Study site specific study deviations will be submitted to Investigators periodically.
Other	IRB, FDA	Accurate, complete, and current information about any aspect of the investigation. (21 CFR 812.150(b)(10))
Premature Termination or Suspension of Clinical Study	IRB/EC, Investigators, and Regulatory Authorities, where applicable	The Sponsor will provide prompt notification of termination or suspension and reason(s) to Investigator and where required to IRB/EC and RAs.

Table 18: Sponsor reports for Europe, Middle East and Africa

Report	Submit to	Description/Constraints
Premature Termination or Suspension of the Clinical Investigation	Investigators, IRB/EC, Relevant Authorities and Head of the Institution	Provide prompt notification of termination or suspension and reason(s). (ISO14155:2020)
Withdrawal of IRB/EC approval	Investigators, Head of Institution, IRB/EC and Relevant Authorities	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.
Withdrawal of CA approval	Investigators, Head of Institution, IRB/EC, and Relevant Authorities	Investigators, IRBs/ECs will be notified only if required by local laws or by the IRB/EC.
Progress Reports	IRB/EC and Regulatory Authorities, if required	This will be submitted to the IRB/EC only if required by the IRB/EC).

Report	Submit to	Description/Constraints
Final Report	Investigators, IRB/EC, and Regulatory Authorities, if required	For studies with study sites complying to ISO14155:2020: • The Investigator shall have the opportunity to review and comment on the final report. • If a Clinical Investigator does not agree with the final report, his/her comments shall be communicated to the other Investigator(s). • The Coordinating Investigator shall sign the report. If no Coordinating investigator is appointed, then the signature of the Principal Investigator in each study site should be obtained. (ISO14155:2020)
Study Deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate Clinical Investigator(s), are reported on the CRFs and the final report of the Clinical Investigation. (ISO14155:2020) Study site specific study deviations will be submitted to Investigators periodically.

Table 19: Sponsor reports for Canada

Report	Submit to	Description/Constraints
Premature Termination or Suspension of the Clinical Investigation	Investigators, IRB/EC, Relevant Authorities, and Head of the Institution	Provide prompt notification of termination or suspension and reason(s).
Recall and Device Disposition	Investigators, Head of Institution, IRB/EC, Relevant Authorities,	Notification as per local requirements in Canada
Study Deviation	Investigators	Ensure that all deviations from the CIP are reviewed with the appropriate Clinical Investigator(s), are reported on the CRFs and the final report of the Clinical Investigation. Study site specific study deviations will be submitted to Investigators periodically.
Final Report	Health Canada, Investigators, and IRB/EC, Relevant Authorities	The Final Report will be submitted to Health Canada, Investigators, Ethics Committees, and relevant authorities after completion or termination of this study.

18. Publication and Use of Information

The Sponsor is committed to the publication and dissemination of clinical study results, regardless of study outcomes. Any publication or presentation relating to the DIAMOND-AF II Study will require that the Sponsor or financial supporter is included. A publication plan will be prepared to provide more details around the management of publications generated from this study. Registering and posting the study results on a publicly accessible database (e.g. ClinicalTrials.gov) will be based on the posting rules stipulated.

18.1 Publication Committee

The Sponsor may form a publication committee comprised of study Investigators. Sponsor personnel may serve as members of the committee. This committee will manage study publications with the goal of publishing findings from the data. The publication committee will develop the final publication plan as a separate document.

19. Suspension or Early Termination

19.1 Premature Termination of the Study

The Sponsor 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 these 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 the Sponsor to suspend or discontinue development of the device.

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 the Sponsor. The IRB/EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

19.2 Investigator/study site termination or suspension

The Sponsor 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 the Sponsor 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 the Sponsor notifies the investigational center otherwise.

19.3 Investigator/EC Termination of Participation

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

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

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 the Sponsor.

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21. Version History

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
A	Not Applicable, New Document	N/A- Initial Release	N/A- Initial Release	N/A- Initial Release	Cathy Mantor- ACT
B	• Revised ACT to Epix Therapeutics; added names of EKG Core Labs and steering committee member; removed asymptomatic from secondary effectiveness endpoint; added electrocardiograms as an option for documentation of PeAF; extended Holter window to within 180 days of procedure; clarified sample size justification with inclusion of performance goal; added statistical hypotheses to section 7.11; revised analyses population definitions to match SAP; added CV/Pulmonary exam, neuro/insertion site evaluations to one month follow up; clarified event recordings for symptomatic and scheduled events after blanking period. • Clarified primary safety endpoint to procedural and/or device related event; added asymptomatic AF/AT/AFL events to secondary endpoint; added	• Reflects company name change; clarification of endpoints based on regulatory and steering committee feedback; and administrative updates/corrections.	N/A- historical revision from 12Nov2018.	N/A- historical revision from 12Nov2018.	Elizabeth De Spain- EPIX Therapeutics

