The FARAPULSE ADVENT Trial

A Prospective Randomized Pivotal Trial of the FARAPULSE Pulsed Field Ablation System Compared with Standard of Care Ablation in Patients with Paroxysmal Atrial Fibrillation

CLINICAL INVESTIGATION PLAN (CIP) NUMBER: CS0934 REVISION D

SPONSOR:
FARAPULSE, INC.
3715 HAVEN AVE. SUITE 110
MENLO PARK, CA 94025
USA

ISSUE DATE: OCTOBER 13, 2021

This study is to be performed in accordance with the U.S. Code of Federal Regulations, Good Clinical Practice (GCP) and ethical principles consistent with the Declaration of Helsinki.

PROTOCOL AGREEMENT FORM

Study Title: The FARAPULSE ADVENT Trial, Revision D, October 13, 2021

I, the undersigned, have read and understand this clinical study, including the appendices. I will implement and conduct the clinical study in strict compliance with the study protocol and in accordance with good clinical practices (GCP) and all applicable laws and regulations. I will ensure that all persons assisting in this study are adequately informed about the protocol, study product(s) and their clinical study-related duties and functions.

I agree to maintain all study related information supplied by FARAPULSE Inc. in strictest confidence. When information regarding this study is submitted to an Institutional Review Board (IRB), it will be forwarded with a requirement that all study related material is to be held strictly confidential.

_____	_____	_____
Principal Investigator	Signature	Date

TABLE OF REVISIONS

Revision	Date	DCO #	Change Description
A	October 20, 2020	20-235	Initial Release for IDE submission
B	November 15, 2020	20-255	Modifications for IDE resubmission
C	March 17, 2021	21-136	Modifications for IDE resubmission Revision approved for trial initiation (April 16, 2021)
D	November 01, 2021	21-355	Modifications for Study Design Consideration IDE submission, maintenance updates and typographical corrections.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PRIMARY STUDY CONTACTS

SPONSOR	John Allison, Vice President Clinical Affairs, Regulatory Affairs and Quality Assurance FARAPULSE, Inc. 3715 Haven Ave. Suite 110 Menlo Park, CA 94025 USA Tel: +1.650.422.3633 Email: jallison@farapulse.com
PRINCIPAL INVESTIGATOR	Vivek Reddy, MD, Principal Investigator Mount Sinai Hospital One Gustav L Levy Place, Box 1030 New York, NY 10029 USA Tel: +1.212.241.7114 Email: vivek.reddy@mountsinai.org
CLINICAL RESEARCH ORGANIZATION	Patricia Bobzin, Director, Medical Devices Medpace Medical Device 3787 95th Ave NE Suite 100 Blaine, MN 55014 USA Tel: +1.612.234.8500 Fax: +1.513.527.0368 Email: p.bobzin@medpace.com
ARRHYTHMIA CORE LAB	HeartcoR Solutions LLC 2403 Harnish Drive, Suite 201 Algonquin, IL 60102 USA
CARDIAC IMAGING CORE LAB	Medpace Core Laboratories 5365 Medpace Way Cincinnati, OH 45227 USA
BRAIN IMAGING CORE LAB	Medpace Core Laboratories 5365 Medpace Way Cincinnati, OH 45227 USA

PROTOCOL SUMMARY

SPONSOR NAME	FARAPULSE, Inc.
TITLE OF STUDY	The FARAPULSE ADVENT Trial A Prospective Randomized Pivotal Trial of the FARAPULSE Pulsed Field Ablation System Compared with Standard of Care Ablation in Patients with Paroxysmal Atrial Fibrillation
CIP NUMBER / REVISION	CS0934 Revision D
PRIMARY OBJECTIVE	To determine whether there is valid scientific evidence that endocardial ablation using the FARAPULSE Pulsed Field Ablation System is both safe and effective for treating drug-resistant symptomatic PAF.
PRIMARY CLINICAL HYPOTHESIS	Pulmonary vein isolation (PVI) created by the FARAPULSE Pulsed Field Ablation System is not inferior in safety and effectiveness to treatment with approved catheter ablation technologies – force-sensing radiofrequency ablation (RFA) or cryoballoon ablation (CBA) – in the treatment of drug-resistant symptomatic PAF.
INVESTIGATIONAL DEVICES **SECTION 2**	FARAPULSE™ Pulsed Field Ablation System • FARAWAVE™ Pulsed Field Ablation Catheters and FARASTAR™ Catheter Connection Cable • FARASTAR™ Pulsed Field Ablation Generator, FARASTAR™ Stimulation Module, FARASTAR™ Recording System Module and associated cables • FARADRIVE™ Steerable Sheath
INTENDED USE **SECTION 2.2**	The FARAPULSE Pulsed Field Ablation System is indicated for the treatment of drug-resistant, recurrent, symptomatic PAF.

STUDY SUMMARY AND SCHEDULE **SECTION 4**	This is a prospective, adaptive, multi-center, randomized safety and effectiveness pivotal study comparing the FARAPULSE Pulsed Field Ablation System with standard of care ablation with force-sensing RF catheters and cryoballoon catheters indicated for the treatment of PAF. Subjects with documented drug-resistant (Class I to IV) PAF who have had ≥ 2 PAF episodes within 6 months of enrollment will undergo percutaneous endocardial ablation for PVI. Subjects with typical right-sided (isthmus-dependent) atrial flutter (AFL) may undergo ablative interruption of the cavo-tricuspid isthmus (CTI). Class I / III antiarrhythmic drugs (AADs) will be discontinued at Day 60 ± 10, subject to Investigator discretion. **Safety:** Subjects will be followed at 7 days, 30 days, 90 days, 6 months and 12 months for adverse events (AEs). A composite device- and procedure-related serious adverse event (SAE) rate will be compared between randomization groups for non-inferiority. **Effectiveness:** Subjects will be monitored with weekly scheduled plus symptom-driven event monitoring, as well as 6 and 12-month Holter monitoring, for freedom from recurrent arrhythmia (atrial fibrillation [AF], AFL or atrial tachycardia [AT]) after the Blanking Period (Days 0 - 90). The proportion of subjects free of post-blanking recurrent arrhythmia (AF, AFL or AT), re-ablation or Class I / III AAD use will be compared between randomization groups for non-inferiority.
SAMPLE SIZE SUMMARY **SECTION 4.4**	A maximum of 900 subjects may be enrolled in this study. **Roll-In Subjects:** Up to 105 subjects (the first 1-3 Enrolled Subjects at each site) will be treated with the FARAPULSE devices in a manner consistent with the randomized Pulsed Field Group and will be analyzed and reported separately. **ITT Subjects:** An estimated 450 MITT Subjects will be required to support the proposed non-inferiority outcomes. Interim sample size re-estimation may decrease this number to 350 or increase it to a maximum of 750. Up to 45 additional subjects (6%) may be enrolled to compensate for those ITT Subjects who do not meet the criteria for the MITT Population.
INVESTIGATIONAL SITES **SECTION 4.5**	Up to 35 investigational sites in the United States. No site may enroll more than 45 ITT Subjects (excludes Roll-In Subjects and ITT Subjects who do not qualify for the MITT population) with an intended minimum of 10 subjects per site. Should interim sample size re-estimation lead to an increase in the number of MITT Subjects greater than 450, each site will be limited to 10% of the increased total.

DURATION OF STUDY AND SUBJECT PARTICIPATION SECTION 4.6	Study start-up, inclusive of site initiation and Investigator training, is estimated to take 6 months. The enrollment period for the first 600 subjects (105 Roll-Ins plus 495 ITT Subjects) is estimated to take 18 months and subjects will be followed for up to 13 months. There will be a 3-month period of site close-out visits, for a planned study duration of approximately 40 months. Coronavirus Disease 2019 (COVID-19)-related disruptions and interim sample size re-estimation may alter this timeframe. Subject participation is anticipated to be 13 ± 1 months to allow for screening, pre-procedural diagnostic procedures, randomization, treatment and 12±1 months of study follow-up. If a subject requires a Rescheduled Index Procedure, this may prolong participation by up to 2 to 3 months.
SCHEDULE OF EVENTS AND ASSESSMENTS SECTION 4.7	• **Baseline Assessment** • **Index Procedure / Rescheduled Index Procedure:** cardiac ablation (Day 0) • **Pre-Discharge Assessment** • **Day 7 Assessment:** clinical assessment (Window Days 7 to 11) • **Day 30 Assessment:** clinical assessment (Window Day 30 ± 7) • **Day 60 Event Monitor (EM) Training and AAD Discontinuation:** (Window Day 60 ± 10) • **Day 90 Assessment:** clinical assessment, cardiac magnetic resonance imaging (MRI) / computed tomography (CT) scan, begin weekly scheduled and symptomatic event monitoring (Window Day 90 ± 14) • **Month 6 Assessment:** clinical assessment, Holter (Window Day 180 ± 30) • **Month 12 Assessment:** clinical assessment, Holter, QoL and cardiac MRI/CT if Day 90 study showed pulmonary vein stenosis (PVS) (Window Day 360 ± 30) • **Re-Ablation Procedure** • **Unscheduled Assessment** • **COVID-19-Related Disruptions of Study Assessments**
ANTICOAGULATION SECTION 5.1	Anticoagulation will be guided by the 2017 Heart Rhythm Society Expert Consensus Statement and the 2019 American Heart Association /American College of Cardiology / Heart Rhythm Society Focused Update relating to this issue.

INDEX PROCEDURE SECTION 5.2	**Index Procedure / Rescheduled Index Procedure:** All subjects will be screened for completion of a minimum of 3 weeks of systemic anticoagulation and the absence of atrial thrombus just prior to or at the time of the Index Procedure and will be rescheduled if these conditions are not met. **PVI:** Subjects will undergo an attempt to isolate all PVs or their anatomic equivalent with the randomized devices: • Pulsed Field Group with the FARAPULSE Pulsed Field Ablation System • Thermal Group with either a study-approved RFA or CBA system. Sites will use either RFA or CBA exclusively to treat subjects randomized to the Thermal Group. **CTI:** Subjects in either the Pulsed Field or Thermal Groups with a past history of CTI-mediated (typical) AFL, who manifest typical AFL during a procedure or within the Blanking Period, or who have inducible typical flutter, may undergo ablation of the CTI at the discretion of the Investigator using any approved RF catheter during the Index / Rescheduled Index Procedure or any re-ablation procedure. **Other Ablation:** Other ablation is not permitted under this protocol except when the Investigator determines that subject welfare requires ablation for an accessory pathway, atrioventricular nodal reentrant tachycardia (AVNRT), treatment-emergent left-sided AFL or incessant AT.
RE-ABLATION PROCEDURES SECTION 5.4	Re-ablation under this protocol requires documentation of Detectable AF, AFL or AT. When performed, re-ablation will be performed utilizing an approved study ablation catheter (RFA or CBA) at Investigator discretion. Any re-ablation procedure for AF, AFL or AT during study follow-up constitutes a Treatment Failure. However, CTI ablation or re-ablation for right-sided typical AFL may be performed at any time during study follow-up and does not constitute a Treatment Failure.

NEUROLOGIC ASSESSMENT SUBJECTS **SECTION 5.8**	A subset of study sites qualified and willing to perform the standardized brain MRI post-ablation will be established and designated as NAS sites. NAS sites will be selected to generate a minimum of 80 NAS Subjects, balanced approximately equally between RFA and CBA control sites. All ITT Subjects at NAS sites free of contraindications to MRI will be consented for post-procedure MRI until the study enrollment target of evaluable scans is met. The MRI will be performed using standardized parameters to elicit characteristics of silent cerebral events (SCEs) and silent cerebral lesions (SCLs). If a post-procedural SCE or SCL is confirmed, then the NAS subject will undergo a pre-discharge neurological assessment and a follow-up brain MRI during the 90 Day Assessment window.
ANTIARRHYTHMIC DRUGS **SECTION 5.9**	Antiarrhythmic drugs (AADs), except for amiodarone, may be utilized during the Blanking Period at the Investigator's discretion. On Day 60 ± 10 each subject will be contacted by telephone to stop all AADs. Class I / III AADs should be stopped at the Day 60 Assessment. However, at the Investigator's discretion, Class I / III AADs may be continued up to Day 90 without creating a Treatment Failure. The use of amiodarone at any time during the study, except intra-procedurally to control an arrhythmia, or the use of Class I / III AADs after Day 90, constitute a Treatment Failure.

PRIMARY SAFETY ENDPOINT **SECTION 7.1**	The primary safety endpoint is the Composite Safety Endpoint (CSE) defined as the proportion of Intent-to-Treat (ITT) Subjects with one or more of the following device- or procedure-related SAEs as adjudicated by the CEC. **Early onset:** Any of the following with an Onset Date within 7 days of the Index / Rescheduled Index procedure: • Death • Myocardial infarction • Persistent phrenic nerve palsy • Stroke • Transient ischemic attack (TIA) • Peripheral or organ thromboembolism • Cardiac tamponade / perforation • Pericarditis • Pulmonary edema • Vascular access complications • Heart block • Gastric motility/pyloric spasm disorders **Late onset:** Either of the following with an Onset Date at any time through the completion of 12-month follow-up visit: • PVS • Atrio-esophageal fistula
SECONDARY SAFETY ENDPOINT **SECTION 7.2**	1. Aggregate PV Cross-Sectional Area
ADDITIONAL SAFETY ANALYSES **SECTION 7.3**	1. Severe Ablation Complications 2. Nonserious / Serious CSEs 3. Post-Blanking Direct Current Cardioversions 4. Post-Blanking Arrhythmia Hospitalizations 5. Any Related SAE 6. Any Related Stroke or TIA 7. Categorized PV Dimensional Changes 8. Thermal Group RF Ablation / Cryoablation Safety Assessment 9. Learning Curve Safety Assessment

PRIMARY EFFECTIVENESS ENDPOINT **SECTION 7.4**	The primary effectiveness endpoint is Treatment Success in Modified Intent-to-Treat (MITT) subjects, defined as: 1. Acute Procedural Success AND 2. Chronic Success, defined as freedom from: a. At the Index / Rescheduled Index Procedure: Use of a non-randomized treatment modality for PVI b. After the Blanking Period: i. Occurrence of any Detectable AF, AFL or AT (excluding CTI-dependent flutter confirmed by EP study) ii. Any cardioversion for AF, AFL or AT (excluding for CTI-dependent flutter) iii. Use of any Type I or Type III antiarrhythmic medication for the treatment of AF, AFL or AT c. At any time: i. Re-ablation for AF, AFL or AT (other than for CTI-dependent flutter) ii. Use of amiodarone, , except intra-procedurally to control an arrhythmia Endpoint status will be assessed through the Month 12 Assessment (Day 360 ± 30).
SECONDARY EFFECTIVENESS ENDPOINT **SECTIONS 7.5**	The secondary effectiveness endpoint is the same as the primary effectiveness endpoint but will be tested for superiority rather than non-inferiority.
ADDITIONAL EFFECTIVENESS ANALYSES **SECTION 7.6**	1. Acute Procedural Success 2. Acute Vein Success 3. Chronic Success 4. Chronic Success Allowing Re-ablation 5. Chronic Success Allowing AADs 6. Treatment Success Allowing Re-ablation 7. Treatment Success Allowing AADs 8. Treatment Success with PVI/CTI Only 9. Early Recurrence of AF 10. Rate of Re-ablation 11. PVI Durability at Re-ablation 12. CTI Ablation Failure 13. Thermal Group RF Ablation/ Cryoablation Effectiveness Assessment 14. AF Symptom Assessment 15. Learning Curve Effectiveness Assessment

PROCEDURAL ASSESSMENTS SECTION 7.7	1. Assessments of procedure durations a. Procedure time (initiation of venous access to venous access closure) b. Left atrial dwell time (total time an ablation catheter is in the left atrium [LA]) c. Total ablation time (first ablation to last ablation) d. Total mapping time (total time spent mapping) e. Fluoroscopy time (total duration of exposure) 2. Characterization of lesion sets: a. PVI ablations b. CTI ablations c. For subjects undergoing required LA ablation for an accessory pathway, AVNRT, left-sided AFL or incessant AT, description of lesion sets utilized
QUALITY OF LIFE ASSESSMENT SECTION 7.8	Quality of Life (QoL) will be assessed at baseline and 12 months using two assessments. These assessments will be tested for nominal p values between Pulsed Field Subjects and Thermal Subjects: 1. The EuroQol standardized questionnaire of health states (EQ-5D-3 L) 2. The Atrial Fibrillation Effect on Quality of Life (AFEQT) instrument for the measurement of health-related quality of life
RANDOMIZATION SECTION 9.2	Subjects who meet the inclusion and exclusion criteria will be randomized using a 1:1 allocation ratio. Each site will utilize only one control modality – either RFA or CBA – and will use that modality for all subjects randomized to the Thermal Group. Site activation and enrollment will be monitored and when necessary controlled to maintain a minimum 40% proportion of Thermal Subjects in either the RFA or CBA modality.
POPULATIONS FOR ANALYSIS SECTION 9.4	Several analysis populations are defined for this study, including: • Safety Subjects • Modified Intent-to-Treat (MITT) Subjects • Per Protocol (PP) Subjects
ASSESSMENT OF THE PRIMARY SAFETY ENDPOINT SECTION 9.5	The primary safety endpoint for this study is the Composite Safety Endpoint (CSE) which will be analyzed as a test of non-inferiority of the event rate at 12 months using a non-inferiority margin of 8%. Statistical methods are Bayesian.

ASSESSMENT OF THE PRIMARY EFFECTIVENESS ENDPOINT **SECTION 9.6**	The primary effectiveness endpoint for this study is Treatment Success which will be analyzed as a test of non-inferiority of the event rate at 12 months using a non-inferiority margin of 15%. Statistical methods are Bayesian.
SAMPLE SIZE CONSIDERATIONS **SECTION 9.7**	Although the pre-specified statistical analysis methods are Bayesian, standard frequentist considerations are used to guide sample size selection. **Parameter selection:** Published IDE studies with available information comparing new devices with approved control devices have all used non-inferiority designs with one-sided alpha of 0.05 and 15% effectiveness margins and either 8% or 9% safety margins. **Sample size requirements for safety:** The sample size for primary safety was estimated for a Farrington-Manning test with PASS 13 indicates that, for 1:1 randomization, 90% power, alpha=0.05 (one-sided), CSE rate in both Groups of 0.08 and non-inferiority margin of 0.08. Assuming a 5% rate of loss-to-follow-up (LTFU), 450 subjects are needed. Uncertainty in the CSE rate motivates the use of a design wherein the sample size is adaptively determined, with possible sample sizes ranging from 350 to 750. **Sample size requirements for effectiveness:** The sample size required for the primary effectiveness endpoint was estimated by PASS 13 for 1:1 randomization, 90% power, alpha=0.05 (one-sided), success rates in each group of 0.65 and non-inferiority margin of 0.15. Assuming a 10% rate of LTFU, 382 subjects are needed. Uncertainty in the Treatment Success rate motivates the use of a design wherein the sample size is adaptively determined, with possible sample sizes ranging from 200 to 550. **Number of Enrolled Subjects:** The primary population for the analysis of effectiveness is the MITT Population. The Safety Population should be similar but will not be smaller. Considering the joint sample size needs of the primary safety and effectiveness objectives, the primary analysis population may range from a minimum of 350 to a maximum of 750. To achieve a sample size of 750 MITT Subjects, up to 900 subjects may be enrolled consisting of 750 MITT and up to 105 Roll-In Subjects and up to 45 ITT Subjects (6%) who do not meet the criteria for the MITT Population.

ANALYSIS PLAN **SECTION 9.8**	This trial is designed using Bayesian statistical techniques. The sample size will be determined adaptively via a Goldilocks design, with possible sample sizes of N=350, 450, 550, 650, and 750. At each of the four interim sample size assessments, the predictive probability that the trial will end in a determination of non-inferiority for both safety and effectiveness will be computed and compared to pre-specified thresholds. A determination will be made to stop enrollment for predicted success, to stop enrollment for predicted futility, or to continue enrollment to the next larger sample size. Once subject accrual has stopped, all accrued subjects will be followed to 12 months, and then the inferential tests of non-inferiority will occur as described in **Sections 9.5 and 9.6**.
CORE LABORATORIES **SECTION 10**	A qualified Arrhythmia Core Lab (ACL) will be established to receive, review and assess all protocol-stipulated ECGs, EMs and Holter monitors. A qualified Cardiac Imaging Core Lab (CICL) will be established to receive, review and assess all protocol-stipulated cardiac MRIs and CTs. A qualified Brain Imaging Core Lab (BICL) will be established to receive, review and assess all protocol-stipulated brain MRIs for NAS Subjects.
CLINICAL EVENTS COMMITTEE **SECTION 12.2.4**	An independent panel of 3 electrophysiologists will review AEs, adjudicate seriousness and relatedness of potential SAEs and adjudicate primary safety and effectiveness outcomes. This group will consist of a panel of 3 experienced, independent physicians who are not Investigators and will be supported by one or more Medical Monitors and staff as required. The CEC will convene regularly during the study to review, classify and/or adjudicate AEs reported in this investigation as well as primary and secondary study outcomes.
DATA AND SAFETY MONITORING BOARD **SECTION 12.2.5**	An independent panel of physicians, trialists and a statistician will assess study progress and key study outcomes. This group will include at least 2 experienced, independent physicians who are not Investigators and an independent statistician not involved in the routine operation of the study. The Data and Safety Monitoring Board (DSMB) will convene regularly during the study to assess overall event rates to ensure the integrity of the clinical study and the rights, safety and welfare of study subjects.

INCLUSION CRITERIA **SECTION 3.3.1**	Patients are required to meet all the following inclusion criteria to participate in this study: 1. Patients with drug-resistant symptomatic PAF meeting all the following criteria: a. Paroxysmal: AF that terminates spontaneously or with intervention within 7 days of onset. b. Frequency: i. Physician documentation of recurrent PAF (two or more episodes) within 6 months, AND ii. At least one (1) documented episode by a recording such as ECG, EM, Holter monitor or telemetry strip within 12 months of enrollment. c. Drug failed: Failed AAD treatment, meaning therapeutic failure of at least one (1) AAD (Class I to IV) for efficacy and / or intolerance. 2. Patients who are ≥ 18 and ≤ 75 years of age on the day of enrollment. 3. Patient who are willing and capable of: a. Providing informed consent to undergo study procedures AND b. Participating in all examinations and follow-up visits and tests associated with this clinical study.

EXCLUSION CRITERIA SECTION 3.3.2	Patients will be excluded from participating in this study if they meet <u>any one</u> of the following exclusion criteria: 1. AF that is any of the following: a. Persistent (both early and longstanding) by diagnosis or continuous duration > 7 days b. Requires four (4) or more direct-current cardioversions in the preceding 12 months c. Secondary to electrolyte imbalance, thyroid disease, alcohol or other reversible / non-cardiac causes 2. Any of the following atrial conditions: a. Left atrial anteroposterior diameter ≥ 5.5 cm (by MRI, CT or TTE) b. Any prior atrial endocardial or epicardial ablation procedure, other than right sided cavotricuspid isthmus ablation or for right sided SVT c. Any prior atrial surgery d. Intra-atrial septal patch or interatrial shunt e. Atrial myxoma f. Current LA thrombus g. LA appendage closure, device or occlusion, past or anticipated h. Any PV abnormality, stenosis or stenting (common and middle PVs are admissible) 3. At any time, one (1) or more of the following cardiovascular procedures, implants or conditions: a. Sustained ventricular tachycardia or any ventricular fibrillation b. Hemodynamically significant valvular disease: i. Valvular disease that is symptomatic ii. Valvular disease causing or exacerbating congestive heart failure iii. Aortic stenosis: if already characterized, valve area < 1.5cm or gradient > 20 mm Hg iv. Mitral stenosis: if already characterized, valve area < 1.5cm or gradient > 5 mm Hg v. Aortic or mitral regurgitation associated with abnormal LV function or hemodynamic measurements c. Hypertrophic cardiomyopathy d. Any prosthetic heart valve, ring or repair including balloon aortic valvuloplasty e. Pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices f. Any inferior vena cava (IVC) filter, known inability to obtain vascular access or other contraindication to femoral access

(CONTINUED NEXT PAGE)

EXCLUSION CRITERIA SECTION 3.3.2 **(CONTINUED FROM PRIOR PAGE)**	g. History of rheumatic fever h. History of congenital heart disease with any residual anatomic or conduction abnormality 4. Any of the following procedures, implants or conditions: a. At baseline: i. New York Heart Association (NYHA) Class III/IV ii. Left ventricular ejection fraction (LVEF) < 40% iii. Symptomatic hypotension iv. Uncontrolled hypertension (SBP > 160 mmHg or DBP > 95 mmHg on two BP measurements at baseline assessment) v. Symptomatic resting bradycardia vi. Implantable loop recorder or insertable cardiac monitor, b. Within the 3 months preceding the Consent Date: i. Myocardial infarction ii. Unstable angina iii. Percutaneous coronary intervention iv. Heart failure hospitalization v. Treatment with amiodarone vi. Pericarditis or symptomatic pericardial effusion vii. Gastrointestinal bleeding c. Within the 6 months preceding the Consent Date: i. Heart surgery ii. Stroke, TIA or intracranial bleeding iii. Any thromboembolic event iv. Carotid stenting or endarterectomy 5. Diagnosed disorder of blood clotting or bleeding diathesis 6. Contraindication to, or unwillingness to use, systemic anticoagulation 7. Patient who is not on anticoagulation therapy for at least 3 weeks prior to the ablation procedure 8. Contraindication to both CT and MRI 9. Sensitivity to contrast media not controllable by premedication 10. Women of childbearing potential who are pregnant, lactating, not using medical birth control or who are planning to become pregnant during the anticipated study period 11. Medical conditions that would prevent participation in the study, interfere with assessment or therapy, significantly raise the risk of study participation, or modify outcome data or its interpretation, including but not limited to: a. Body Mass Index (BMI) > 40.0 b. Solid organ or hematologic transplant, or currently being evaluated for an organ transplant
(CONTINUED NEXT PAGE)	

EXCLUSION CRITERIA SECTION 3.3.2 **(CONTINUED FROM PRIOR PAGE)**	c. Severe lung disease, pulmonary hypertension, or any lung disease involving abnormal blood gases or requiring supplemental oxygen d. Renal insufficiency with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, or any history of renal dialysis or renal transplant e. Active malignancy or history of treated malignancy within 24 months of enrollment (other than cutaneous basal cell or squamous cell carcinoma) f. Clinically significant gastrointestinal problems involving the esophagus or stomach including severe or erosive esophagitis, uncontrolled gastric reflux, gastroparesis, esophageal candidiasis or active gastroduodenal ulceration g. Active systemic infection h. COVID-19 disease i. Current confirmed, active COVID-19 disease ii. Current positive test for SARS-CoV-2 iii. Confirmed COVID-19 disease not clinically resolved at least 3 months prior to the Consent Date. i. Other uncontrolled medical conditions that may modify device effect or increase risk, including uncontrolled diabetes mellitus (HgbA1c > 8.0% if test result already obtained) or active alcohol abuse j. Sleep apnea and: i. An apnea-hypopnea index (AHI) ≥ 15, or ii. An AHI of ≥ 5 and ≤14 with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease or history of stroke, unless compliant with continuous positive airway pressure (CPAP) treatment. k. Predicted life expectancy less than one (1) year 12. Clinically significant psychological condition that in the Investigator's opinion would prohibit the subject's ability to meet the protocol requirements 13. Current or anticipated enrollment in any other randomized, interventional or Food and Drug Administration (FDA)-regulated clinical study (data collection for registries or retrospective studies is permitted) 14. Employees / family members of: a. FARAPULSE or any of its affiliates or contractors b. The Investigator, sub-Investigators, or their medical office or practice, or healthcare organizations at which study procedures may be performed

Abbreviations and Acronyms

AAD	Antiarrhythmic drug
ACL	Arrhythmia Core Laboratory
ACT	Activated clotting time
ADC	Apparent diffusion coefficient
ADE	Adverse Device Effect
AE	Adverse event
AF	Atrial fibrillation
AFEQT	Atrial Fibrillation Effect on QualiTy-of-Life Questionnaire
AFL	Atrial flutter
AT	Atrial tachycardia
AVNRT	Atrioventricular nodal reentrant tachycardia
BICL	Brain Imaging Core Laboratory
BMI	Body Mass Index
BUN	Blood urea nitrogen
CBA	Cryoballoon ablation
CEC	Clinical Events Committee
CHA_2DS_2-VASc	A clinical prediction rule for stroke
CHF	Congestive heart failure
CICL	Cardiac Imaging Core Laboratory
CIP	Clinical Investigation Plan (synonymous with study protocol)
COVID-19	COrona VIrus Disease 2019: an illness caused by SARS-CoV-2
CPS	Chronic Procedural Success
CRF	Includes CRF (case report form) and eCRF (electronic CRF)
CRO	Clinical research organization
CSE	Composite Safety Endpoint
CT	Computed tomography
CTI	Cavo-tricuspid isthmus
CXR	Chest X-ray
DSMB	Data and Safety Monitoring Board
DWI	Diffusion weighted image
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EM	Event monitor
EQ-5D-3 L	EuroQol standardized questionnaire of health states
ETW	Early Termination / Withdrawn
FDA	Food and Drug Administration
FLAIR	Fluid-attenuated inversion recovery
HCT	Hematocrit
HGB	Hemoglobin
ICE	Intracardiac echocardiography
ICF	Informed consent form
INR	International normalized ratio

IRB	Institutional Review Board
IRE	Irreversible electroporation
ITT	Intent(ion)-to-Treat
IVC	Inferior vena cava
LA	Left atrium or left atrial
LBBB	Left bundle branch block
LTFU	Lost-to-follow-up
MITT	Modified Intent(ion)-to-Treat
MRI	Magnetic resonance imaging
NOAC	Novel oral anticoagulant
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
PAF	Paroxysmal atrial fibrillation
PFA	Pulsed field ablation
PP	Per Protocol
PV	Pulmonary vein
PVI	Pulmonary vein isolation
PVS	Pulmonary vein stenosis
RFA	Radiofrequency ablation
SADE	Serious Adverse Device Effect
SAE	Serious adverse event
SCE	Silent cerebral events
SCL	Silent cerebral lesions
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TTE	Transthoracic echocardiography
UADE	Unanticipated Adverse Device Effect
V	Volts

1. Introduction

1.1 Background and Rationale

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, affecting approximately 2.2 million people in the United States and 4.5 million in the European Union.[1, 2]. The incidence increases with advancing age, affecting 6% of the population over age 60 and 10% of the population over age 80[3, 4]. Age-adjusted population trending projects 16 million people in the United States will have AF by 2050[5].
AF remains a significant cause of morbidity and mortality in industrialized societies. The annual risk of AF-related stroke is 5% per year and 1 of every 6 strokes diagnosed occurs in the presence of AF.[6] Therefore, patients with AF require long-term anticoagulation to prevent embolic events. Failure to manage AF may also lead to anatomic and electrical remodeling of the left atrium (LA), tachycardia-induced cardiomyopathy and reduced left ventricular function (heart failure). AF remains an extremely costly public health burden, with annual per patient cost of care approaching €3000 (approximately $3,200 U.S.)[7]

The Heart Rhythm Society (HRS) 2017 Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[8] defines several different stages of AF. Paroxysmal AF (PAF) is defined as AF that terminates spontaneously or with intervention within 7 days of onset.

1.2 Irreversible Electroporation

Al-Sakere 2007[9] described irreversible electroporation (IRE) as a non-thermal tissue ablation technique in which intense short duration electrical fields are used to permanently open pores in cell membranes, thus producing non-thermal tissue ablation. Their study, using a mouse model, showed complete regression in 92% of treated tumors. IRE ablation has a tissue-specific mechanism of ablation. The tissue injury from IRE ablation occurs at the cellular level with loss of homeostasis leading to necrosis or apoptosis.[10, 11, 12, 13] IRE ablation typically spares the extracellular matrix, which facilitates rapid wound healing.[14, 15, 16, 17, 18]

Thomson 2011[19] reported a case-series study (N=38) assessing the safety of IRE for treating liver, kidney or lung cancers in humans. The first four patients showed signs of transient ventricular arrhythmia, so subsequent patients were all treated using electrocardiogram (ECG)-synchronized delivery of electroporation pulses. There were 2 further arrhythmias and 2 cases of inadvertent damage to neighboring organs. Approximately 68% of tumors were completely ablated. The authors concluded that IRE is safe for clinical use, provided ECG-synchronized delivery is used.

A research group led by FHM Wittkampf in Utrecht investigated the potential effectiveness and safety of epicardial electroporation in AF ablation procedures using porcine models. Wittkampf 2011[20] (N=10) used a circular ablation catheter and showed that PVI was achieved in all animals, with no sign of stenosis at 3-week follow-up. Van Driel 2014[21] (N=6) confirmed this result out to 3-month follow-up. Neven 2014[22] (N=5) showed that electroporation lesion depth depended on the level of electrical energy applied, reaching 8 mm at 300 joules.

Van Driel 2015[23] (N=20) showed that electroporation could create deep lesions close to the phrenic nerve without damage to the nerve. Neven 2014[24] similarly showed that neighboring coronary arteries were undamaged by electroporation (N= 5). These animal studies suggest that IRE can safely create deep lesions in heart tissue without harming adjacent tissues.

1.3 Summary of FARAPULSE Preclinical Studies

FARAPULSE Inc. (hereinafter FARAPULSE) has performed multiple preclinical animal studies investigating the safety and efficacy of the FARAPULSE™ Pulsed Field Ablation System. These studies demonstrate that pulsed field ablation (PFA) using the FARAPULSE technology reliably produces homogeneous, well-demarcated and transmural lesions in porcine atrial tissue. Seven- and 30-day studies show mild to moderate inflammatory and healing responses consistent with radiofrequency ablation lesions.

Areas of critical interest that cannot be directly assessed in the clinical studies performed to date include:

- **Esophageal Sparing:** FARAPULSE performed a preclinical study[25] to assess the effect of PFA application on the esophagus in a relevant preclinical porcine model. A cohort of swine underwent ablation of the esophagus, which was mechanically deflected to be in close apposition with the inferior vena cava (IVC) which contained the PFA catheter. A control cohort, which underwent clinically representative radiofrequency ablation (RFA) was also assessed. After a high-dose delivery of the PFA and RFA energies, the animal subjects were survived to 25 days.

  Pathological analysis demonstrated that no PFA subjects showed any gross or histological sign of ablation-related injury to the esophageal tissues. However, all RF control subjects showed ablation-related injury to the esophagus, ranging from mucosal lesions to esophageal fistula.

- **Phrenic Nerve Sparing:** FARAPULSE performed a preclinical study[26] to assess the safety and efficacy of the PFA waveform directly adjacent to the phrenic nerve. Right superior pulmonary vein (RSPV), inferior common pulmonary vein (ICPV) and superior vena cava (SVC) isolation were performed using the FARAWAVE Pulsed Field Ablation Catheter in a relevant preclinical porcine model.

  None of eleven porcine subjects showed any diminution of phrenic nerve function after treatment at the maximum (2.0 kV) and minimum (1.4 kV) voltages under investigation.

- **Pulmonary Vein Effects:** FARAPULSE performed a preclinical study[27] to assess the safety and efficacy of ablation using the FARAWAVE Pulsed Field Ablation Catheter in a relevant preclinical porcine model. Six porcine subjects underwent ablation of the RSPV and ICPV at 2.0 kV and were then survived for 30 days.

Pathological analysis demonstrated that no subjects showed any degree of PV narrowing or flow impairment in the treated veins. This study also investigated durability of pulmonary vein isolation (PVI) and histological transmurality at 30 days, showing that both assessments were present in 91.6% of the treated PVs.

These results support the safety and performance of the system.

1.4 Summary of FARAPULSE Clinical Studies for PAF

1.4.1 The IMPULSE Study

FARAPULSE, Inc. conducted a safety and feasibility study[28] at Na Homolce Hospital in Prague, Czech Republic and Hôpital Cardiologique du Haut-Leveque in Pessac, France under the "IMPULSE" Protocol, CS0188. This study was conducted using a version of the FARAPULSE Pulsed Field Ablation System which functioned similarly to the system which will be used in the IDE investigation and the results are summarized below.

Clinical investigation population: Adult patients with PAF who provided informed consent to participate in the study.

Methodology: In this pre-market, multi-center study, subjects who had signed the informed consent underwent baseline assessment, received treatment with the investigational device and were assessed prior to discharge, and at 30 days, 3 months, 6 months and 12 months following the index procedure. A remapping procedure was required as part of the 3-month assessment. A core laboratory analyzed ECG data from the Event Monitors (EMs) and Holter monitors. Adverse events (AEs) were reviewed and where necessary adjudicated by a Clinical Events Committee (CEC).

Results: A total of 40 subjects enrolled and were treated in this study with a mean age of 58.2±9.1 years. A majority of subjects were male, 70% (28/40).

The primary safety endpoint of the study was the incidence of early-onset (within 7 days of the PFA ablation procedure) primary adverse events (AEs). One subject had a qualifying peri-procedural cardiac tamponade resolving with drainage, for a rate of 2.5% (1/40).

The primary feasibility endpoint of the study was the proportion of subjects that achieved Acute Procedural Success, defined as the percutaneous endocardial creation of electrically isolating lesions around the ostia of the PVs using the FARAPULSE Pulsed Field Ablation System. The procedural success rate was 100% (40/40).

Secondary safety endpoints, included the rate of all serious adverse events (SAEs) reported at the different follow-up time points, as adjudicated by the CEC, with 7.5% (3/40) of subjects reporting an SAE between index procedure and 30 days (2 AF events, 1 cardiac tamponade), 0.0% (0/40) of subjects reporting an SAE between 30 days and 3 months, 7.5% (3/40) of subjects reporting an SAE between 3 months and 6 months (1 arteriovenous fistula, 2 ATs) and 2.5% (1/40) of subjects reporting an SAE between 6 months and 12 months (1 urinary calculus).

No pulmonary vein stenosis (PVS), esophageal lesions or phrenic nerve impairment was observed in any subject.

The secondary feasibility endpoint was long-term technical success, defined as electrical isolation of the PVs assessed during an electroanatomical mapping procedure performed 3-months following the index procedure, with 41.2% (14/34) of subjects achieving technical success.

For the 40 enrolled subjects, 156 veins were treated at the index procedure, 100% (156/156) were successfully isolated and 70% of ablated PVs remained isolated at the 3-month remapping procedure. Thirty-one (31) of 40 subjects (77.5%) remained free from post-blanking AF, atrial flutter (AFL) or atrial tachycardia (AT) after a mean follow-up of 356 days.

Ten (10) device deficiencies were reported in 8 subjects, none of which were deemed serious or resulted in any associated AEs in subjects. Of the ten deficiencies, one device deficiency was related to a 3rd party guidewire. All procedures were completed as planned and all subjects were successfully treated. All deficiencies were investigated and most resolved with several others under ongoing investigation.

Conclusion: These results support the safety and feasibility of the FARAPULSE Pulsed Field Ablation System in the treatment of patients with PAF, with a low rate of primary AEs through 7 days, a high rate (100%) of procedural success and a rate of arrhythmia recurrence consistent with other technologies.

1.4.2 The PEFCAT Study

FARAPULSE, Inc. has completed enrollment in a two-center single arm open label safety and feasibility study[29] of the treatment of PAF at Na Homolce Hospital in Prague, Czech Republic and Hôpital Cardiologique du Haut-Leveque in Pessac, France under the "PEFCAT" Protocol, CS0267. This study was conducted using the FARAPULSE Pulsed Field Ablation System, very similar in function to the system which will be used in the IDE investigation.

Clinical investigation population: Subjects with documented drug-resistant (Class I to IV) symptomatic PAF who have had ≥ 2 episodes within 6 months of enrollment.

Methodology: In this pre-market, multi-center study, subjects who had signed the informed consent underwent baseline assessment, received treatment with the investigational device and were assessed prior to discharge, and at 30 days, 75 days, 6 months and 12 months following the index procedure. A remapping procedure was required as part of the 75-day assessment. A core laboratory analyzed ECG data from the EMs and Holter monitors. AEs were reviewed and where necessary adjudicated by the CEC.

Results: A total of 71 subjects enrolled and were treated in this study with a mean age of 57.2±10.5 years. A majority of study subjects were male, 78.9% (56/71).

The primary safety endpoint of the study was a composite safety endpoint including early-onset and late-onset events. One subject had a prolonged hospitalization for a 1.5mm AV fistula between the right superficial femoral artery and the right common femoral vein that resolved during 5 days of hospitalization. A second subject had a pericardial effusion following a protocol-specified remap procedure that included PFA, which resolved after drainage. The proportion of subjects with one or more composite safety events was 2.8% (2/71).