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	definition of significant pericardial effusion; revised inclusion criteria to include electrocardiogram option; revised sample size and statistical analysis performance goals. • Changed pregnancy test language on to clarify that the pregnancy screening test needs to be done within 7 days prior to the study procedure; not "enrollment"; Corrected omission of "AT" in "hospitalizations due to recurrent AF/AT/AFL". • Aligned primary safety endpoint composite list of SAEs throughout protocol.				
C	• Clarified the primary effectiveness endpoint to account for any occurrences of AF/AT/AFL; removed "asymptomatic" from 2nd; secondary endpoint; updated Sample Size Justification and Statistical Analysis. • Returned "Extended Hospitalization" to the list of primary endpoint composite list of SAE's. • Added "Administer a follow-up NIH Stroke Scale assessment" to the One-Month Follow-Up Visit.	• FDA Recommendation • Removed under Revision B • Clarify that the NIH Stroke Scale is performed at the visit.	N/A- historical revision from 07Dec2018.	N/A- historical revision from 07Dec2018.	Elizabeth De Spain- EPIX Therapeutics

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	• Removed "Ablations of complex fractionated atrial electrograms are not allowed."	• Included in protocol in error.			
D	• Updated sponsor address. • In the primary safety endpoint, changed the word "procedural" to "procedure" and changed "...and clinically symptomatic pulmonary vein stenosis..." to "and severe or clinically symptomatic pulmonary vein stenosis..." • Revised sample size justification to add revised justification to support selected PGs; removed secondary superiority effectiveness endpoint.	• Administrative Changes • Clarification of PG selection and determination.	N/A- historical revision from 31Jan2019.	N/A- historical revision from 31Jan2019.	Elizabeth De Spain- EPIX Therapeutics
E	• Updated TRAC-AF study section (Section 5.5, Table 2 and Table 4)	• Updated section to include final study data results.	N/A- historical revision from 14Mar2019.	N/A- historical revision from 14Mar2019.	Elizabeth De Spain- EPIX Therapeutics
F	**Changes made in regards to Study Analysis and overall CIP Content:** • Updated study contact information. • Removed "Death" definition within table of definitions.	• Changed to reflect primary Sponsor study contact • Inaccurately defines Death as "Cardiovascular related death post ablation". Removed for consistency within the CIP.	N/A- All study documents updated according to the ISO14155:2020 Revision. Also merged from EPIX SOP's to MDT SOP's concurrently. None of the changes being made to the CIP impact the	N/A- All study documents updated according to the ISO14155:2020 Revision. Also merged from EPIX SOP's to MDT SOP's concurrently.	Jessi Maumee- CRS

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	• Removed "Epix Therapeutics" throughout document. • Added 'drug for treatment of atrial fibrillation.' to 3.0 Synopsis- Inclusion Criteria, as inconsistent Study Inclusion Criteria. • Updated Sample Size to 351. • Added alternate Follow-up methods. • Added "Device Deficiency" to "Follow Up and Data Collection Schedule" table 8. • Clarified throughout the CIP: Commercial devices are allowed for use during	• Changed to "Sponsor" throughout the document. • Inconsistent language. • The increase in the enrollment size (from 300 to 351 enrollments globally) is required to ensure sufficient power is maintained to evaluate our primary safety endpoint and primary effectiveness in the desired persistent AF patient cohort. • To allow more flexibility due to COVID-19 pandemic. • Incorporated to help clarify when a device deficiency should be reported. • Added statement to help clarify the use of commercial device in repeat	performance of the device, principles of operation, and safety and efficacy of the study. There are no changes to primary endpoints. The modification made to secondary endpoints will not affect the study design or statistical analysis of the primary endpoints and other secondary endpoints.		

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	repeat ablation procedures post effectiveness period, and will be documented in a CRF. • Updated Clinical Events Committee language to remove 'not' from the statement: " o "The three (3) voting members who serve on the CEC to provide independent, unbiased review and adjudication of clinical events throughout the trial will not also be DSMB members." • Updated "Statistical Design and Methods" section: o ITT definition updated to: "All subjects that signed ICF and meet eligibility criteria* regardless of whether they receive study treatment. (*eligibility criteria as approved by the FDA)" o mITT definition updated to: "ITT population in which treatment is at least attempted (i.e. catheter inserted into vascular)" o Per Protocol definition updated to:	ablations post blanking period. • Revised statement to clarify that CEC members are also DSMB members. • The proposed modifications to the analysis populations will exclude all subjects with insufficient documentation of persistent AF (i.e. physician note + 2 ECGs or 24 Hr Holter) from the primary analysis of the study. However, safety and efficacy data from these excluded subjects will be analyzed in a supplemental analysis and included in the final clinical report.			