The primary feasibility endpoint of the study was Acute Procedural Success, defined as the percutaneous endocardial creation of a complete, electrically isolating set of lesions around the ostia of the pulmonary veins (PVs) using the FARAPULSE Pulsed Field Ablation System during the first procedure, as clinically assessed by entrance and/or exit block performed ≥ 20 minutes after the last PVI lesion is made. The procedural success rate was 100% (71/71).

Secondary safety endpoints included the rate of device or procedure-related SAEs at 30 days, 75, days, 6 months and 12 months, with reported rates between 0.0% and 4.2%. Additional secondary safety endpoint results at 12 months included: stroke/CVA (0.0% [0/71]), transient ischemic attack (TIA) (0.0% [0/71]), major bleeding related to anticoagulation treatment (0.0% [0/71]), cardioversion (5.6% [4/71]) and arrhythmia-related hospitalization (7.0% [5/71]).

No PVS, esophageal lesions or phrenic nerve impairment was observed in any subject.

Chronic Procedural Success (CPS) was defined as persistent electrical isolation of all initially ablated PVs assessed during an electroanatomical mapping procedure performed 75 days following the index procedure. The rate of Chronic Procedural Success was found in 74.2% (46/62) of treated and remapped subjects.

Therapeutic Success was defined as freedom from post-blanking AF, AFL or AT, or post-blanking ablation for AF, AFL or AT using the study device, or ablation for AF, AFL or AT with a non-study device at any time. The overall rate of Therapeutic Success was 67.6% (46/68); for subjects taking antiarrhythmic drugs (AADs) the rate was 51.9% (14/27) and for subjects not taking AADs 78.0% (32/41).

Sixty-eight (68) of 71 subjects remained in the study past Day 90 and as of the cut-off date for this analysis 54/68 (79.4%) were free from recurrent arrythmia through a mean follow-up of 325 days.

For the 71 enrolled subjects, 279 veins were treated at the index procedure and 100% (279/279) were successfully isolated. Of subjects that attended the 75-day remapping procedure, 90.9% (221/243) were durably isolated.

Device performance was generally excellent, with 16 device deficiencies reported in 12 subjects, none of which were deemed serious or resulted in any associated AEs in subjects. All procedures were completed as planned and all subjects were successfully treated. All deficiencies were investigated and most resolved with several others under ongoing investigation.

Conclusion: These results support the safety and feasibility of the FARAPULSE Pulsed Field Ablation System in the treatment of patients with PAF, with a low rate of acute and long-term primary safety endpoint events and a high rate (100%) of procedural success.

1.4.3 The PEFCAT II Study

FARAPULSE has completed enrollment in the multicenter, single arm open label PEFCAT II expanded safety and feasibility study[30] of the FARAPULSE Pulsed Field Ablation System as well as the FARAFLEX Pulsed Field Ablation Catheter. Subjects were enrolled at both the Na Homolce Hospital in Prague, Czech Republic and the 'University Hospital in Split Croatia under the "PEFCAT II" Protocol, CS0571. This study investigated PVI and cavo-tricuspid isthmus (CTI) ablation using the FARAWAVE and FARAFLEX Pulsed Field Ablation Catheters.

Clinical investigation population: Subjects with documented drug-resistant (Class I to IV) symptomatic PAF who have had ≥ 2 episodes within 6 months of enrollment.

Methodology: In this pre-market, multi-center study, subjects who had signed the informed consent underwent baseline assessment, received treatment with the investigational device and were assessed prior to discharge, and at 30 days, 75 days, 6 months and 12 months following the index procedure. A remapping procedure was required as part of the 75-day assessment. A core laboratory analyzed ECG data from the EMs and Holter monitors. AEs were reviewed and where necessary adjudicated by the CEC.

Results: A total of 10 subjects enrolled and were treated in this study with a mean age of 56.0±14.2 years. There was equal number of males 50.0% (5/10) and females 50% (5/10).

The primary safety endpoint of the study was a CSE including early-onset and late-onset events. No primary events occurred giving a rate of 0.0% (0/10).

The primary feasibility endpoint of the study was acute procedural success, defined as above. The procedural success rate was 100% (10/10).

Secondary safety endpoints included the rate of device or procedure-related SAEs, stroke, cardioversion and arrhythmia-related hospitalizations. The rates of these events were 0.0% (0/10).

CPS – defined as persistent electrical isolation of all initially ablated PVs – was found in 77.8% (7/9) of subjects.

Acute CTI Success – defined as the creation of bi-directional electrical block across the cavotricuspid isthmus – was found in 100% (4/4) of subjects undergoing CTI ablation.

Therapeutic Success – defined as freedom from occurrence of AF, AFL or AT, or post-blanking ablation for AF, AFL or AT using the study device, or ablation for AF, AFL or AT with a non-study device at any time – was 80.0% (8/10), 0.0% (0/1) in

subjects on AADs and 88.9% (8/9) in subjects off AADs, at a mean follow-up of 200 days.

For the 10 enrolled subjects, 39 veins were treated at the index procedure and 100% (39/39) were successfully isolated. For subjects that underwent the 75-day remapping procedure, 94.3% (33/35) of treated PVs were durably isolated.

There have been no device deficiencies reported for this study through the analysis date.

Conclusion: These results support the safety and feasibility of the FARAPULSE Pulsed Field Ablation System in the treatment of patients with PAF, with a rate of 0.0% for acute and long-term primary safety endpoint events and a high rate (100%) of procedural success.

1.4.4 Clinical Sub-Studies

Several investigator-initiated sub-studies were undertaken during the clinical investigations cited above.

- **Esophageal Assessment:** Thirty-eight (38) subjects enrolled in the PEFCAT study underwent esophagogastroduodenoscopy following ablation using the FARAWAVE Pulsed Field Ablation Catheter to isolate all PVs.[31]

  None (0%) of these studies revealed any ablation-related findings.

  In another study of imaged PVs, Cochet et al compare post-procedure lesion imaging from subjects receiving FARAPULSE PFA, radiofrequency and cryoballoon ablation for PVI. Consistent with its underlying mechanism, FARAPULSE PFA demonstrated no gadolinium enhancement of the esophagus suggestive of injury (0/18 subjects). Radiofrequency (6/16 subjects) and cryoballoon (4/7 subjects) ablation did create signals for esophageal injury on magnetic resonance imaging (MRI).[32]

  Phrenic Nerve Assessment: An analysis of the first 117 PFA subjects with PAF who underwent PVI using the FARAWAVE Pulsed Field Ablation Catheter showed 100% of treated veins were isolated acutely. Pre- and post-ablation phrenic functional testing was performed either by catheter pacing proximal to the region of ablation or by free inspiration fluoroscopic imaging of the diaphragm.

  No subject (0%, 0/117) showed any diminution of phrenic function.[33]

- **Pulmonary Vein Morphology:** Data regarding baseline and 3-month computed tomography (CT) imaging from IMPULSE and PEFCAT (PFA ablated PVs) and TOCCASTAR and HEARTLIGHT (control subjects with RF ablated PVs) was re-analyzed and compared.[34]

  A total of 303 PVs showed that the average percent change in PV ostial diameters was reduced significantly more in RF subjects compared with PFA subjects ($p < 0.001$). When analyzed in standardized percentile change

categories, the distribution of size changes was significantly worse in RF-treated PVs compared with PF-treated PVs ($p < 0.001$).

Table 1 Impact of Ablation Energies on 3-Month PV Dimensions

Ostial % diameter change	RFA PVs	PFA PVs	p-value
Long axis	-11.8 ± 16.3	+1.7 ± 9.9	< 0.001
Short axis	-12.7 ± 18.8	+3.4 ± 12.7	< 0.001

Frequency Distribution of PV Dimensional Change					
Energy	**Total**	**Mild (30-50%)**	**Moderate (50-70%)**	**Severe (70-100%)**	**p-value**
RFA (n=166)	14.5% (24)	11.4% (19)	1.8% (3)	1.2% (2)	< 0.001
PFA (n=137)	0.7% (1)	0.7% (1)	0% (0)	0% (0)	

PV = pulmonary vein.
Kuroki et al, Ostial Dimensional Changes after PVI: PFA vs RFA. E-published Heart Rhythm Journal 2020.

- **Peri-Procedural Brain MRI:** Eighteen (18) subjects enrolled in the IMPULSE and PEFCAT studies have undergone peri-procedural post-ablation brain MRI scans to assess for silent cerebral events (SCEs) and/or silent cerebral lesions (SCLs).

  Two of these subjects (2/18, 11%) showed diffusion-weighted positive lesions (SCEs) at approximately one day post procedure. One of these subjects, with a prior history of TIA, experienced a possible TIA one day post procedure presenting as a complaint of 15 minutes of difficulty speaking that was inapparent to observing medical staff; this event was captured in the AE dataset as a TIA.[35]

These results support the safety and performance of the system.

1.5 Rationale for Conducting This Pivotal Study

Catheter ablation for PAF with a variety of energy sources and catheter configurations has been demonstrated to be a safe and effective procedure. The FARAPULSE Pulsed Field Ablation System has undergone preclinical and clinical testing to demonstrate its preliminary safety and effectiveness for isolating PVs quickly and with minimal complications, using a standard catheter-based endocardial procedure. The System has undergone preclinical testing in representative models to demonstrate that it can isolate PVs and create other cardiac lesions quickly, durably and with minimal complications, using a standard catheter-based endocardial procedure. Clinical data from 131 endocardially ablated human subjects demonstrates the creation durable lesions when assessed at 75-day remapping procedures, freedom from recurrent PAF in greater than 80% of subjects and an excellent safety profile.

This pivotal study constitutes the multicenter randomized study of FARAPULSE PFA technology compared with existing RFA and CBA technologies for marketing approval in the United States and other countries.

1.6 Risks, Benefits and Mitigation

1.6.1 Potential Risks

As detailed in **Section 1.4**, the risk profile associated with the FARAPULSE Pulsed Field Ablation System and the ablation procedure is expected to be consistent with similar devices currently in clinical use for percutaneous cardiac ablation for treatment of PAF.

The FARAPULSE Pulsed Field Ablation System utilizes PFA to produce continuous transmural cardiac lesions to treat AF using an ablation procedure that is similar to other commercially available percutaneous ablation catheters. More specifically:

- The device system is used during percutaneous endocardial ablation procedures like other commercially approved catheter systems.
- The device system is composed of similar biocompatible materials.
- The device uses standard percutaneous techniques for ablation procedures.
- The device utilizes a specialized generator to deliver ablation energy.
- The device has similar procedural properties as compared to the planned commercially approved control devices:
    - The device is similar to CBA devices in that it circumferentially ablates an entire PV during each delivery
    - The device can be manipulated in the same manner as RFA and CBA catheters
    - The device uses metal electrodes for ablation energy delivery (RF catheters) and sensing (RFA and CBA catheters.)

A difference between the FARAPULSE Pulsed Field Ablation System and other commercially approved thermal AF ablation systems is that PFA uses non-thermal IRE energy for tissue ablation, delivered through electrodes embedded in the FARAPULSE Pulsed Field Ablation Catheter for delivery of such energy in the PVs.

Based on the available preclinical and clinical data and the substantial similarities to other approved ablation technologies, the anticipated risks are generally equivalent in type, severity and frequency to those associated with commercially released systems being used for percutaneous cardiac ablation procedures.

1.6.2 Potential Benefits

There are no *guaranteed* benefits from participation in this study. European feasibility studies of 131 PAF subjects have shown early valid scientific evidence for safety and effectiveness similar to existing approved technologies.

This study may have the following *potential* benefits:

- To provide treatment to subjects with PAF using an investigational device which has demonstrated the ability to isolate PVs endocardially, to reduce the subsequent occurrence of symptomatic AF in treated subjects and potentially to reduce the risk for severe ablation complications associated with thermal ablation such as phrenic nerve palsy or atrio-esophageal fistula.

- To provide information gained from the conduct of this study that may benefit other persons with the same medical condition.
- To generate additional data demonstrating that the endocardial creation of electrically isolating lesions via PFA applied using the FARAPULSE Pulsed Field Ablation System is a safe and effective treatment for drug-resistant, recurrent, symptomatic PAF.

1.6.3 Risk Mitigation and Summary

FARAPULSE has conducted bench, in-vivo and clinical testing to optimize safe use of the device during clinical investigation and the devices are in compliance with the applicable requirements of the 21 CFR 820 Subpart C, Design Controls of the Quality System Regulation, ISO 13485 and ISO 14971.

The clinical study is designed to mitigate risk by the selection of skilled Investigators, experienced sites, eligibility criteria to eliminate higher risk subjects and the carefully controlled design of the clinical investigational plan. Careful monitoring and comprehensive oversight by independent monitors and physicians are also planned.

The potential therapeutic improvement associated with the FARAPULSE Pulsed Field Ablation System has been recognized by the FDA, which was granted Breakthrough Pathway status to the technology in 2019.

To receive this Breakthrough Pathway designation, the FDA was required to find that FARAPULSE Pulsed Field Ablation System:

> "… offers significant advantages over existing approved or cleared alternatives, including the potential, compared to existing approved alternatives, to reduce or eliminate the need for hospitalization, improve patient quality of life, facilitate patients' ability to manage their own care (such as through self-directed personal assistance), or establish long-term clinical efficiencies."

Based on the Sponsor's evaluation of the investigational devices and their performance and the design of this pivotal investigation, the Sponsor has conducted an analysis of the benefits and risks of the FARAPULSE Pulsed Field Ablation System for the treatment of PAF. The conclusion of this review is that this investigation is justified because the overall potential benefit to the population outweighs the risks and foreseeable risks which have been mitigated as fully described in this submission.

2. Investigational Devices

2.1 Names of Investigational Devices

The FARAPULSE Pulsed Field Ablation System is comprised of the following:

- FARAWAVE Pulsed Field Ablation Catheters and Connection Cables
- FARASTAR Pulsed Field Ablation Generator, including
  - FARASTAR Stimulation Module
  - FARASTAR Recording System Module
  - Associated cables
- FARADRIVE Steerable Sheath

2.2 Intended Use

The FARAPULSE Pulsed Field Ablation System is indicated for the treatment of drug-resistant, recurrent, symptomatic paroxysmal atrial fibrillation.

2.3 FARAPULSE Pulsed Field Ablation System

The FARAPULSE Pulsed Field Ablation System consists of the FARAWAVE Pulsed Field Ablation Catheter, the FARASTAR Pulsed Field Ablation Generator and the FARADRIVE Steerable Sheath. These components, sub-components and model numbers are listed in **Table 2** and depicted in **Figure 1**

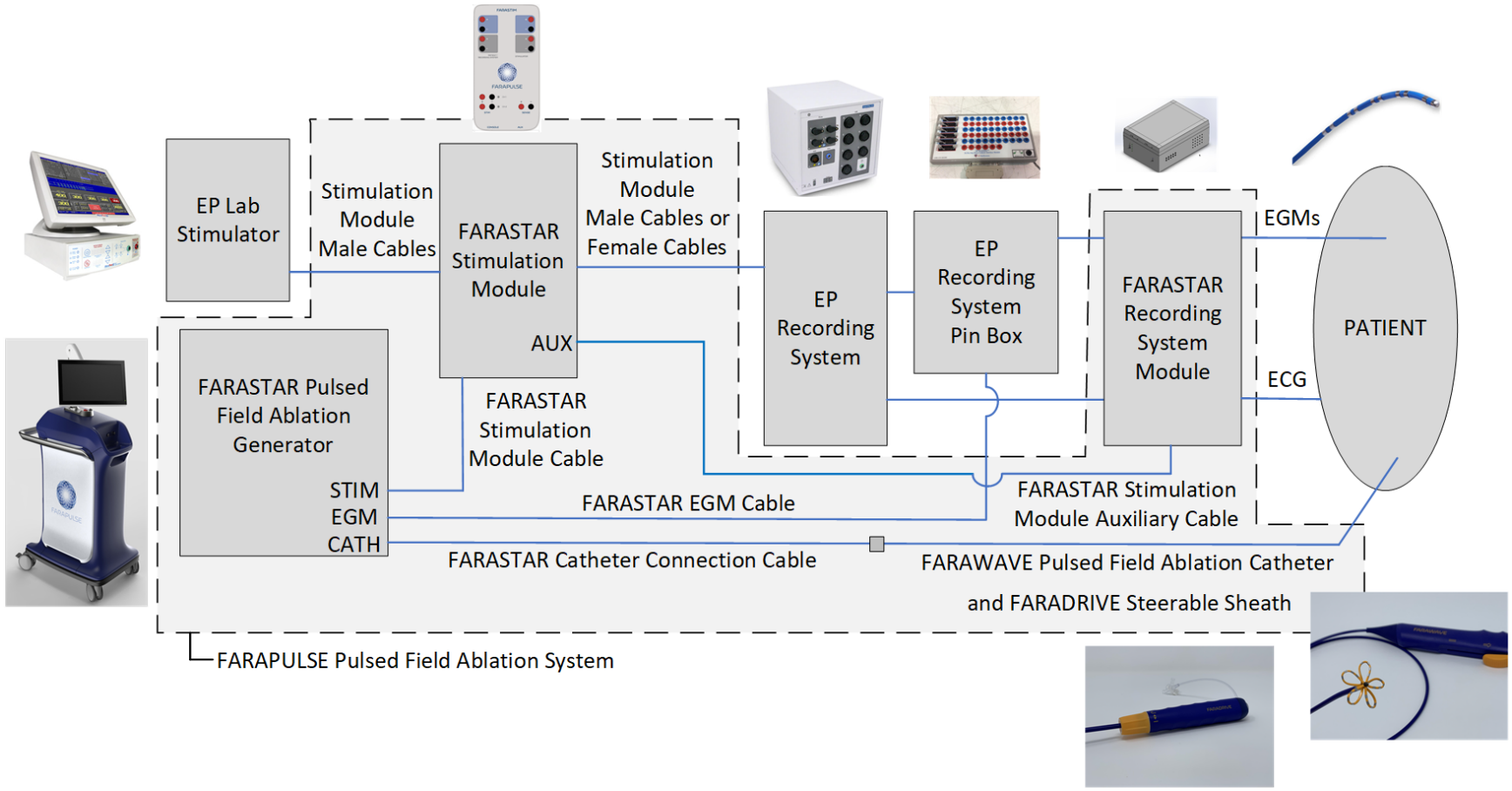
Table 2 FARAPULSE Pulsed Field Ablation System Components

Component	Subcomponents	Model Numbers
FARAWAVE Pulsed Field Ablation Catheter	1. FARAWAVE Pulsed Field Ablation Catheter (fully deployed diameters of 31mm and 35mm) 2. FARASTAR Catheter Connection Cable	41C601 (31mm) 41C602 (35mm) 41C604
FARASTAR Pulsed Field Ablation Generator and related equipment	1. FARASTAR Pulsed Field Ablation Generator 2. FARASTAR Stimulation Module 3. FARASTAR Stimulation Module Cable 4. FARASTAR EGM Cable 5. FARASTAR Recording System Module 6. FARASTAR Stimulation Module Auxiliary Cable 7. FARASTAR Stimulation Module Male Cable 8. FARASTAR Stimulation Module Female Cable 9. FARASTAR Stimulation Module Y-Cable – Long 10. FARASTAR Stimulation Module Y-Cable – Short 11. FARASTAR Recording System Module Catheter Pin Cable 12. FARASTAR Accessories Cable Set	61C601 61C603 61C604 61C605 61C607 61C608 61C609 61C610 61C611 61C612 61C613 61C606
FARADRIVE Steerable Sheath	FARADRIVE Steerable Sheath and Dilator	21C602

For Instructions for Use (IFU) documentation please refer to the following:

- FARAWAVE Pulsed Field Ablation Catheter Instructions for Use - LBL0913
- FARASTAR Pulsed Field Ablation Generator System Use Manual - LBL0914
- FARADRIVE Steerable Sheath Instructions for Use - LBL0771

Figure 1 FARAPULSE Pulsed Field Ablation System Components



AUX = Stimulation Module output signal that is active during energy delivery and is used by the Recording System Module to disconnect the patient ECG and Diagnostic catheter electrodes from the EP Lab Recording system during PFA to reduce the risk of interference, **CATH** = Generator PFA output to FARAWAVE catheter, **ECG** = electrocardiogram signals, **EGM** = Generator output of intracardiac signals from the FARAWAVE Electrodes when not delivering energy; disconnected from FARAWAVE during energy delivery, **EGMs** = electrogram signals, **EP** = Electrophysiology, **Lab** = laboratory, **STIM** = Generator output of two internal stimulation channels and a trigger output signal active during energy delivery.