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	"Subset of the mITT population who did not have any major protocol deviations (i.e. eligibility criteria violations, or ablation treatment with a non-study catheter)." • Added specification that the primary safety and effectiveness endpoints will be analyzed using the Kaplan-Meier method. • Remove the following five (5) secondary objectives as insufficient data was collected to support analysis of these endpoints: o Rate of asymptomatic pericardial effusion of 1cm or more in size as documented by echocardiography up to 30 days following the index procedure. o Time to achieve initial PVI at index procedure (minutes), defined as time of delivery of first RF ablation with the investigational catheter until confirmation of PVI via entrance block following a 20-minute waiting period. o Ability to perform first-pass PV antral isolation.	• Insufficient data was collected in the EPIX database to support analysis of these endpoints. Therefore, Medtronic proposes to delete these endpoints from the CIP. Removal of these endpoints will not affect the study design or statistical analysis of the primary endpoints and other secondary endpoints.			

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	○ Ability to perform first-pass linear block for any lines performed during the procedure. ○ Rate of occurrence of electrically reconnected PVs following a 20-minute waiting period assessed by entrance block at index procedure. • Add one (1) secondary objective per previous discussion with FDA, regarding the DIAMOND-AF study. ○ 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.	• Upon FDA request, this endpoint was added to the DIAMOND-AF protocol (G170227), and since it is also applicable to the DIAMOND-AF II study Medtronic is proposing to include this objective into the DIAMOND-AF II investigational protocol. Furthermore, Medtronic updated the secondary endpoints verbiage by removing any "symptomatic" or "asymptomatic" verbiage from these endpoints per FDA feedback in the DIAMOND AF Study. • The current CIP describes that the included secondary endpoints			

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	• Transition the following seven (7) secondary objectives into ancillary objectives: o Total procedure time (minutes), defined as time of investigational catheter insertion into the vasculature to time of last procedural ablation catheter removed. o Total treatment device time (minutes), defined as time of delivery of first RF ablation with the investigational catheter to removal of the treatment catheter. o Mean cumulative RF Time (minutes). o Mean duration of RF ablations (seconds). o Total fluid infused through the investigational catheter (mL). o Total fluoroscopy time (minutes). o Number of re-hospitalizations due to atrial fibrillation recurrence after blanking period.	characterize the performance of the DiamondTemp Ablation System. However, these secondary endpoints mostly summarize the ablation procedure (e.g. mean duration, cumulative time etc.) and contribute less to the performance of the DiamondTemp Ablation System. Therefore, these are transitioned into ancillary objectives. • Incorporated region/model number within the			

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	• Updated "Product Description" to table format. **Changes made in regards to the ISO14155:2020 Updates/ Merge to Medtronic (MDT) SOP's and Templates:** • Entire CIP has been merged to the MDT Template. Various section headers have been rearranged and reformatted to match the MDT Template. • Removed "Protocol Signature Page", and replaced with "Investigator Statement" page. • The following sections have been updated per the MDT Template/ ISO14155:2020: o "Rationale" o "Investigational Device Description" o "Product Use" o "Product Storage" o "Product Return" o "Product Accountability" o "Study Site Requirements" o "Subject Consent" o "Subject Death" o "Statement of Compliance o "Data Management"	"Product Description". • All of the below changes were made to incorporate the ISO14155:2020 update while also merging to the MDT SOP's/Templates.			

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
	○ "Direct Access to Source Data/Documents" ○ "Confidentiality" ○ "Liability/Warranty/ Insurance Information" ○ "Publication and Use of Information" ○ "Investigator Reports" • Added section "Scheduled Follow-up Visit Windows". • "Procedure" section updated to include comment on Standard of Care and routine practice at institutions. • "Subject Exit, Withdrawal or Discontinuation" section updated to clarify that all ongoing AE's at study exit will be reviewed by Investigator to determine final status of the event. • "Study Completion" Section updated to include comment on subjects being followed by standard of care after study has been completed. • "Subject Lost to Follow-Up" sections updated to include statement on confirming vital status of the subject per ICF. • "Potential Risks" section updated to include ISO14971 requirement per				