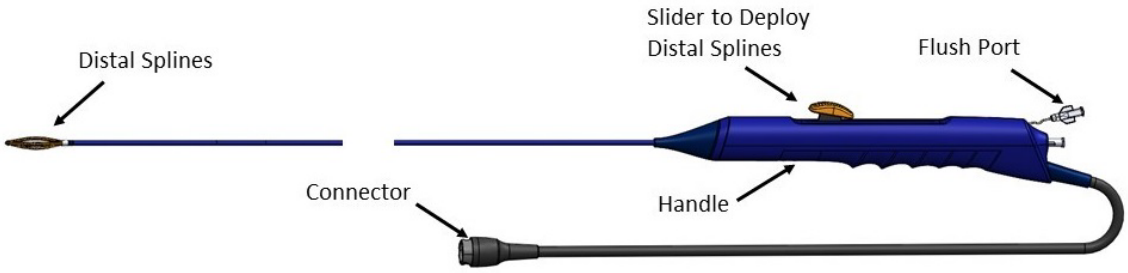
2.3.1 FARAWAVE Pulsed Field Ablation Catheter

The FARAWAVE Pulsed Field Ablation Catheter consists of 2 components: The FARAWAVE Pulsed Field Ablation Catheter and the FARASTAR Catheter Connection Cable, which are used together. Both components are sterile and single use only.

The FARAWAVE Pulsed Field Ablation Catheter is offered in 2 different sizes (31-mm [41C601] and 35-mm [41C602] fully deployed diameters) to accommodate varying PV anatomy. Selection of either catheter will be at the Investigator's discretion.

The FARAWAVE Pulsed Field Ablation Catheter is a multi-electrode catheter that connects electrically to the FARASTAR Pulsed Field Ablation Generator (**Figure 2**). It consists of a distal section with electrodes arranged on splines, a shaft section and a proximal handle with a manually operated deployment control.

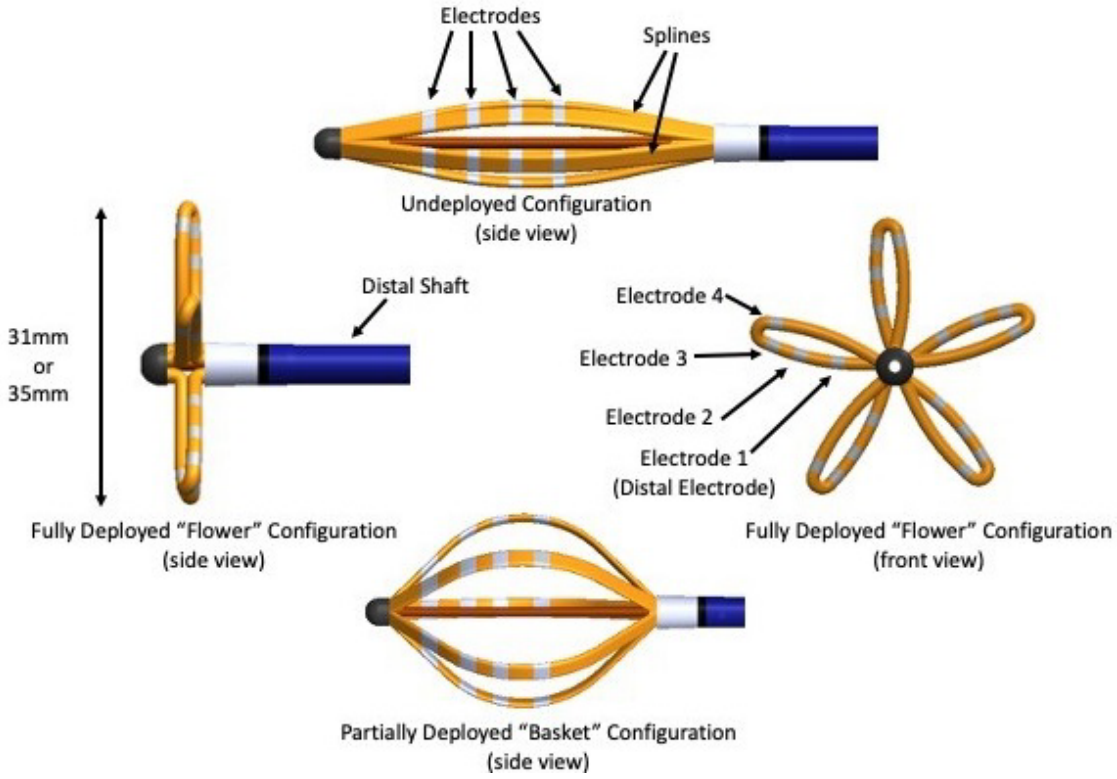
Figure 2 FARAWAVE Pulsed Field Ablation Catheter



(Continued next page)

The FARAWAVE Pulsed Field Ablation Catheter has five (5) variably deployable splines. The five splines are undeployed during insertion and removal and during use can deploy continuously from an undeployed state through a basket-shaped configuration to a fully deployed flower-shaped configuration with five petals (See **Figure 3**).

Figure 3 FARAWAVE Pulsed Field Ablation Catheter - Deployed States



Each spline has 1 electrode that is separately wired from the others on that spline to facilitate connection to a mapping or recording system via a cable supplied with the system. The handle includes a flush port for saline infusion, a deployment control knob with a guidewire lumen hub that can be connected to a hemostasis valve and a short cable that terminates in a single connector for attachment to the FARASTAR Catheter Connection Cable. The other end of the Connection Cable attaches to the front panel of the FARASTAR Pulsed Field Ablation Generator. The Connection Cable is packaged sterile and is single-use only. The PFA energy is delivered from the FARASTAR Pulsed Field Ablation Generator over the set of ablation catheter electrodes.

Additional details are provided in the IFU LBL0913 for the specific use and procedural steps of the FARAWAVE Pulsed Field Ablation Catheter.

2.3.2 FARASTAR Pulsed Field Ablation Generator

The FARASTAR Pulsed Field Ablation Generator consists of the following components:

- FARASTAR Pulsed Field Ablation Generator
- FARASTAR Stimulation Module
- FARASTAR Stimulation Module Cable
- FARASTAR EGM Cable
- FARASTAR Recording System Module
- FARASTAR Stimulation Module Auxiliary Cable
- FARASTAR Stimulation Module Male Cable
- FARASTAR Stimulation Module Female Cable
- FARASTAR Stimulation Module Y-Cable – Long
- FARASTAR Stimulation Module Y-Cable – Short
- FARASTAR Recording System Module Catheter Pin Cable

The FARASTAR Pulsed Field Ablation Generator is a 12-channel output unit that generates a pulsed voltage waveform that can be delivered to the FARAWAVE Pulsed Field Ablation Catheter. The user selectable voltage options for the FARAWAVE Pulsed Field Ablation Catheter are 1800V, 1900V and 2000V.

The FARASTAR Pulsed Field Ablation Generator includes a 2 channel Cardiac Stimulator that can be connected to user supplied pacing catheters through the FARASTAR Stimulation Module. While the Generator may be synchronized with the Cardiac Stimulator outputs, that feature will not be necessary in this clinical study.

Details regarding the generator are provided in the FARASTAR Pulsed Field Ablation Generator User Manual LBL0914.

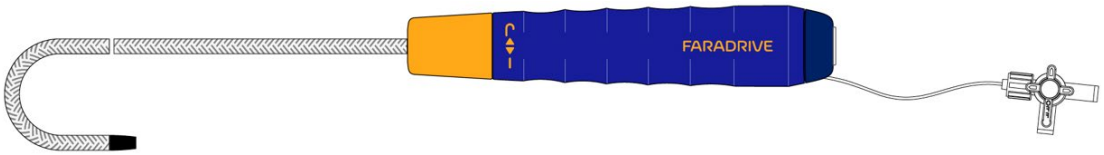
2.3.3 FARADRIVE Steerable Sheath

The FARAWAVE Pulsed Field Ablation Catheter is used exclusively with the FARADRIVE Steerable Sheath.

The FARADRIVE Steerable Sheath consists of two (2) primary components, the Steerable Sheath and the Dilator, which are used together. Both components are sterile and single use only.

The FARADRIVE Steerable Sheath is comprised of a distal steerable section and a shaft section which connect to the handle. The handle includes a knob to control the deflection of the distal tip and a flush port for infusion of saline or contrast. The Dilator is intended for insertion through the sheath lumen and includes a shaped tip for dilation for vascular or chamber access (**Figure 4**). Details regarding the sheath are provided in the FARADRIVE Steerable Sheath IFU LBL0771.

Figure 4 FARADRIVE Steerable Sheath



2.4 Device Accountability

The FARAPULSE Pulsed Field Ablation System will be stored in a secure location and access will be controlled. Records will be maintained to document the physical location of inventory from shipment to investigational sites by Sponsor or contract manufacturing facility through use and / or return or disposal.

The site will be responsible for maintaining a Device Accountability Log provided by the Sponsor or its designated representative. At a minimum the following will be recorded: date of receipt, FARAPULSE Pulsed Field Ablation System components identification number (Generator, Ablation Catheter and Steerable Sheath lot and / or serial number), expiration date, date of use, subject unique identification code and date of disposal or return of the device.

If there is a product Device Deficiency / Malfunction or other need to return the system or system components to the Sponsor or contract manufacturer, the Sponsor or designee will be contacted for safe product disposal and/ or return details. Appropriate case report forms (CRFs) will be completed in the event of a Device Deficiency / Malfunction.

The Investigator is responsible for ensuring that the investigational devices are used only under the Investigator's supervision and are only used according to this protocol, training and any subsequent amendments or updates. The Investigator will not supply an investigational device to any person not authorized and trained to participate in the study. The Investigator shall document on the CRFs the lot numbers and / or serial numbers of the devices used during each case.

2.5 Return of Devices

All unused investigational devices will be returned to the Sponsor or designee upon completion of the clinical study. Any investigational device that does not meet performance specifications will also be returned to the Sponsor or designee for analysis per Sponsor procedures. The Investigator or designated representative is responsible for device accountability and disposition of all used and unused devices. The Sponsor or its designated representative will conduct device reconciliation at the completion of subject enrollment or at the conclusion of the study.

3. Study Population

3.1 Subject Recruitment

Subjects will be recruited from the clinical practice of, or by referral to, the Investigators. Modest compensation may be provided to Enrolled Subjects for their participation in the study and travel costs may be reimbursed.

3.2 Subject Screening

3.2.1 Screening Procedures

Routine clinical evaluations that would be performed as part of the normal clinical care of patients being considered for participation in this study may be performed prior to informed consent and the data used as part of the screening assessment. If the subject is subsequently consented and enrolled in the study, the results of such tests may be used as study data and if used will be entered on the appropriate CRF.

Site personnel will use care in reviewing the patient's clinical status in relation to each inclusion and exclusion criterion and ensure that appropriately documented results are available prior to concluding that the subject meets study inclusion and exclusion criteria.

Screening procedures do not have to be completed on a single day.

Subjects who become Screen Failures at any time may not be enrolled, randomized or participate in any further study procedures unless their disqualifying finding(s) becomes fully resolved.

3.2.2 Screening Log

A Screening Log will be maintained for all consented subjects who undergo formal screening for possible enrollment, identified by a Subject Screen Number, noting the date screening was completed and the reason(s) for rejection (the specific inclusion / exclusion criteria failed), or that the subject was enrolled. The Investigator will maintain the information linking the Subject Screen Number to subject identifiers.

3.3 Study Eligibility Criteria

3.3.1 Inclusion Criteria

Patients are required to meet <u>all</u> the following inclusion criteria to participate in this study:

1. Patients with drug-resistant symptomatic PAF meeting <u>all</u> the following criteria:
    a. <u>Paroxysmal:</u> AF that terminates spontaneously or with intervention within 7 days of onset.
    b. <u>Frequency</u>:
        i. Physician documentation of recurrent PAF (two or more episodes) within 6 months, AND
        ii. At least one (1) documented episode by a recording such as ECG, EM, Holter monitor or telemetry strip within 12 months of enrollment.

c. Drug failed: Failed AAD treatment, meaning therapeutic failure of at least one (1) AAD (Class I to IV) for efficacy and / or intolerance.

2. Patients who are ≥ 18 and ≤ 75 years of age on the day of enrollment.
3. Patients who are willing and capable of:
   a. Providing informed consent to undergo study procedures, AND
   b. Participating in all examinations and follow-up visits and tests associated with this clinical study.

3.3.2 Exclusion Criteria

Patients will be excluded from participating in this study if they meet any one of the following exclusion criteria:

1. AF that is any of the following:
   a. Persistent (both early and longstanding) by diagnosis or continuous duration > 7 days
   b. Requires four (4) or more direct-current cardioversions in the preceding 12 months
   c. Secondary to electrolyte imbalance, thyroid disease, alcohol or other reversible / non-cardiac causes
2. Any of the following atrial conditions:
   a. Left atrial anteroposterior diameter ≥ 5.5 cm (by MRI, CT or TTE)
   b. Any prior atrial endocardial or epicardial ablation procedure, other than right sided cavotricuspid isthmus ablation or for right sided SVT
   c. Any prior atrial surgery
   d. Intra-atrial septal patch or interatrial shunt
   e. Atrial myxoma
   f. Current LA thrombus
   g. LA appendage closure, device or occlusion, past or anticipated
   h. Any PV abnormality, stenosis or stenting (common and middle PVs are admissible)
3. At any time, one (1) or more of the following cardiovascular procedures, implants or conditions:
   a. Sustained ventricular tachycardia or any ventricular fibrillation
   b. Hemodynamically significant valvular disease:
      i. Valvular disease that is symptomatic
      ii. Valvular disease causing or exacerbating congestive heart failure
      iii. Aortic stenosis: if already characterized, valve area < 1.5cm or gradient > 20 mm Hg
      iv. Mitral stenosis: if already characterized, valve area < 1.5cm or gradient > 5 mm Hg
      v. Aortic or mitral regurgitation associated with abnormal LV function or hemodynamic measurements
   c. Hypertrophic cardiomyopathy
   d. Any prosthetic heart valve, ring or repair including balloon aortic valvuloplasty

   e. Pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices
   f. Any IVC filter, known inability to obtain vascular access or other contraindication to femoral access
   g. History of rheumatic fever
   h. History of congenital heart disease with any residual anatomic or conduction abnormality
4. Any of the following procedures, implants or conditions:
   a. At baseline:
      i. New York Heart Association (NYHA) Class III or IV
      ii. LVEF < 40%
      iii. Symptomatic hypotension
      iv. Uncontrolled hypertension (SBP > 160 mmHg or DBP > 95 mmHg on two (2) BP measurements at baseline assessment)
      v. Symptomatic bradycardia
      vi. Implantable loop recorder or insertable cardiac monitor*
   b. Within the 3 months preceding the Consent Date:
      i. Myocardial infarction
      ii. Unstable angina
      iii. Percutaneous coronary intervention
      iv. Heart failure hospitalization
      v. Treatment with amiodarone
      vi. Pericarditis or symptomatic pericardial effusion
      vii. Gastrointestinal bleeding
   c. Within the 6 months preceding the Consent Date:
      i. Heart surgery
      ii. Stroke, TIA or intracranial bleeding
      iii. Any thromboembolic event
      iv. Carotid stenting or endarterectomy
5. Diagnosed disorder of blood clotting or bleeding diathesis
6. Contraindication to, or unwillingness to use, systemic anticoagulation
7. Patient who is not on anticoagulation therapy for at least 3 weeks prior to the ablation procedure
8. Contraindication to both CT and MRI
9. Sensitivity to contrast media not controllable by premedication
10. Women of childbearing potential who are pregnant, lactating, not using medical birth control or who are planning to become pregnant during the anticipated study period
11. Medical conditions that would prevent participation in the study, interfere with assessment or therapy, significantly raise the risk of study participation, or modify outcome data or its interpretation, including but not limited to:
    a. Body Mass Index (BMI) > 40.0

* If an implantable loop recorder or insertable cardiac monitor is explanted prior to study enrollment it must not be replaced for the duration of the subject's participation in the study.

b. Solid organ or hematologic transplant, or currently being evaluated for an organ transplant
c. Severe lung disease, pulmonary hypertension, or any lung disease involving abnormal blood gases or requiring supplemental oxygen
d. Renal insufficiency with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, or any history of renal dialysis or renal transplant
e. Active malignancy or history of treated malignancy within 24 months of enrollment (other than cutaneous basal cell or squamous cell carcinoma)
f. Clinically significant gastrointestinal problems involving the esophagus or stomach including severe or erosive esophagitis, uncontrolled gastric reflux, gastroparesis, esophageal candidiasis or active gastroduodenal ulceration
g. Active systemic infection
h. COVID-19 disease
    i. Current confirmed, active COVID-19 disease
    ii. Current positive test for SARS-CoV-2
    iii. Confirmed COVID-19 disease not clinically resolved at least 3 months prior to the Consent Date
i. Other uncontrolled medical conditions that may modify device effect or increase risk, including uncontrolled diabetes mellitus (HgbA1c > 8.0% if test result already obtained) or active alcohol abuse
j. Sleep apnea and:
    i. An apnea-hypopnea index (AHI) ≥ 15, or
    ii. An AHI of ≥ 5 and ≤14 with documented symptoms of excessive daytime sleepiness, impaired cognition, mood disorders or insomnia, or documented hypertension, ischemic heart disease or history of stroke,

    unless compliant with continuous positive airway pressure (CPAP) treatment.
k. Predicted life expectancy less than one (1) year

12. Clinically significant psychological condition that in the Investigator's opinion would prohibit the subject's ability to meet the protocol requirements.
13. Current or anticipated enrollment in any other randomized, interventional or FDA-regulated clinical study (data collection for registries or retrospective studies is permitted)
14. Employees / family members of:
    a. FARAPULSE or any of its affiliates or contractors
    b. The Investigator, sub-Investigators, or their medical office or practice, or healthcare organizations at which study procedures may be performed

3.4 Subject Status and Disposition Definitions

3.4.1 General Pre-Screening

Potential subjects screened for enrollment prior to signing informed consent who fail one (1) or more study eligibility criteria determined by routine clinical assessments or the medical record need not be documented.

3.4.2 COVID-19 Pre-Screening

Screening for COVID-19 status will follow each investigational site's then-current requirements.

Patients may proceed to informed consent and full screening unless any of the following conditions exist:

- They fail the investigational site's then-current requirements in relation to COVID-19 status and study participation.
- They currently have confirmed, active COVID-19 disease or a positive test for SARS-CoV-2.
- They have had confirmed COVID-19 disease not clinically resolved at least 3 months prior to the Consent Date.

The results of COVID-19 screening may be used as study data for any consented subject.

3.4.3 Screened Subjects

A Screened Subject is any subject who has not failed pre-screening and who has signed an informed consent. Each Screened Subject will be recorded in the Screening Log with the date of informed consent and the result of the screening process.

Should an AE occur that is associated with a screening procedure or test and with onset prior to randomization, it will be recorded in a Screening AE CRF. Such AEs are not part of the ADVENT Trial, its data or analyses and will not be entered into the study database. A listing and summary of Screened Subjects will be provided along with any screening-associated AEs.

3.4.4 Screen Failure Subjects

A Screen Failure Subject is any subject who has signed an informed consent and who is then excluded due to failure of one or more study eligibility criteria at any time before randomization.

Subjects who become Screen Failures will be recorded in the Screening Log including all eligibility criteria that were the cause of the Screen Failure. Screen Failure Subjects will have a Study Exit CRF completed on the date that Screen Failure is determined. No study data on events with an onset date after the Exit Date may be collected or included as part of the study database or analyses.

3.4.5 Enrolled Subjects

An Enrolled Subject is any subject who has signed the informed consent document AND who has been determined to meet all pre-procedural study eligibility criteria prior to randomization.

3.4.6 Roll-In Subjects

Roll-In Subjects are Enrolled Subjects who are treated with the FARAPULSE Pulsed Field Ablation System under the provisions of **Section 5.6**. Roll-In Subjects are not randomized and will be analyzed and reported separately.

3.4.7 Intent-to-Treat Subjects

An Intent-to-Treat (ITT) Subject is an Enrolled Subject who is randomized to either the Pulsed Field Group or the Thermal (Control) Group.

3.4.8 Safety Subjects

A Safety Subject is an ITT Subject who has had a study ablation catheter inserted into the body at an Index / Rescheduled Index Procedure.

3.4.9 Modified Intent-to-Treat Subjects

A Modified Intent-to-Treat (MITT) Subject is an ITT Subject who receives any energy delivery for PVI with the randomized endocardial ablation catheter at an Index / Rescheduled Index Procedure.

3.4.10 Completed Subjects

A Completed Subject is an ITT Subject who completes the Month 12 Assessment either in-person or remotely. The date on which the Month 12 Assessment is completed is the Completed Subject's Exit Date and a Study Exit CRF will be completed. No study data on events with an onset date after the Exit Date may be collected or included as part of the study database or analyses.

3.4.11 Incomplete Subjects

An Incomplete Subject is any ITT Subject who does not become a Completed Subject. Anticipated reasons for failure to become Completed Subjects include withdrawal of consent by a subject, death or incapacity of a subject, lost-to-follow-up (LTFU) status and termination by the Investigator.

A LTFU Subject is an ITT Subject who ceases to participate in study follow-up procedures or who fails to respond to contact attempts. The Investigator will attempt to contact such a subject 2 or more times within 60 days and if there is no return to study participation, the subject will be deemed LTFU. The Investigator will document that a minimum of two attempts were made to contact the subject, including sending a certified letter if current address is known, prior to terminating the subject from the study.

The date on which a subject is determined to be an Incomplete Subject is their Exit Date, and a Study Exit CRF will be completed including the reason for becoming an Incomplete Subject.

No study data on events with an onset date after the Exit Date may be collected or included as part of the study database or analyses. However, if an Incomplete Subject's exit is due to an AE, the Investigator should, if subject consent is documented, follow the subject until the AE has resolved or is considered stable, but in any case, not more than 390 days have passed since the Index / Rescheduled Index Procedure. The data related to that AE may be collected and included in the study database and analyses under such consent.

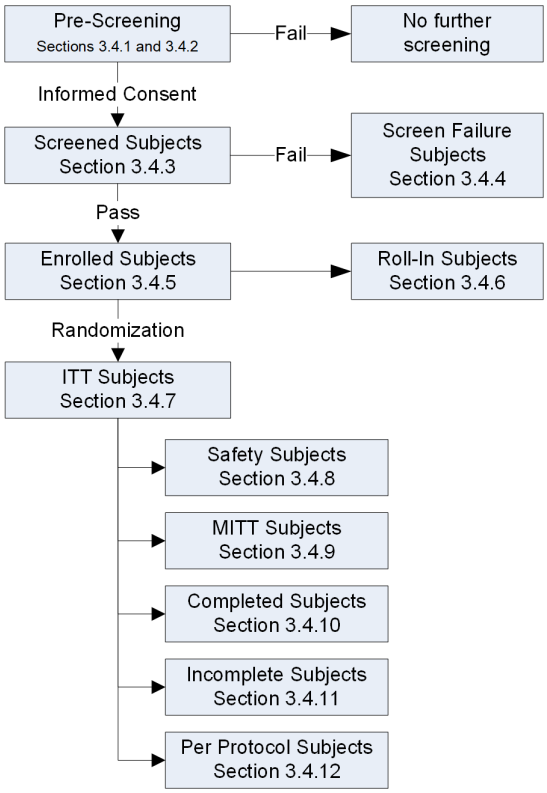
3.4.12 Per Protocol Subjects

A Per Protocol (PP) Subject is a Safety or ITT Subject without major protocol deviations that would affect the completeness, accuracy and reliability of the study data. Major protocol deviations[2] that exclude subjects from a PP Population are the following:

- Failure to meet any of the following study entry criteria:
  - Arrhythmia different than PAF (Inclusion Criterion 1)
  - Prior cardiovascular procedures, implants or conditions (Exclusion Criteria 3 and 4)
  - Medical conditions (Exclusion Criterion 11)
- Failure to receive the randomized ablation treatment for PVI as specified in this protocol (**Section 5.2** or **Section 5.3**)
- Receipt of a prohibited study drug (amiodarone, except intra-procedurally to control an arrhythmia)
- In addition, the data of Severe COVID-19 Subjects will be censored beginning on the Onset Date of infection.

3.5 Subject Disposition Chart

Figure 5 Subject Disposition Chart



MITT = modified intent-to-treat, **ITT** = intent-to-treat

[2] Major protocol deviations also include such events as failure of informed consent, confidentiality violations and actions that may affect the subject's rights, safety or well-being. These, while serious, generally do not impact the validity of data collected and so are not part of the per protocol exclusions for outcome assessment.

3.6 Subject Informed Consent

All subjects must provide documented informed consent using the Institutional Review Board (IRB)-approved informed consent form (ICF) / electronic informed consent form (eICF) before undergoing any study-related procedures. If electronic consent is utilized it will conform to the FDA Guidance Document "Use of Electronic Informed Consent, Questions and Answers", dated December 2016 (or subsequent revised versions as applicable).

Since it may become necessary during this study to access study-specific protected healthcare information from remote clinical sites, the ICF / eICF will include this permission in the consent process.

Subjects cannot be asked to sign the ICF / eICF until the study has been fully approved by the institution's IRB and the Sponsor or their clinical research organization (CRO) representative has received and reviewed the IRB-approved ICF / eICF. Subjects who meet the general eligibility criteria will be asked to sign an ICF / eICF as approved by the relevant regulatory authorities before any study-specific tests or procedures are performed.

The Investigator or a designated member of their staff should communicate with the subject to obtain written informed consent. As far as possible, non-technical language shall be used that is understandable to the subject. The background of the proposed study and the benefits and risks of the procedures and study should be explained. The subject should be provided with ample time to read the ICF / eICF and discuss it with their family and physician. The subject shall be informed that their participation in the clinical investigation is confidential. The ICF / eICF must be read and understood by the subject and the subject's questions answered. The ICF / eICF must be signed and dated by both the subject and physician / designee overseeing informed consent prior to subject enrollment and before the subject undergoes any study-related procedures. All subjects are to receive copies of their signed and dated ICF / eICF. A copy of the approved ICF / eICF along with a copy of each subject's signed ICF / eICF will be maintained by the Investigator in a designated clinical study administrative file or electronic record system. Subjects may not be consented after receiving any medication that might alter their ability to comprehend the consent form (e.g., sedatives, narcotics, etc.). Study personnel should explain that even if a subject agrees to participate in the study and signs the ICF / eICF, the subject may not be eligible to participate if the subject fails to meet the screening criteria.

Written informed consent must be obtained prior to performing any protocol-driven tests or any procedures that are not standard of care for a percutaneous ablation procedure that the subject is scheduled to undergo. Once written consent has been obtained, the subject will be entered on a Screening Log, which will be maintained at each site. All subjects who provide written informed consent will be entered into the Screening Log regardless of whether they are enrolled in the study.

3.7 Subject Enrollment

Subjects that meet all the eligibility criteria and are deemed suitable by the Investigator will be invited to participate in the study.

When initial screening indicates that the subject will likely meet the inclusion and exclusion requirements and agrees to participate in the study, formal written informed consent using the current IRB-approved ICF will be obtained.

Provisional subject enrollment occurs when the ICF has been signed. Enrollment is confirmed when all study eligibility requirements are determined to have been met.

If one or more of the required pre-enrollment assessments – including cardiac CT/MRI, transthoracic echocardiography (TTE), laboratory tests and ECG – have not been obtained prior to signing the ICF, then the enrollment is considered provisional until that assessment has been obtained and the criteria met.

Regardless of the sequence of ICF completion and pre-procedural enrollment assessments, if study eligibility criteria are not met, the subject is a Screen Failure and is not enrolled.

Study eligibility criteria are determined at the time of study entry. In the instance that information received after an Index Procedure / Rescheduled Index Procedure reveals that an inclusion or exclusion criterion – determined prior to the Index Procedure / Rescheduled Index Procedure to have been met – is found to have been incorrectly assessed, this does not change the enrolled status of the subject, who remains in the study.

Each Enrolled Subject will be assigned a unique study identification code to protect each subject's confidential health information. The unique study identification code will not include date of birth or subject's first and last initials and will be used to link study data and other study information to the subject in lieu of the subject name. The Subject Name Log will be used to link the unique study identity code to the subject and will be maintained at the site. This log will remain confidential and will not be provided to the Sponsor but only used for reference when monitoring at the study site.

3.8 Subject Randomization

Subjects excluding Roll-In Subjects – who are determined by the Investigator at the time of assessment to have met all pre-randomization inclusion and exclusion criteria, who have signed an ICF and who are scheduled for the Index Procedure – will be randomized. The study staff will confirm documented inclusion / exclusion success prior to requesting randomization.

3.9 Subject Completion or Exit

When a subject completes the study at the Month 12 Assessment, exceeds 390 days of follow-up without a Month 12 Assessment, or exits prior to such completion, they will return to standard medical care and a study termination/exit CRF will be completed, including the reason for exit.

Subjects may voluntarily withdraw from the study at any time for any reason. The Investigator may terminate the subject without subject consent at any time to protect the subject's rights, safety or welfare. Subjects leaving the study prior to completion will continue to receive appropriate medical care without prejudice.

4. Study Summary and Schedule

4.1 Study Objective and Hypothesis

The primary objective of this pivotal study is to determine whether there is valid scientific evidence that endocardial ablation using the FARAPULSE Pulsed Field Ablation System is both safe and effective for treating drug-resistant symptomatic PAF.

The primary clinical hypotheses of this pivotal study are that PVI created by the FARAPULSE Pulsed Field Ablation System is not inferior in safety and effectiveness to treatment with approved catheter ablation technologies (force-sensing radiofrequency or cryoballoon ablation) in the treatment of drug-resistant symptomatic PAF.

4.2 Study Overview

This is a prospective, adaptive, multi-center, randomized safety and effectiveness pivotal study comparing the FARAPULSE Pulsed Field Ablation System with standard of care ablation with force-sensing RF catheters and cryoballoon catheters indicated for the treatment of PAF. Subjects will undergo ablation for PVI with the randomized treatment and if indicated CTI ablation using an RF catheter. Subjects will be followed at 7 days (telephonic), 30 days, 90 days, 6 months and 12 months for AEs, recurrence of arrhythmia after a 90-day Blanking Period and other relevant outcome measures.

4.3 Subject Confidentiality

Enrolled Subjects will be assigned a unique, pseudo-anonymous identifier that will be used to maintain confidentiality of each subject's medical information. Subject names will not be captured on the CRFs. All subject identifiers except the unique pseudo-anonymous identifier should be redacted from any images or other data submitted from the participating site to the Sponsor or the Sponsor's designated reviewers for analysis. All information concerning subjects or their participation in this study will be considered confidential. Only the authorized Sponsor, designated representative personnel, designated consultants and regulatory agencies will have access to these confidential files.

4.4 Sample Size Summary

A maximum of 900 subjects may be enrolled in this study.

Roll-In Subjects: Up to 105 subjects (the first 1 to 3 Enrolled Subjects at each site) will be treated with the FARAPULSE devices in a manner consistent with the randomized Pulsed Field Group and will be analyzed and reported separately.

ITT Subjects: An estimated 450 MITT Subjects will be required to support the proposed non-inferiority outcomes. Interim sample size re-estimation may decrease this number to 350 or increase it to a maximum of 750. Up to 45 additional subjects (6%) may be enrolled to compensate for those ITT Subjects who do not meet the criteria for the MITT Population.

4.5 Investigational Sites

The clinical study will be conducted at up to 35 qualified investigational sites in the United States. No site may enroll more than 45 ITT Subjects (excludes Roll-In Subjects and ITT Subjects who do not qualify for the MITT population) with an intended minimum of 10 subjects per site. Should interim sample size re-estimation lead to an increase in the number of MITT Subjects greater than 450, each site will be limited to 10% of the increased total.

4.6 Duration of Study and Subject Participation

Study start-up, inclusive of site initiation and Investigator training, is estimated to take 6 months. The enrollment period for the first 600 subjects (105 Roll-Ins plus 495 ITT Subjects) is estimated to take 18 months and subjects will be followed for up to 13 months. There will be a 3-month period of site close-out visits, for a planned study duration of approximately 40 months. Coronavirus Disease 2019 (COVID-19)-related disruptions and interim sample size re-estimation may alter this timeframe.

Subject participation is anticipated to be 13 ± 1 months to allow for screening, pre-procedural diagnostic procedures, randomization, treatment and 12±1 months of study follow-up. If a subject requires a Rescheduled Index Procedure, this may prolong participation by up to 2 to 3 months.

4.7 Schedule of Events and Assessments

Subjects will complete the following visits and assessments as indicated below and as summarized in **Table 3**, (ITT Subjects) and **Table 4**, (Roll-In Subjects).

Assessments that are stipulated as remote may also be performed in-person at the investigational site at the Investigator's discretion with subject agreement.

All protocol-stipulated assessments below will be entered into the appropriate CRFs.

Assessments are to be performed within the specified assessment windows.

When COVID-19-related disruptions (**Section 6.3.8**) interfere with the performance of protocol-stipulated follow-up assessments, study sites and Sponsor personnel will adjust procedures to optimize data acquisition while protecting the health, safety and welfare of all study participants. Study subjects, sites, IRBs and the FDA will be informed of COVID-19-related changes in the study.

This protocol does not specify how remote assessments should be performed, but these will be specified in related study documentation and may be modified as necessary during the conduct of the study. The method(s) used during the course of this study to interact with study participants and to acquire data remotely will be consistent with relevant FDA Guidance Documents and will be reported in the Clinical Study Report.

4.7.1 Baseline Assessment

Type of Assessment: In-person at investigational site
The completion of the Baseline Assessment requires an in-person visit. Such assessments must be deferred if this is not possible.

The below baseline data will be generated in the window beginning 30 days prior to the Consent Date and ending on the date of the Index Procedure, unless otherwise specified. This data will include:

- Demographics including gender, height and weight
- Pertinent medical and cardiovascular history
- AAD and anticoagulation medication history
- Cardiac physical examination
- Pregnancy test (all women of child-bearing potential)
- Hematocrit, hemoglobin, electrolytes, blood urea nitrogen (BUN), creatinine
- COVID-19 testing by site
    - PCR for SARS-CoV-2 virus or equivalent testing, or
    - Confirmation of successful vaccination with an FDA-approved vaccine
- 12-lead ECG. ECGs with any arrhythmia will include a rhythm strip for ACL submission.
- Imaging (within the window beginning 90 days prior to the Consent Date and ending on the date of the Index Procedure)
    - TTE
    - Cardiac CT or MRI establishing PV dimensions
- NYHA Classification
- National Institutes of Health Stroke Scale (NIHSS) score by NIHSS-certified site personnel
- CHA_2DS_2-VASc score
- AF symptom assessment
- Quality of Life Measures:
    - The EuroQol standardized questionnaire of health states (EQ-5D-3 L)
    - The Atrial Fibrillation Effect on QualiTy-of-Life Questionnaire (AFEQT) quality of life assessments

Introduction to the EM / Holter Device: At the Baseline Assessment, the subject will receive an introduction to EMs, Holters, the hardware and how it will be utilized during the follow-up period. The importance of compliance with these critical assessments will be stressed.

4.7.2 Index Procedure / Rescheduled Index Procedure

Type of Assessment: In-person at investigational site
The performance of the Index Procedure / Rescheduled Index Procedure and the Pre-Discharge Assessment both require an in-person visit. The Index Procedure / Rescheduled Index Procedure must be deferred if this is not possible.

The Index Procedure will be performed according to **Section 5.2**. Procedural data will be collected including:

- Transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE) will be utilized prior to transseptal puncture for exclusion of LA thrombus.
- Pregnancy test (all women of childbearing potential if baseline pregnancy test obtained more than 30 days prior to procedure)
- Post-ablation 3D electroanatomical maps (at Investigator discretion)
- Post-ablation fluoroscopic examination of diaphragm motion to assess phrenic nerve response
- Adverse events
- Procedural times
- Lesion set data
- Peri-procedural anticoagulation data:
  - For subjects on a novel oral anticoagulant (NOAC) whether NOAC therapy was interrupted for procedure
  - For subjects on warfarin, a pre-treatment international normalized ratio (INR) value
  - Heparin administration and timing
- Device deficiencies and malfunctions
- For Thermal Subjects:
  - The specific thermal technology used, including manufacturer/model
  - The use of any esophageal monitoring, cooling or manipulation during the ablation procedure

4.7.3 Pre-Discharge Assessment

Type of Assessment: In-person at investigational site

Prior to hospital discharge study data will be collected including:

- Adverse events
- Hematocrit, hemoglobin, electrolytes, BUN, creatinine
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications.
- Cardiac rhythm as determined by a 12-lead ECG. ECGs with any arrhythmia will include a rhythm strip for ACL submission.
- Occurrence, date, indication and outcome of any cardioversion(s)
- Assessment of subject blinding

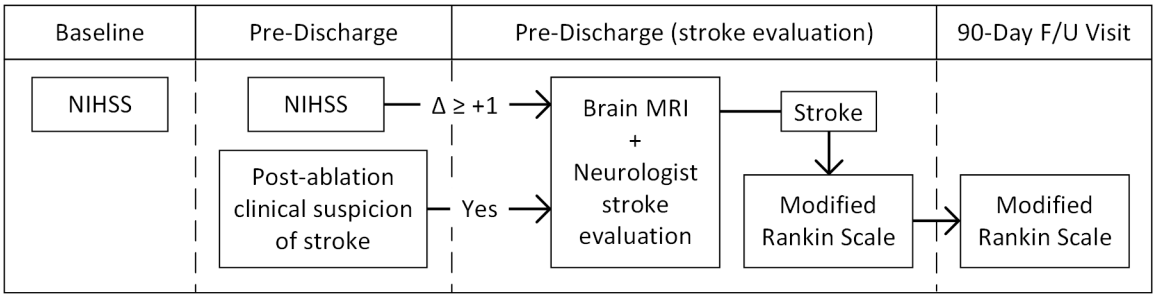
EM Training: The subject will be reminded regarding the use of the EM hardware, the importance of event monitoring and of the importance of the Day 60 EM Training.

Pre-Discharge Stroke Evaluation for non-Neurologic Assessment Subjects:

- NIHSS score by NIHSS-certified site personnel
- If either of the following occurs:
  - The post-procedure NIHSS score has increased by 1 or more points over the pre-procedure NIHSS score OR
  - There is a clinical suspicion of stroke or TIA

Then a consulting neurologist will perform a stroke assessment and include the results of a concurrent brain MRI. This assessment will be sufficient to determine with reasonable certainty whether a stroke, TIA or neither have occurred, using the definitions in **Table 5**. If a stroke is diagnosed the subject will be assessed using a Modified Rankin Scale. Please refer to **Figure 6**.

Figure 6 Pre-Discharge Stroke Evaluation, Non-NAS Subjects

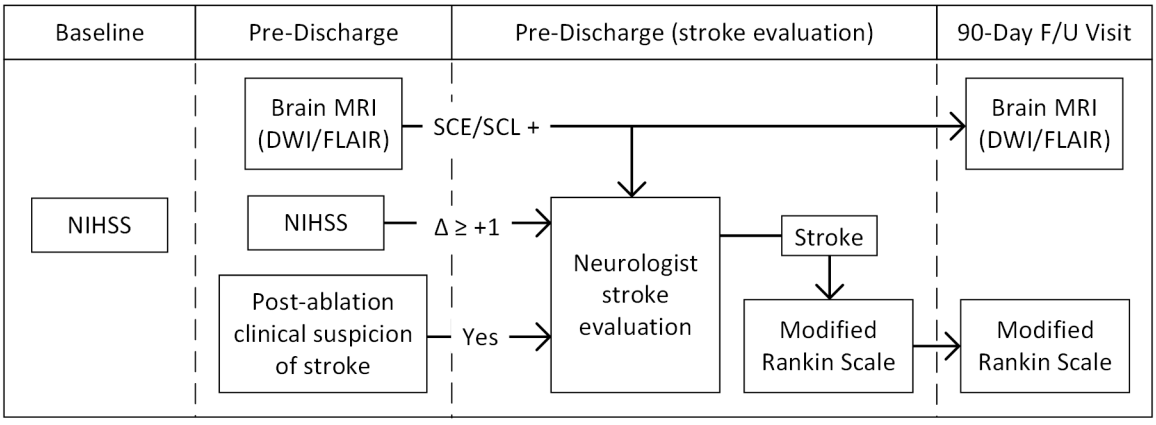


Pre-Discharge Stroke Evaluation for Neurologic Assessment Subjects:

- A post-procedure brain MRI as specified in **Section 5.8**.
- NIHSS score by NIHSS-certified site personnel
- If any of the following occurs:
  - The brain MRI is positive for SCE or SCL findings
  - The post-procedure NIHSS score has increased by 1 or more points over the pre-procedure NIHSS score OR
  - There is a clinical suspicion of stroke or TIA

Then a consulting neurologist will perform a stroke assessment and review the NAS-stipulated brain MRI. This assessment will be sufficient to determine with reasonable certainty whether a stroke, TIA or neither have occurred, using the definitions in **Table 5**. If a stroke is diagnosed the subject will be assessed using a Modified Rankin Scale. Please refer to **Figure 7**.