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	ISO14155:2020. Also included reference to IB". • Entire "Adverse Event" section updated to reflect MDT templated verbiage. No content change made to this section. • "Adverse Event Reporting Timeline" updated to include requirement of reporting to IRB/EC or FDA/CA per local/regional regulations. • Added "Product Complaint Reporting" per MDT template/ ISO14155:2020 • Added "Investigator Records" section per MDT template/ ISO14155:2020. • "Study Design" updated to include number of investigational products used per subject, as well as indicated the max number of enrollments per site. • Entire Analysis section within the CIP have been updated according to the changes noted above, as well as to incorporate the ISO14155:2020 updates, while also merging to the MDT Template.				
G	• Increased enrollment from 351 to up to 400	• The increase in the enrollment size (from 351 to up to 400 enrollments globally) is required	None of the changes being made to the CIP Version G impact the	N/A- No study documents affected as a result of these changes being	

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		to ensure sufficient power is maintained to evaluate our primary safety and effectiveness objectives in the desired persistent AF patient population.	performance of the device, principles of operation, and safety and efficacy of the study.	made to the CIP Version G.	
	• Updated "Analysis Populations" definition in section 14.1: o ITT definition updated to: "All subjects that sign ICF and attempt study treatment (i.e. catheter inserted into vascular)" o mITT definition updated to: "Subset of the ITT population who meet eligibility criteria"	• Per FDA Recommendations in G180153/S010			
	• Added sensitivity analysis using the ITT population to the analysis of primary objectives in section 14.4	• Per FDA Recommendations in G180153/S010			
	• Section 10.7.3- Removed the requirement for NIHSS and AFEQT to be completed for repeat ablation procedures	• The database does not support collection of these datapoints. Furthermore, collection of the NIHSS and AFEQT at the repeat ablation			

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		procedure are not required for analysis of study endpoints/ objectives.			
	• Section 7.3- Addition of the statement: "No human and/or animal tissues or their derivatives are found within the study product."	• Added per ISO 14155:2020 Requirement			
	• Section 10.8- Addition of the statement: "The use of waivers is prohibited for deviating from the CIP".	• Added per ISO 14155:2020 Requirement			
	• Updated section 7.2 and table 7 to add commercial DiamondTemp ablation system devices (unidirectional and bidirectional catheters, the RF Generator, Irrigation Pump, and its accessories) as they are market-released in the US.	• As this is an indication expansion study in US and same procedural steps are applicable as commercial use of the Diamondtemp system for this study, Investigational centers in the US will utilize the commercially released DiamondTemp Ablation Catheters, RF Generator (and future commercially released generators), Irrigation pump and			

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		its accessories for the remainder of this study.			
	• Included "Investigator Role" within the Investigator Statement	• Updated language to match the updated Medtronic CIP Template			
	• Section 8.4: Updated the "monitoring and auditing" responsibility language within per Medtronic template.	• Updated language to match the updated Medtronic CIP Template			
	• Section 8.4: Added the statement, "Any data collection completed by Medtronic personnel will be clearly identified as such."	• Updated language to match the updated Medtronic CIP Template			
	• Section 7.6: Updated the product return instructions per Medtronic requirements.	• Updated language to match the updated Medtronic CIP Template			
	• Section 13.3: Clarified the following comment: "All events will be analyzed by the Core Lab to determine arrhythmia recurrence."	• Updated language to match the updated Medtronic CIP Template			
H	• Changed enrollment from 400 to 376	• Version G of the protocol was not released to sites. Upon discussion with steering committee, it was determined to	None of the changes being made to the CIP Version H impact the performance of the device,	No study document affected	Rob van der Straaten

Version	Summary of changes	Justification of changes	Potential impact of the change on performance, effectiveness, or safety or other endpoints	Identification of the affected study documents	Author(s)/ Title
		request for the exact number of subjects that failed I/E criteria that were enrolled in the study Contract with CRO is terminated	principles of operation, and safety and efficacy of the study.		
	• Deleted High Tech Med Consult (Czech Republic) as CRO from the from the synopsis • Added the following to the Statement of Compliance: The study will comply with ISO 14155:2020 upon site activation on CIP version H, with noted exceptions outlined throughout the CIP and applicable study documents. ISO14155:2020 exception for US; all activation related requirements will be conducted/collected in separate parts with exception of a formal SIV/visit report • Deleted from 16.1 "The Investigator/institution guarantees direct access to original source documents by Sponsor personnel, their	• To clarify SIV documentation • Duplicative language that is also captured under 16.1.2 Monitoring Procedures			

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	designees, and appropriate regulatory authorities." • Minor changes throughout the protocol	• Administrative changes/corrections			