Figure 7 Pre-Discharge Stroke Evaluation, NAS Subjects



4.7.4 Day 7 Assessment

Type of Assessment: Remote
Window: Days 7 – 11
The Day 7 Assessment is essential to establish the primary safety endpoint and every effort must be made to complete this assessment between Day 7 and Day 11.
If the assessment is delayed, the onset date of an AE must be elicited as carefully as possible to establish whether it occurred within the interval between the ablation procedure and Day 7, or thereafter.

Subjects will be assessed remotely between Day 7 and 11 post-Index Procedure / Rescheduled Index Procedure. Study data will be collected by interview, including:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications.
- Recurrent arrhythmia, cardioversions, ablations or hospital admissions since discharge
- The date, time and communication method(s) used to collect the data remotely

4.7.5 Day 30 Assessment

Type of Assessment: Remote
Window: 30 ± 7 Days

Discharged subjects will be assessed remotely 30 days (± 7 days) post-Index Procedure / Rescheduled Index Procedure. (Any subject who continues to be hospitalized 30 days post-ablation will have their 30-Day Visit assessment performed in-hospital). Study data will be collected by interview including:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications.
- Recurrent arrhythmia, cardioversions, ablations or hospital admissions since 7-day telephonic assessment
- The date, time and communication method(s) used to collect the data remotely

4.7.6 Day 60 EM Training and AAD Discontinuation

Type of Interaction: Remote
Window: 60 ± 10 Days

EM Training: At Day 60 ± 10 days following the Index Procedure / Rescheduled Index Procedure, the subject will receive an EM and receive remote training regarding its use and the importance of event monitoring. The subject will be instructed to begin

using the EM at the time of the Day 90 Assessment and weekly thereafter and also for any symptomatic episodes throughout the remainder of study follow-up.

AAD Treatment: During this same subject interaction, Class I / III AADs should be stopped – if they have not already been discontinued – to allow assessment of off-drug freedom from recurrent AF, AFL or AT (the primary effectiveness endpoint). See **Section 5.9**.

4.7.7 Day 90 Assessment

Type of Assessment: In-person at investigational site required; remote only for documented COVID-19 related disruption.
Window: 90 ± 14 Days
If a COVID-19-related disruption prevents an in-person visit within the visit window: • As much data as possible may be collected remotely. • A cardiac MRI or CT scan performed at another healthcare site may be utilized, preferably with the same modality as the baseline scan, or the imaging procedure may be delayed for up to 3 months. • If a fluoroscopic examination is required due to prior diminished phrenic nerve response, an inspiration/expiration chest X-ray (CXR) performed in-person or at another healthcare site may be substituted.

Subjects will be assessed at Day 90 ± 14 days following the Index Procedure / Rescheduled Index Procedure.

EM Review: During this assessment, the subject will be queried as to their understanding and use of the EM. Remedial training will be supplied as required.

The subject will be instructed to begin weekly scheduled and symptomatic use of the EM and the critical importance of full compliance for study success will be stressed.

Study data will be collected at the 90-Day Visit including:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications
- Recurrent arrhythmia, cardioversions, ablations or hospital admissions since last visit
- Radiologic examination of the diaphragm (fluoroscopic sniff test or inspiration/expiration CXR) if the post-Index / Rescheduled Index Procedure fluoroscopy indicated diminished phrenic nerve response and resolution has not been previously demonstrated
- Cardiac rhythm as determined by a 12-lead ECG at the time of the visit (in-person assessment only). ECGs with any arrhythmia will include a rhythm strip for ACL submission.
- Cardiac CT or MRI scan of the same type as the baseline scan to assess the dimensions of the PVs. For subjects with a CICL-confirmed 70% or greater PV

diameter reduction, a Month 12 follow-up Cardiac CT or MRI scan of the same type as baseline will be scheduled to assess PV dimensions.
- Follow-up brain MRI as specified in **Section 5.8.2** (only for NAS Subjects with a confirmed post-procedural SCE or SCL on the post-procedural brain MRI)
- For any subject diagnosed with stroke during the Pre-Discharge Assessment, a Modified Rankin Scale assessment.
- If data is collected remotely, the date, time and communication method(s) used to collect the data remotely.

4.7.8 Month 6 Assessment

Type of Assessment: Remote
Window: 180 ± 30 Days
If a COVID-19-related disruption interferes with the performance of this assessment: • As much data as possible may be collected remotely, in or out of window.

Subjects will be assessed remotely at 6 months (180 days ± 30 days) following the Index Procedure / Rescheduled Index Procedure.

Holter Monitor: Within the 180 ± 30-day window for this visit, the subject will be contacted, receive remote training regarding the use of the EM hardware for Holter monitoring, and complete a 72-hour monitoring session.

EM Review: During this remote assessment EM compliance will be reviewed for weekly scheduled and ad hoc symptomatic monitoring and retraining of the subject provided as needed.

Study data will be collected at the 6-Month Visit including:
- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications
- Recurrent arrhythmia, cardioversions, ablations or hospital admissions since last visit
- The date, time and communication method(s) used to collect the data remotely

4.7.9 Month 12 Assessment

Type of Assessment: In-person at investigational site required; remote only for documented COVID-19 related disruption.
Window: 360 ± 30 Days
If a COVID-19-related disruption interferes with the performance of this assessment: • As much data as possible may be collected remotely, in or out of window.

- The absence of a 12-lead ECG during a remote assessment is not a protocol deviation but the subject should make an EM transmission at the time of the assessment.
- A cardiac MRI or CT scan, if required because of PVS being detected at the 90 Day Assessment, may be performed at another healthcare site if required, utilizing if at all possible the pre-specified CICL imaging protocol.
- If a fluoroscopic examination is required due to prior diminished phrenic nerve response, an inspiration/expiration chest X-ray (CXR) performed in-person or at another healthcare site may be substituted.

Subjects will be assessed at 360 days ± 30 days following the Index Procedure / Rescheduled Index Procedure. The Month 12 Assessment cannot be completed prior to the performance of the 72 hour Holter monitor procedure.

Holter Monitor: Within the 360 ± 30-day window for this visit and prior to the date of the Month 12 Assessment, the subject will be contacted, receive remote training regarding the use of the EM hardware for Holter monitoring, and complete a 72-hour monitoring session.

Study data will be collected at the 12-Month Assessment including:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications
- Recurrent arrhythmia, cardioversions, ablations or hospital admissions since last visit
- Radiologic examination of the diaphragm (fluoroscopic sniff test or inspiration/expiration CXR) if the post-Index / Rescheduled Index Procedure fluoroscopy indicated diminished phrenic nerve response and resolution has not been previously demonstrated (in-person assessment only)
- Cardiac rhythm as determined by a 12-lead ECG at the time of the visit (in-person assessment only). ECGs with any arrhythmia will include a rhythm strip for ACL submission.
- AF Symptom Assessment
- Quality of Life:
  - EQ-5D-3 L
  - AFEQT
- Assessment of subject blinding
- For subjects with a 3-month cardiac imaging (MRI or CT) showing a CICL-confirmed 70% or greater PV diameter reduction, a repeat cardiac imaging procedure of the same type to assess PV dimensions.
- If data is collected remotely, the date, time and communication method(s) used to collect the data remotely

At the completion of all components of the Month 12 Assessment a Study Exit CRF will be completed.

4.7.10 Re-Ablation Procedures

Re-ablation under this protocol requires documentation of Detectable AF, AFL or AT.

Each subject undergoing an anticipated PVI re-ablation procedure on Day 76 or later must have a Cardiac CT or MRI scan of the same type as the baseline scan obtained prior to the procedure to assess the dimensions of the PVs.[3]

When performed, PVI re-ablation will be performed utilizing an approved study ablation catheter (RFA or CBA) at Investigator discretion for both Pulsed Field and Thermal Subjects. Other energy modalities may not be used.

Any re-ablation procedure for AF, AFL or AT during study follow-up constitutes a Treatment Failure, and therefore during such procedures other sites may be ablated at Investigator discretion.

CTI ablation or re-ablation for right-sided typical AFL may be performed at any time during study follow-up and does not constitute a Treatment Failure.

Other sites may be ablated at Investigator discretion using a commercially available ablation system.

For subjects undergoing a re-ablation procedure the following data will be collected:

- For subjects with a re-ablation scheduled on Day 76 or later, the Day 90 cardiac CT or MRI scan of the same type as the baseline scan will be performed prior to re-ablation to assess the dimensions of the PVs.
- During any re-ablation procedure in which LA access is performed a mapping procedure will characterize the reconnection status for each originally treated PV to characterize lesion durability.
- For subjects who received ablation of the CTI, the persistence of nonconductivity in targeted tissue will be evaluated with either pacing maneuvers or electroanatomical mapping.
- Lesion set data

4.7.11 Unscheduled Assessments

Type of Assessment: Either remote or in-person at investigational site.

Any unscheduled follow-up assessments that occur throughout study follow-up will be documented. Study data will be collected including:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and/or antiarrhythmic medications
- Recurrent arrhythmia, cardioversions, ablations or hospital admissions since last visit
- EM compliance will be reviewed for weekly scheduled and ad hoc symptomatic monitoring and retraining of the subject provided as needed.

[3] The protocol-specified Day 90 cardiac imaging qualifies for this purpose if obtained prior to a re-ablation.

- Cardiac rhythm as determined by a 12-lead ECG
  - At the investigational site: required. ECGs with any arrhythmia will include a rhythm strip for ACL submission.
  - At another health care site: not required but should be obtained if available. The absence of a 12-lead ECG is not a protocol deviation.
  - Remote, not at a health care site: not required. An EM submission should be requested.
- If data is collected remotely, the date, time and communication method(s) used to collect the data remotely

4.7.12 COVID-19-Related Disruption of Study Assessments

To avoid study disruptions or missing data related to COVID-19 impacts, such as COVID-19 illness or COVID-19 restrictions on movement, association or access to health care facilities, every effort will be made to gather study data by all available means and from any available sources. This includes use of communications media and the acquisition of health-related information from other health care facilities and providers.

Telephonic and telemedicine assessments may be used. Important considerations for study visits through video conferencing include:

- The Investigator or study personnel who will conduct remote visits should be trained on how to conduct telemedicine video conferencing visits.
- Procedures should be put in place to maintain a study subject's privacy, as would be done for a clinical visit.
- Both the Investigator and the study subject should confirm their respective identities with one another before engaging in a real-time video conference visit according to an identity verification plan developed by the Sponsor.

The date and time of the real-time video interaction, the location of the study subject and the location of the Investigator or personnel conducting the remote visit should be documented in the electronic case report form (eCRF).

Every effort will be made to gather all available study data within the visit window, but if that is not possible data will be gathered outside of the visit window.

Critical assessments to receive priority include:

- Occurrence and characterization of AEs
- Symptoms of arrhythmia recurrence
- Cardiac CT or MRI scans
- Brain MRIs
- Follow-up assessments of phrenic nerve function
- Event monitoring
- Holter monitoring

For all such COVID-19-related missed or out of window assessments, specific information will be captured that explains the basis of the missing data and its relation to COVID-19 for missing information (e.g., from missed visits or subject discontinuations)

4.8 Schedule of Events

Table 3 Schedule of Events – ITT Subjects

Assessment	Baseline[1] (In-person)	Index Procedure (In-person)	Pre-Discharge (In-person)	Day 7 (7-11 days) (Remote[2])	Day 30 (± 7 days) (Remote[2])	Day 60 (± 10 days) (Remote[2])	Re-Ablation Procedures (In-person)	Day 90 (90 ± 14 days) (In-person)	Month 6 (180 ± 30 days) (Remote[2])	Month 12 (360 ± 30 days) (In-person)	Unscheduled (In-person/ Remote[2])
Informed consent, baseline assessments	X[3]										
AAD and anticoagulant medications	X		X	X	X	D/C AADs	X	X	X	X	X
Recurrent arrhythmia, cardioversions, ablations, hospital admissions			X	X	X		X	X	X	X	X
Pregnancy test	X[4]	X[4]					X[4]				
COVID-19 testing by site	X										
12-lead ECG	X		X					X		X	X
HCT, HGB, electrolytes, BUN, creatinine	X		X								
Transthoracic echocardiogram (TTE)	X										
Event monitors	Training		Training			Training		Weekly + symptomatic transmissions			X
72-Hour continuous ECG (Holter)	Training		Training						X	X	
Cardiac CT/MRI for PV dimensions	X						X[5]	X		X[6]	
TEE/ICE to exclude LA thrombus		X[7]					X[7]				
NIHSS	X		X								
Radiologic examination of diaphragm		X					X	X[8]		X[8]	
AF Symptom Assessment	X									X	
EQ-5D-3 L & AFEQT assessments	X									X	
Non-NAS subjects: Neuro assessment			X[9]					X[9]			
NAS subjects: Neuro assessment			X[10]					X[10]			
Assessment of subject blinding			X							X	
Adverse events		X	X	X	X		X	X	X	X	X

[1] All Baseline Assessments must be generated in the window beginning 30 days (90 days for TTE and cardiac CT/MRI) prior to the Consent Date and ending on the date of the Index Procedure.
[2] Assessments that are defined as remote may also be performed at the investigational site (non-remote) at Investigator discretion and subject agreement.
[3] Baseline assessments include the inclusion/exclusion criteria and the data stipulated in **Section 4.7.1**.
[4] Females of childbearing potential only. The pre-procedural pregnancy test is not required if the Index Procedure / Rescheduled Index Procedure is within 30 days of the baseline pregnancy test.
[5] For re-ablations occurring Day 1-75, pre-procedural imaging is not required. For re-ablations scheduled for Day 76 or later, ensure the Day 90 cardiac MRI/CT is performed before re-ablation.
[6] Month 12 cardiac MRI/CT only if 3-month imaging revealed any PV with ≥ 70% reduction in PV measured diameter.
[7] Performed at the beginning of the procedure prior to ablation. See **Section 5.3** for managing subjects whose procedure is delayed by intracardiac thrombus.
[8] Only if resolution of phrenic nerve palsy has not yet been demonstrated. May be performed either by fluoroscopic sniff test or inspiration/expiration CXR.
[9] Non-NAS subjects: If NIHSS score has increased by 1 or more points or if there is a clinical suspicion of stroke/TIA, then a consulting neurologist will perform a stroke assessment and include the results of a concurrent brain MRI. If stroke is diagnosed, a Modified Rankin Scale assessment will be performed prior to discharge and again at 3 months.
[10] NAS subjects: If NIHSS score has increased by 1 or more points, if there is a clinical suspicion of stroke/TIA, or if the post-procedural brain MRI is positive for SCE or SCL findings then a consulting neurologist will perform a stroke assessment and include review of the NAS post-procedural brain MRI. If stroke is diagnosed, a Modified Rankin Scale assessment will be performed prior to discharge and again at 3 months.

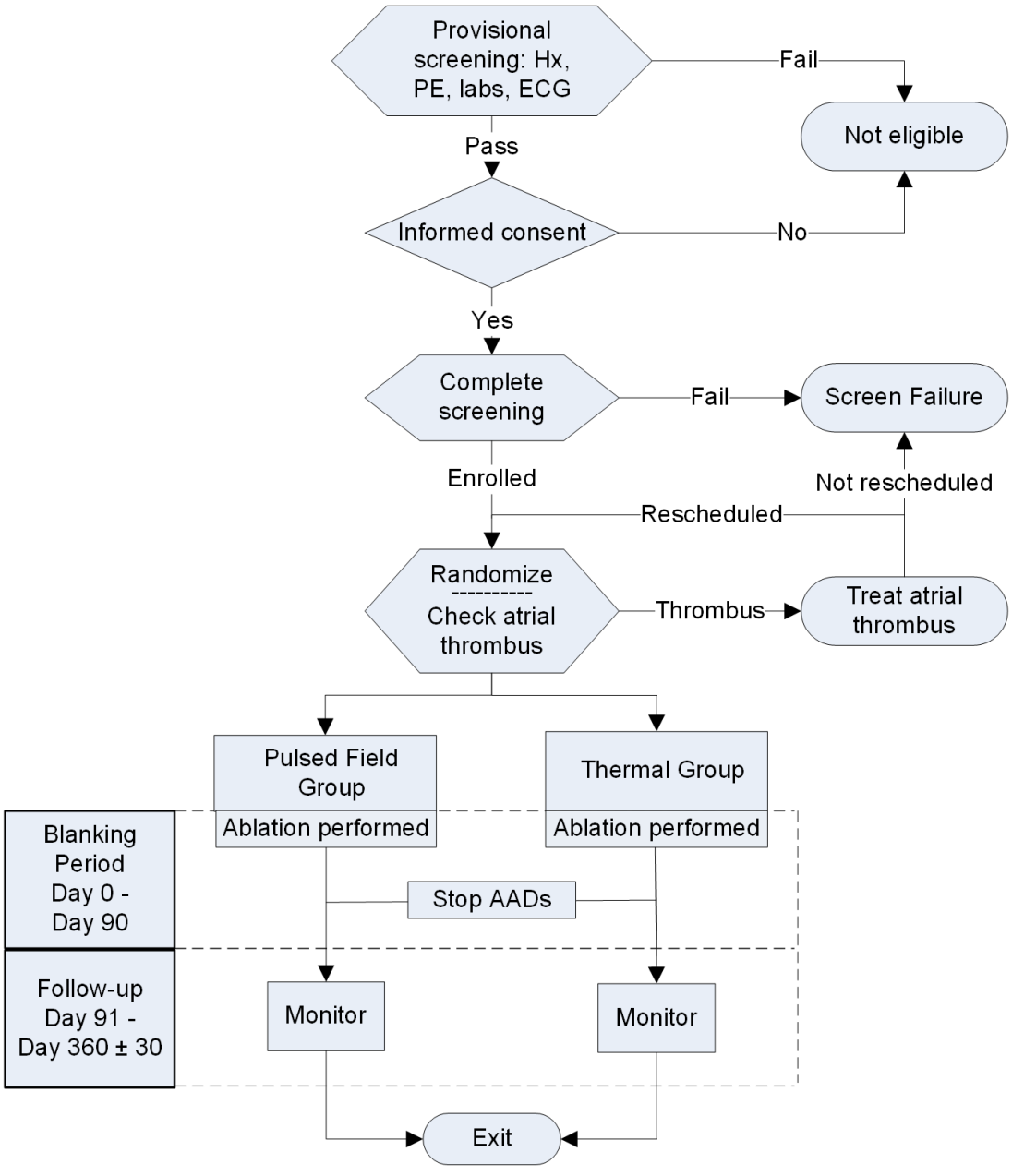
Table 4 Schedule of Events – Roll-In Subjects

Assessment	Baseline[1] (In-person)	Index Procedure (In-person)	Pre-Discharge (In-person)	Day 7 (7-11 days) (Remote[2])	Day 90 (90 ± 14 days) (In-person)	Month 6 (180 ± 30 days) (Remote[2])	Month 12 (360 ± 30 days) (In-person)	Unscheduled (In-person/ Remote[2])
Informed consent, baseline assessments	X[3]							
AAD and anticoagulant medications	X		X	X	X	X	X	X
Recurrent arrhythmia, cardioversions, ablations, hospital admissions			X	X	X	X	X	X
Pregnancy test	X[4]	X[4]						
COVID-19 testing by site	X							
12-lead ECG	X		X		X		X	X
HCT, HGB, electrolytes, BUN, creatinine	X		X					
Transthoracic echocardiogram (TTE)	X							
Cardiac CT/MRI for PV dimensions	X							
TEE/ICE to exclude LA thrombus		X[5]						
NIHSS	X		X					
Radiologic examination of diaphragm		X			X[6]		X[6]	
AF Symptom Assessment	X						X	
Neuro assessment			X[7]		X[7]			
Adverse events		X	X	X	X	X	X	X

[1] All Baseline Assessments must be generated in the window beginning 30 days (90 days for TTE and cardiac CT/MRI) prior to the date of enrollment and ending on the date of the Index Procedure.
[2] Assessments that are defined as remote may also be performed at the investigational site (non-remote) at Investigator discretion and subject agreement.
[3] Baseline assessments include the inclusion/exclusion criteria and the data stipulated in **Section 4.7.1**.
[4] Females of childbearing potential only. The pre-procedural pregnancy test is not required if the Index Procedure is within 30 days of the baseline pregnancy test.
[5] Performed at the beginning of the procedure prior to ablation. See **Section 5.3** for managing subjects whose procedure is delayed by intracardiac thrombus.
[6] Only if resolution of phrenic nerve palsy has not yet been demonstrated. May be performed either by fluoroscopic sniff test or inspiration/expiration CXR.
[7] If NIHSS score has increased by 1 or more points or if there is a clinical suspicion of stroke/TIA, then a consulting neurologist will perform a stroke assessment and include the results of a concurrent brain MRI. If stroke is diagnosed, a Modified Rankin Scale assessment will be performed prior to discharge and again at 3 months.

4.9 Subject Flow Chart

Figure 8 Subject Flow Chart



Hx = history, **PE** = physical examination, **ECG** = electrocardiogram, **AAD** = antiarrhythmic drug

4.10 Control of Systematic Error and Bias

Subjects will be randomized in this controlled study and key evaluators (CEC, Arrhythmia Core Laboratory [ACL] and Cardiac Imaging Core Laboratory [CICL]) for primary and secondary outcome assessments will be blinded.

Error and bias are controlled by additional means, including a comprehensive set of study procedures as defined in the protocol which ensure consistent management, site and data monitoring and outcome measure assessment. Follow-up Holter monitoring and event monitoring data, and all MRI/CT dimensions of PVs, will be assessed objectively and without knowledge of subject treatment status by third parties according to standard protocols. SAEs and the primary effectiveness and safety outcomes will be reviewed by an independent CEC (**Section 12.2.4**).

A complete Clinical Study Report and dataset will allow scientific and clinical reviewers to independently assess potential error and bias.

5. Study Procedures

5.1 Anticoagulation

Anticoagulation will be guided by the 2017 Heart Rhythm Society Expert Consensus Statement[8] and the 2019 American Heart Association / American College of Cardiology / Heart Rhythm Society Focused Update[36] relating to this issue.

Adjustments for subject welfare may be made by Investigators based on clinical judgment and do not constitute protocol deviations.

Throughout the study:

- Subjects with a CHA_2DS_2-VASc score ≥ 2 (men) or ≥ 3 (women) should receive oral anticoagulants throughout the study.
- NOACs are recommended over warfarin for eligible subjects.
- Subjects on warfarin should have at least monthly INR assessment.

Peri-procedural:

- Non-anticoagulated subjects will be placed on therapeutic anticoagulation for a minimum of 3 weeks prior to an ablation procedure regardless of baseline CHA_2DS_2-VASc score.
- Subjects taking warfarin should continue warfarin through the procedure.
- Subjects taking a NOAC should have either continued NOAC (rivaroxaban) or a single dose interruption in NOAC with a restart shortly after the procedure, at Investigator discretion.
- A heparin bolus will be delivered prior to or immediately following transseptal puncture. Procedural activated clotting times (ACTs) will be sampled regularly throughout the procedure and maintained at a minimum of 300 seconds.

Post-ablation:

- If the subject is not otherwise indicated for anticoagulation, suitable anticoagulation will be maintained for a minimum of 2 months following any ablation procedure.

Thereafter, decisions regarding anticoagulation should be based on the subject's stroke risk and bleeding risk profiles.

5.2 Index Procedure

Subjects will be screened for completion of a minimum of 3 weeks of systemic anticoagulation prior to the Index Procedure and if this condition has not been met the subject will be rescheduled under the procedure defined in **Section 5.3**.

Subjects will undergo sedation / anesthesia according to institutional protocol. They will then be prepared in conventional sterile fashion for a cardiac catheterization procedure.

Femoral vein access will be obtained via Seldinger technique.

Use of ultrasound guidance is recommended, but not required, for femoral venous access.

A heparin bolus will be delivered prior to or immediately after transseptal puncture. Procedural ACTs will be regularly monitored and maintained at a minimum of 300 seconds.

Commercially approved diagnostic catheters may be placed before or after transseptal access is established at the Investigator's discretion. Transseptal access to the LA will be obtained using commercially approved devices, establishing guidewire access to the LA.

TEE within 48 hours of the procedure or ICE during the procedure will be utilized prior to transseptal puncture for exclusion of LA thrombus. If the study reveals atrial thrombus, the investigational procedure will not begin or will be terminated, no ablation will be performed and the subject will be rescheduled under the procedure defined in **Section 5.3**.

Pre-ablation and post-ablation voltage maps are not required.

Pulsed Field Subjects:

The use of ICE is required for Pulsed Field Ablation procedures.

The FARADRIVE Steerable Sheath will be prepared and advanced via guidewire to the LA.

Esophageal temperature monitoring, esophageal cooling and esophageal deviation are unnecessary during ablation with the FARAWAVE Pulsed Field Ablation Catheter and should not be utilized.

The FARAWAVE Pulsed Field Ablation Catheter will then be prepared and advanced to the LA through the FARADRIVE Steerable Sheath. After confirming an ACT of 300 or greater, ablation of the PVs to achieve isolation will be performed according to the approved IFU documents and institutional practice.

Ablation will be attempted in every clinically relevant PV, including any vein with an active muscular sleeve. Small anomalous PVs that are electrically silent need not be attempted.

PVI ablation may be repeated at the Investigator's discretion. Each addressable PV will be ablated in turn. The isolating effect of the PVI ablation(s) will be checked periodically and then finally twenty (20) minutes after the last PVI ablation. Adenosine may be used for the final assessment but is not required.

At the conclusion of the PVI ablation procedure, the FARAWAVE Pulsed Field Ablation Catheter will be undeployed and withdrawn from the FARADRIVE Steerable Sheath.

The functional status of both phrenic nerves will be assessed before the study is concluded.

Thermal Subjects:

All Investigators at a given site must use only 1 of the 2 categories of Thermal Group technology for ablation, either a force-sensing irrigated RFA catheter or a CBA catheter, indicated for the treatment of PAF. A site's Thermal Group technology will be determined prior to the initiation of enrollment at that site and maintained without exception throughout the study.

A commercially approved sheath will be prepared and advanced via guidewire to the LA. Commercially approved diagnostic catheters may be placed via conventional technique at the Investigator's discretion. A baseline 3D electroanatomical map may also be made at the Investigator's discretion.

Esophageal protection (temperature monitoring, deviation or cooling) using the site's customary method is required, unless subject welfare precludes such usage.

The site's predetermined technology ablation catheter will be prepared and advanced to the LA through the sheath. Ablation of the PVs to achieve isolation will be performed according to the approved IFU documents and institutional practice.

Ablation will be attempted in every clinically relevant PV, including any vein with an active muscular sleeve. Small anomalous PVs that are electrically silent need not be attempted.

PVI ablation may be repeated at the Investigator's discretion. The isolating effect of the PVI ablation(s) will be checked periodically and then finally twenty (20) minutes after the last PVI ablation. Adenosine may be used for the final assessment but is not required.

At the conclusion of the PVI ablation procedure, the ablation catheter should be withdrawn from the sheath according to the manufacturer's instructions.

The functional status of both phrenic nerves will be assessed before the study is concluded.

All Subjects:

CTI ablation: Ablation of the CTI may be performed in both Pulsed Field Subjects and Thermal Group Subjects using any approved catheter in subjects with a past history of cavo-tricuspid isthmus-mediated (typical) AFL, subjects who manifest typical AFL during a procedure or within the Blanking Period, or subjects who have inducible typical flutter. Bidirectional block should be demonstrated after the last CTI ablation.

The CTI ablation data will be documented in the CRF and does not constitute a Treatment Failure.

Other Ablation: Other ablation is not permitted under this protocol except when the Investigator determines that subject welfare requires ablation for an accessory pathway, AVNRT, treatment-emergent left AFL or incessant AT, using any approved ablation catheter. This decision and the associated ablation data will be documented in the CRF and does not constitute a Treatment Failure.

5.3 Rescheduled Index Procedure

Subjects found during the Index Procedure to have LA thrombus will have their Index Procedure rescheduled to allow treatment of the thrombus, including a minimum of 3 weeks of continuous therapeutic anticoagulation consistent with **Section 5.1**. The Reschedule Index Procedure will follow the requirements of **Section 5.2**.

This rescheduling is permissible and does not create an Acute Procedural Failure. For adjustment of follow-up assessments please see **Section 5.5** below. References to "Index Procedure" in this protocol should be assumed when appropriate to include "Rescheduled Index Procedure" as well if not otherwise specified.

5.4 Re-Ablation Procedures

Re-ablation under this protocol requires documentation of Detectable AF, AFL or AT. When performed, re-ablation will be performed utilizing an FDA-approved study ablation catheter (RFA or CBA) at Investigator discretion.

Any re-ablation procedure for AF, AFL or AT any time during study follow-up constitutes a Treatment Failure.

However, CTI ablation or re-ablation for right-sided typical AFL may be performed at any time during study follow-up and does not constitute a Treatment Failure.

Cardiac imaging:

- For anticipated PVI re-ablations occurring Day 1-75, pre-procedural imaging is not required.
- For anticipated PVI re-ablations scheduled for Day 76 or later, ensure the Day 90 cardiac MRI/CT is performed before re-ablation to assess the dimensions of the PVs. The Cardiac CT or MRI scan must be of the same type as the baseline scan obtained prior to the Index / Rescheduled Index Procedure.

TEE within 48 hours of the procedure or ICE during the procedure will be utilized prior to transseptal puncture for exclusion of LA thrombus. If the study reveals atrial thrombus, the investigational procedure will not begin or will be terminated and no ablation will be performed.

Re-ablation does not reset the Blanking Period or otherwise alter the Schedule of Events and Assessments (**Section 4.7**).

Remapping will be performed:

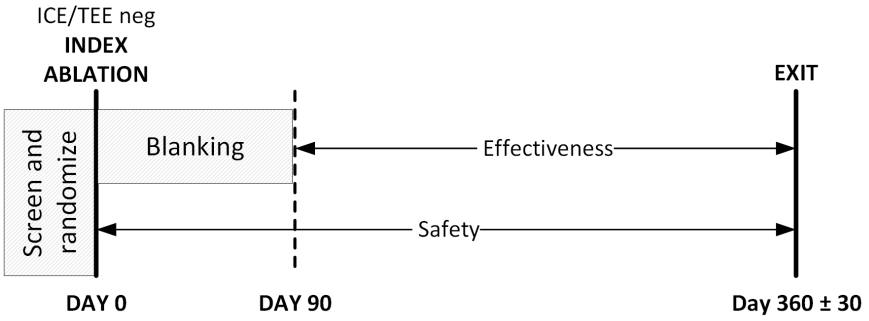
- During any re-ablation procedure in which LA access is performed:
  - Sufficient mapping to establish the durability of isolation of each previously treated PV.
- During any re-ablation procedure in a subject who underwent CTI:
  - Sufficient mapping to establish the durability of a previously treated CTI.

5.5 Start Date, Blanking Period and Index Procedures

The day of the Index Procedure or Rescheduled Index Procedure is the Start Date (Day 0) for follow-up scheduling. The Blanking Period consists of a subject's Day 0 through and including Day 90. During the Blanking Period, any occurrence of Detectable AF, AFL or AT will be documented; however, occurrences of AF, AFL or AT during this time will not be considered Treatment Failures.

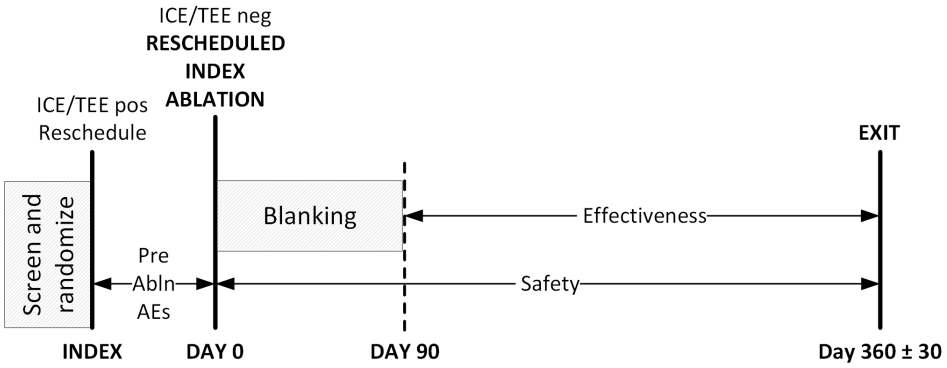
For subjects who undergo ablation at the Index Procedure, the follow-up intervals for safety and effectiveness are depicted in **Figure 9** below:

Figure 9 Index Procedure Blanking and Follow-Up Intervals



For subjects who undergo ablation at a Rescheduled Index Procedure the follow-up intervals for safety and effectiveness are depicted in **Figure 10** below. The follow-up intervals for effectiveness and safety are still based on the day of the ablation procedure (Day 0). Pre-ablation AEs that occur between the Index Procedure and the day before the Rescheduled Index Procedure will not be included in the safety analyses, but will be documented and reported separately, with the day of occurrence being enumerated from the day of the Index Procedure that was deferred.

Figure 10 Rescheduled Index Procedure Blanking and Follow-Up Intervals



5.6 Roll-In Subjects

Up to 105 subjects – to be treated with the FARAPULSE devices – will be consented and treated in a manner consistent with the Pulsed Field Group but will be analyzed and reported separately from the study population.

At each site, these Roll-In Subjects will be the first 1 to 3 sequentially enrolled but non-randomized subjects at that site. Sites with more than 1 Investigator will utilize available Roll-In Subjects jointly as required.

With Sponsor and Investigator agreement, the Roll-In phase at a site will be terminated at or before 3 Roll-In Subjects have been treated and all subsequent subjects at the site will be randomized as study subjects according to protocol requirements.

Roll-In Subjects will:

- Be consented using a Roll-In-specific ICF.
- Follow the Index Procedures as specified in **Section 5.2**.
- Have all study data gathered as specified in **Section 4.7.2** and **Section 4.7.3**.
- Be followed for 12 months post-ablation, completing Day 7 and Month 3, Month 6 and Month 12 Assessments for clinically-detected arrhythmias and screening for the occurrence of AEs
- Be managed according to Investigator or referring physician discretion.
- Have their required study data recorded on a specific and separate CRF set.
- Be analyzed and reported separately from the ITT Subjects.

Roll-In Subjects will not:

- Undergo Quality of Life assessments
- Undergo NAS assessment
- Undergo protocol-specified EM or Holter monitoring
- Undergo protocol-specified cardiac imaging post-procedure

5.7 Blinding

- Investigators: The treating physicians and site-based study personnel are necessarily exposed to a subject's treatment assignment and cannot be blinded. As much as possible, site based study personnel who perform follow-up evaluations will remain blinded to subject treatment assignment.

- Subjects: Study personnel will be trained to avoid disclosing treatment status to study subjects. Study subjects will sign an informed consent that states that they will not be informed of their treatment status until the conclusion of their participation in the study.
- Core Laboratories: The ACL, CICL and Brain Imaging Core Lab (BICL) will remain blinded to treatment assignment throughout the study duration.
- CEC: The CEC will remain blinded as much as possible consistent with accurate adjudication.
- Data and Safety Monitoring Board (DSMB): In general, the DSMB will review unblinded results in order to perform their function of protecting the integrity of the study and the rights, safety and welfare of study subjects.
- Study / CRO staff: Monitoring staff will be unblinded to perform their function. Other Sponsor and CRO staff will be unblinded on a documented need-to-know basis to allow conduct of the study.

5.8 Neurologic Assessment Subjects

Neurologic Assessment Subjects (NAS) are a subset of ITT Subjects who will undergo a post-procedural brain MRI following the ablation procedure.

5.8.1 NAS Sites

A subset of study sites qualified and willing to perform the standardized brain MRI post-ablation will be established and designated as NAS sites. NAS sites will be selected to generate a minimum of 80 NAS Subjects, balanced approximately equally between RFA and CBA control sites. Total NAS enrollment will be limited to a maximum of 40 subjects in the PFA group and 40 subjects in the Thermal Group (RFA/CBA).

- An approximately equal number of RF-control sites and cryoballoon-control sites will be targeted.
- All ITT Subjects at NAS sites free of contraindications to MRI will be consented for post-procedure MRI until the study enrollment target of evaluable scans is met.
- Roll-In Subjects are excluded from participation in the NAS.

5.8.2 Post-Ablation Brain MRI Specifications for NAS Subjects Only

These specification are for the protocol-required brain MRIs of NAS Subjects only.

- Standards and Quality Control: The BICL will establish specific standards for brain MRI performance, train participating sites and interact with sites to ensure that standards and scan quality remain within specification.
- Timing: Post index procedure (between 12 hours to 48 hours post-ablation) brain MRIs will be performed on each NAS subject.
- Parameters: The following scan parameters will be used:
    - 1.5-T scanners
    - 5mm slice thicknesses
    - DWI, FLAIR and ADC assessed for each scan
    - SCE = DWI + and ADC reduced

- SCL = DWI + and ADC reduced and FLAIR +

5.8.3 SCE and SCL Analysis

The frequency and type of SCEs and SCLs will be reported by randomization group, along with potential predictor variables including CHA_2DS_2-VASc status, duration of PAF, history of stroke/TIA, procedure time, LA dwell time and total ablation time, anticoagulation regimen and ACT levels, occurrence of cardioversion or air introduction, frequency of LA catheter exchanges and maximal sheath size.

5.8.4 Follow-Up for Subjects with SCE or SCL Lesions

- Subjects with a site-confirmed post-procedural SCE or SCL will undergo a pre-discharge neurologic assessment as specified in **Section 4.7.3**.
- Subjects with a site-confirmed or BICL-confirmed post-procedural SCE or SCL will undergo a follow-up brain MRI using the parameters specified in **Section 5.8.2** during the 90 Day Assessment window.

5.9 Antiarrhythmic Drugs

AADs, except for amiodarone, may be utilized during the Blanking Period at the Investigator's discretion.

On Day 60 ± 10 each subject will be contacted by telephone to stop all AADs.

Class I / III AADs (see **Section 6.3.4**) should be stopped at the Day 60 Assessment. However, at the Investigator's discretion, Class I / III AADs may be continued up to Day 90 without creating a Treatment Failure. If AADs are required after Day 90 and Class I / III AADs are prescribed, the Investigator should document the reason for utilizing the medication in the eCRF. Notwithstanding the impact on study outcomes, the use of Class I / III AADs for subject welfare as determined by the Investigator during and after the Blanking Period do not constitute protocol deviations.

<u>The use of amiodarone at any time during the study, except intra-procedurally to control an arrhythmia , or the use of Class I / III AADs after Day 90, constitute a Treatment Failure.</u>

6. Study Definitions

6.1 Study Outcomes

The primary and secondary effectiveness endpoints and the primary and secondary safety endpoints, along with specified additional analyses, procedural assessments and quality of life assessments, are defined in **Section 7**.

6.2 Adverse Event Definitions

Definitions relating to AEs, SAEs, procedure relatedness, device relatedness, device effects, malfunctions and deficiencies are defined in **Section 8**.

6.3 Other Definitions

6.3.1 Acute Procedural Success

Demonstration of Acute Vein Success in all attempted PVs using the randomized treatment during the first ablation procedure (Index or Rescheduled Index Procedure). (See **Section 6.3.3**)

6.3.2 Acute Procedural Failure

The absence of Acute Procedural Success, including the use of any non-randomized energy modality for PVI.

6.3.3 Acute Vein Success

Proportion of all attempted PVs isolated using the randomized treatment during the first ablation procedure (Index or Rescheduled Index Procedure), as clinically assessed by entrance block demonstrated ≥ 20 minutes after the last PVI lesion is made with or without adenosine testing.

6.3.4 Antiarrhythmic Drugs, Class I and III

AADs are those pharmaceutical agents approved or used in the United States for the treatment of cardiac arrhythmia. For the ADVENT Trial, the use of Class I and III AADs after the Blanking Period constitute a primary effectiveness endpoint failure. Examples of these agents include but are not limited to:

- Class I, sodium channel blockers: disopyramide, flecainide, procainamide, propafenone quinidine.
- Class III, potassium channel blockers: amiodarone, dofetilide, dronedarone, sotalol.

Should other Class I or III AADs become approved or used in the United States for the treatment of cardiac arrhythmia during the ADVENT Trial, they will be included in the list of AADs that constitute a Treatment Failure if used after the Blanking Period.

6.3.5 Blanking Period

An interval in which recurrent AF, AFL or AT does not constitute a Treatment Failure beginning on Day 0 and running for 90 days thereafter.

- The Blanking Period has no impact on the assessment of AEs.

- For subjects with only an Index Procedure, the Blanking Period will be Day 0 to Day 90 inclusive.
- For subjects who require a Rescheduled Index Procedure, the Blanking Period will be the Study Day of the Rescheduled Index Procedure plus 90 days inclusive.

6.3.6 Chronic Failure

The absence of Chronic Success.

6.3.7 Chronic Success

Defined in **Section 7.4.**

6.3.8 COVID-19-Related Disruptions

A disruption to any study procedure resulting directly or indirectly from the COVID-19 pandemic, including but not limited to participant illness, study site restrictions and limitations, shipping / manufacturing interruptions, significant changes in FDA guidance and / or governmental restrictions on travel, association and the prioritization of healthcare resources.

6.3.9 Dates

- Consent Date: The date a subject signs the ICF.
- Exit Date: The date on which study participation ends.
- Onset Date: The date on which a condition or AE begins.
- Start Date: Day 0, the date of the Index or Rescheduled Index Procedure.

6.3.10 Day (or Study Day)

A Day is an enumerated day of follow-up that begins on an Enrolled Subject's Start Date (Day 0).

6.3.11 Detectable AF, AFL or AT

Detectable AF, AFL or AT is an episode of AF, AFL or AT which:

- Is permanently recorded for review
- Contains at least 30 seconds of continuous interpretable signal
  - Exception: Continuous AF, AFL or AT for the entirety of a 12 lead ECG constitutes Detectable AF, AFL or AT if the continuous interpretable signal is 10 seconds or longer
- Includes symptomatic and asymptomatic episodes.
- Excludes CTI isthmus-dependent AFL when the mechanism is confirmed electrophysiologically.

Such episodes are not AEs under this protocol unless deemed to be caused by an ablation procedure.

6.3.12 Investigational Devices and Procedures

For the purpose of assessing event and outcome rates in study subjects:

- Investigational devices include any protocol-specified ablation catheter, generator/console or sheath, whether FDA approved (radiofrequency ablation or cryoablation systems) or not (FARAPULSE Pulsed Field Ablation System).
- Investigational procedures include any ablation procedure performed by a study investigator for the treatment of AF, AFL or AT, and study-directed CT/MRI testing.

6.3.13 Pre-Ablation Adverse Events

Defined as those AEs that occur between the date of the deferred Index Procedure and the day before the Rescheduled Index Procedure in subjects whose first ablation procedure is rescheduled due to intracardiac thrombus. These are not included in study safety analyses but will be documented and reported separately.

6.3.14 Pulmonary Vein Dimensions

For the purpose of study outcomes:

- PV dimensions will be measured in two roughly orthogonal diameters approximating the longest and shortest diameters at the plane of measurement.
- The measured PV diameter is defined as the geometric mean of these 2 measurements.
- The PV cross-sectional area is computed using the formula for area of an ellipse, where the longest and shortest axis measurements of the PV diameter serve as the major and minor axes of the ellipse, using half of each axis diameter as the radii for calculation.
- Aggregate PV Cross-Section Area is the sum of the calculated PV cross-sectional area of each PV ablated at the Index / Rescheduled Index Procedure, as detailed in the SAP.

6.3.15 Pulmonary Vein Isolation

Complete electrical isolation of a PV confirmed by entrance block, specifically: the percutaneous endocardial creation of an electrically isolating set of lesions around the ostia of a PV, as clinically assessed by entrance block demonstrated ≥ 20 minutes after the last PV lesion is made, with or without adenosine testing.

6.3.16 Pulsed Field Group / Subjects

Subjects randomized to treatment with the FARAPULSE Pulsed Field Ablation System are Pulsed Field Subjects and collectively comprise the Pulsed Field Group.

6.3.17 Severe COVID-19 Subjects

Any study subject who contracts COVID-19 infection during study participation that:

- Requires supplemental oxygen, positive pressure ventilation, and/or intubation OR
- Is associated with any medically serious sequelae of COVID-19, including but not limited to new onset cardiac arrhythmia, heart failure, myocarditis, neurologic dysfunction or other organ dysfunction or thromboembolic disease.

Such subjects will be initially defined by the Investigator and confirmed by the CEC. The Onset Date will be the date of symptom onset in a subsequently clinically confirmed case of COVID-19 infection.

6.3.18 Study Participants

Study participants include patients being screened, Enrolled Subjects, study site personnel, study monitors and other CRO personnel as well as Sponsor personnel.

6.3.19 Thermal Group / Subjects

Subjects randomized to treatment with RFA or CBA are Thermal Subjects and collectively comprise the Thermal Group.

6.3.20 Treatment Failure

The absence of Treatment Success.

6.3.21 Treatment Success

Defined in **Section 7.4**.

7. Outcome Measures

7.1 Primary Safety Endpoint

The primary safety endpoint is the Composite Safety Endpoint (CSE) defined as the proportion of Safety Subjects with one or more of the following device- or procedure-related SAEs as adjudicated by the CEC based on the definitions contained in **Table 5**.

Early onset: Any of the following with an Onset Date within 7 days of the Index / Rescheduled Index procedure:

- Death
- Myocardial infarction
- Persistent phrenic nerve palsy
- Stroke
- TIA
- Peripheral or organ thromboembolism
- Cardiac tamponade / perforation
- Pericarditis
- Pulmonary edema
- Vascular access complications
- Heart block
- Gastric motility/pyloric spasm disorders

Late onset: Either of the following with an Onset Date any time through the completion of 12-month follow-up visit:

- PVS[4]
- Atrio-esophageal fistula

Table 5 Composite Safety Endpoint Definitions

Related SAE	Description/Criteria
Death	AE resulting in subject death
Myocardial infarction	Defined as the presence of any one of the following criteria: (1) detection of ECG changes indicative of new ischemia (new ST- T wave changes or new LBBB) that persist for more than 1 hour (2) development of new pathological Q waves on an ECG (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

[4] For subjects ablated with more than one energy modality, the CEC will – to the extent possible – determine which modality(ies) are related to any observed PVS.

Related SAE	Description/Criteria
Persistent phrenic nerve palsy	Defined as absent phrenic nerve function as assessed by a change from baseline in the elevation of a hemidiaphragm, persisting beyond the end of the procedure that is: • Demonstrated radiographically by either an inspiration / expiration chest X-ray or fluoroscopic sniff test • Not due to a demonstrable pulmonary process such as atelectasis or pleural disease. Persistent: not resolved at the time of the last follow-up visit.
Stroke	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 1 side of the body • Dysphasia or aphasia • Hemianopia, amaurosis fugax, or • Other neurological signs or symptoms consistent with stroke The diagnosis of stroke requires that there be no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences). The duration of the defined neurological deficit(s) must be: • ≥ 24-hours; OR • < 24-hours if o Therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty), OR o Available neuroimaging documents a new hemorrhage or infarct, OR o The neurological deficit results in death.
Transient ischemic attack	Defined as a new focal neurological deficit with: • Symptom resolution within 24 hours • No new tissue injury demonstrated (if neuroimaging is obtained)
Peripheral or organ thromboembolism	A cardiac thrombus that occludes a more distal arterial site other than the central nervous system (see Stroke). Cutaneous petechiae are excluded from this definition.
Cardiac tamponade / perforation	The development of a pericardial effusion post-ablation that results in hemodynamic compromise, requires pericardiocentesis or results in a 1-cm or more pericardial effusion as documented by echocardiography. Cardiac tamponade/perforation should also be classified as “early” or “late” depending on whether it is diagnosed during or following initial discharge from the hospital.
Pericarditis	The development of pericardial inflammation post-ablation that results in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization, or persists for more than 30 days following the ablation procedure.

Related SAE	Description/Criteria
Pulmonary edema	Respiratory compromise resulting from cardiac dysfunction or volume overload leading to increased interstitial lung fluid requiring intubation or parenteral diuretics.
Vascular access complications	Vascular access complication (e.g., groin hematoma, AV fistula, pseudoaneurysm) requiring a significant and invasive intervention (e.g., surgical repair, blood transfusion or thrombin injection).
Heart block	Impairment of AV conduction that is related to a protocol-stipulated cardiac ablation procedure and that requires permanent pacing.
Gastric motility/pyloric spasm disorders	Evidence of impaired gastric motility or pyloric spasm that prolongs hospitalization, requires hospitalization or persists for more than 30 days.
Pulmonary vein stenosis	>70% reduction of an ablated measured PV diameter* compared to the baseline CT/MRI scan, as determined by the CICL.
Atrio-esophageal fistula	Confirmation of a fistulous connection between the atrium and the lumen of the esophagus by radiographic, endoscopic or post-mortem examination

AV = atrioventricular, **CICL** = Cardiac Imaging Core Laboratory, **CT** = computed tomography, **ECG** = electrocardiographic, **LBBB** = left bundle branch block, **MRI** = magnetic resonance imaging, **PV** = pulmonary vein, **SAE** = serious adverse event.
* See Section 6.3.14 for the definition of PV diameter.

7.2 Secondary Safety Endpoint

The secondary safety endpoint is Aggregate PV Cross-Sectional Area, defined as the paired comparison of change in the computed Aggregate PV Cross-Sectional Area (**Section 6.3.14**) between baseline and 3 months in MITT subjects compared between randomization groups (intent-to-treat, regardless of re-ablation with any second energy modality). Supplemental analyses will include MITT single-procedure subjects and the PP population.

7.3 Additional Safety Analyses

Each of these assessments will be tested for nominal p values between Pulsed Field Subjects and Thermal Subjects:

1. **Severe Ablation Complications:** The proportion of subjects in each randomization group with one or more of the following CSE components as defined in Table 4 will be compared between treatment groups.
   - PVS
   - Persistent phrenic nerve palsy
   - Atrio-esophageal fistula
2. **Nonserious / Serious CSEs:** The proportion of subjects in each randomization group with any device or procedure-related AE in the CSE definitions table without regard for serious or nonserious categorization.
3. **Post-Blanking Cardioversions:** The proportion of subjects in each randomization group with 1 or more post-Blanking Period direct-current (electrical) cardioversions.

4. **Post-Blanking Arrhythmia Hospitalizations:** The proportion of subjects in each randomization group with 1 or more post-Blanking Period hospitalizations primarily due to arrhythmia or arrhythmia complications.
5. **Any Related SAE:** The proportion of subjects in each randomization group with any device- or procedure-related SAE.
6. **Any Related Stroke or TIA:** The proportion of subjects in each randomization group with any device- or procedure-related stroke or TIA.
7. **Categorized PV Dimensional Changes:** The distribution of PV dimensional changes between baseline and 3-month MRI/CT scans
    a. Categorized by the % change in the PV diameters: 0-29.9%, 30-49.9%, 50-69.9% and ≥ 70% between randomization groups.
    b. Categorized by the % change in computed cross-sectional areas: 0-49.9%, 50-74.9%, 75-89.9% and ≥ 90% between randomization groups.
8. **Thermal Group RF Ablation / Cryoablation Safety Assessment:** a descriptive comparison of safety outcomes between the two Thermal Group technologies.
9. **Learning Curve Safety Assessment:** For Pulsed Field Group only, per site and per operator learning curve assessment of the primary safety endpoint and supportive assessment of the secondary safety assessment and / or components of the CSE by enrollment sequence.

7.4 Primary Effectiveness Endpoint

Treatment Success: The primary effectiveness endpoint is Treatment Success in MITT Subjects, defined as:

1. **Acute Procedural Success** (**Section 6.3.1**) AND
2. **Chronic Success**, defined as freedom from:
    a. At the Index / Rescheduled Index Procedure: Use of a non-randomized treatment modality for PVI
    b. After the Blanking Period:
        i. Occurrence of any Detectable AF, AFL or AT (**Section 6.3.11**) (excluding CTI-dependent flutter confirmed by EP study)
        ii. Any cardioversion for AF, AFL or AT (excluding for CTI-dependent flutter)
        iii. Use of any Type I or Type III antiarrhythmic medication for the treatment of AF, AFL or AT
    c. At any time:
        i. Re-ablation for AF, AFL or AT (other than for CTI-dependent flutter)
        ii. Use of amiodarone, except intra-procedurally to control an arrhythmia

Endpoint status will be assessed through the Month 12 Assessment (Day 360 ± 30).

7.5 Secondary Effectiveness Endpoint

The secondary effectiveness endpoint is the same as the primary effectiveness endpoint but will be tested for superiority rather than non-inferiority. The proportion of Pulsed Field Subjects with Treatment Success will be assessed for superiority to the proportion of Thermal Subjects with Treatment Success.

7.6 Additional Effectiveness Analyses

Each of these assessments will be tested for nominal p values between Pulsed Field Subjects and Thermal Subjects:

1. **Acute Procedural Success:** (**Section 6.3.1**) Assessed on a per subject basis.
2. **Acute Vein Success:** (**Section 6.3.3**) Assessed on a per vein basis, for all veins and for each category of vein.
3. **Chronic Success** (**Section 7.4**).
4. **Chronic Success Allowing Re-ablation:** Chronic Success (**Section 7.4**) including as successes those subjects who failed only because they underwent a re-ablation procedure during the Blanking Period.
5. **Chronic Success Allowing AADs:** Chronic Success (**Section 7.4**) including as successes those subjects who failed only because they received post-Blanking Period treatment with a Type I / III AAD.
6. **Treatment Success Allowing Re-ablation:** Treatment Success (**Section 7.4**) including as successes those subjects who failed only because they underwent a re-ablation procedure during the Blanking Period.
7. **Treatment Success Allowing AADs:** Treatment Success (**Section 7.4**) including as successes those subjects who failed only because they received post-Blanking Period treatment with a Type I / III AAD.
8. **Treatment Success with PVI/CTI only:** Treatment Success (**Section 7.4**) excluding all subjects whose Index / Rescheduled Index Procedure required atrial ablation other than PVI or CTI.
9. **Early Recurrence of AF:** The proportion of subjects with early recurrence of AF ≤ Day 90 after the initial study ablation.
10. **Rate of Re-ablation:** The proportion of subjects requiring any re-ablation for atrial arrhythmias through 12 months of follow-up.
11. **PVI Durability at Re-Ablation:** For those subjects undergoing any re-ablation procedure with LA access during study follow-up, a per vein and a per subject assessment of PVI durability.
12. **CTI Ablation Failure:** Proportion of subjects who undergo a first CTI ablation at the Index Procedure / Rescheduled Index Procedure who have recurrent typical (right-sided) AFL through 12 months of follow-up.
13. **Thermal Group RF Ablation / Cryoablation Effectiveness Comparison:** A descriptive comparison of effectiveness measures between the two Thermal Group technologies.
14. **AF Symptom Assessment:** A descriptive comparison of the change in AF symptom frequency from baseline to 12 months.
15. **Learning Curve Effectiveness Assessment:** For the Pulsed Field Group only, per site and per operator learning curve assessment of the primary effectiveness endpoint and supportive analyses of related effectiveness and procedural data by enrollment sequence.

7.7 Procedural Assessments

Each of these assessments will be tested for nominal p values between Pulsed Field Subjects and Thermal Subjects:

1. Assessments of procedure durations

a. Procedure time (initiation of venous access to venous access closure)
b. LA dwell time (total time an ablation catheter is in the LA)
c. Total ablation time (first ablation to last ablation)
d. Total mapping time (total time spent mapping)
e. Fluoroscopy time (total duration of exposure)

2. Characterization of lesion sets:
    a. PVI ablations
    b. CTI ablations
    c. For subjects undergoing required LA ablations for an accessory pathway, AVNRT, left-sided AFL or incessant AT, a description of lesion sets utilized

7.8 Quality of Life Assessments

Quality of Life (QoL) will be assessed at baseline and 12 months using two assessments. These assessments will be tested for nominal p values between Pulsed Field Subjects and Thermal Subjects:

1. The EuroQol standardized questionnaire of health states (EQ-5D-3 L) at baseline and 12 months (The EuroQol Group. EuroQol - a new facility for the measurement of health-related quality of life. Health Policy 1990;16:199-209)
2. Atrial Fibrillation Effect on Quality of Life (AFEQT) at baseline and 12 months (Spertus J, Dorian P, Bubien R, et al. Development and validation of the Atrial Fibrillation Effect on QualiTy-of-LIfe (AFEQT) Questionnaire in patients with atrial fibrillation. Circ Arrhythm Electrophysiol 2011;4:15-25)

8. Adverse Events, Device Effects, Malfunctions and Deficiencies

8.1 Anticipated Adverse Events

The following is a list of AEs that may possibly be caused by or associated with the proposed use of the investigational devices and other devices, the failure, misuse or malfunction of the investigational devices or other devices, or the related procedures stipulated by this protocol or associated with this clinical study.

Recurrent AF for the purposes of this protocol is not an AE, but a continuation of a previous condition that is potentially a failure of effectiveness.

- Access site complications (e.g., hematoma, fistula, pseudo-aneurysm, laceration, bleeding) potentially requiring surgical intervention
- Air embolism
- Allergic reaction or fever resulting from contact with catheters or drugs
- Anemia
- Arrhythmia, potentially requiring cardioversion, defibrillation, or rhythm management device
- Arteriovenous fistula
- Back pain
- Bed sores
- Bleeding, hematoma, hemorrhage or aneurysm at vascular access sites
- Blood pressure changes including hypotension or hypertension
- Cardiac tamponade or perforation
- Cardiac arrest or cardiac failure
- Cardiogenic shock
- Catheter entrapment potentially requiring endovascular or surgical intervention
- Conduction system injury, either transient or permanent, potentially requiring pacemaker insertion
- Congestive heart failure
- Coronary artery or vein injury
- Death
- Drug allergic reaction or side effects (e.g., from contrast, steroids, analgesics, anesthetics, anticoagulants, sedatives)
- Embolism with damage to body structures due to presence of thrombus, particulate, device fragments or the introduction of air
- Esophageal injury, ulcer or fistula
- Gastric motility / pyloric spasm disorders
- Hemorrhage
- Hemodynamic compromise
- Hemopericardium
- Hemoperitoneum
- Hemothorax
- Local infection, systemic infection and/or sepsis
- Muscle contractions due to electric stimulation
- Myocardial infarction / ischemia

- Nerve damage
- Organ failure
- Pain
- Perforation (e.g., of diaphragm, liver, lung and/or vessels).
- Pericardial irritation with pain
- Pericardial effusion
- Pericarditis
- Peritonitis
- Phrenic nerve injury with potential paralysis of the diaphragm and breathing impairment
- Pneumomediastinum
- Pneumopericardium
- Pneumoperitoneum
- Pneumothorax
- PV injury, perforation or stenosis
- Risk of cancer or birth defect/harm to fetus from x-ray exposure
- Skin burns/irritation from X-ray exposure
- Stroke / TIA
- Surgical procedure to correct any anticipated AE
- Thrombosis
- Vessel damage, dissection, or occlusion.

8.2 Adverse Event Review and Adjudication

This study will utilize a CEC for the review and adjudication of AEs. All safety analyses will utilize the adjudicated rather than site determination of an AE's characteristics in those instances where the CEC has adjudicated that characteristic to be different than the site's determination. See **Section 12.2.4**.

8.3 Adverse Events

An AE is any 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.

NOTE 1: This definition includes events related to the investigational medical device or the control devices.
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 investigational medical devices.
NOTE 4: This definition excludes medical conditions, findings or abnormalities which are determined to have been present at the time of enrollment, which are defined as pre-existing conditions. Pre-existing conditions will not be included in the AE dataset. However, a worsening of a pre-existing condition during the study does constitute an AE.
NOTE 5: This definition excludes otherwise uncomplicated recurrent AF.

8.4 Serious Adverse Events

An SAE includes any of the following types AEs whether or not related to the investigational device or procedures:

- Any AE resulting in death
- Any AE which is life-threatening
- Any AE resulting in hospitalization, or significant prolongation of an existing hospitalization
- Any AE resulting in a persistent, significant impairment
- Any AE requiring significant medical or surgical intervention to prevent a significant impairment
- Any AE resulting in a congenital anomaly or birth defect

NOTE 1: "Life-threatening" means that the study subject was at a substantial and immediate risk of dying due to that AE as it occurred. "Life threatening" AEs do not include an AE that – had it occurred in a more severe form – might have caused death.

NOTE 2: "Hospitalization" is a physician-ordered inpatient hospital stay from one calendar day to the next or longer. Hospitalization does not include an outpatient facility visit or ER visit.

NOTE 3: A "significant" prolongation is related to the AE, excludes delays waiting for diagnostic results, is medically necessary and extends the hospital stay by at least one calendar day.

NOTE 4: "Persistent" is defined as not resolving by the end of study follow-up.

NOTE 5: "Significant impairment" is defined as a substantial disruption of a person's ability to conduct normal life functions.

NOTE 6: A "significant medical or surgical intervention" indicates a procedure or therapy with significant novel risk or subject discomfort, that results from the AE.
A "significant medical or surgical intervention" does not include oral medication, noninvasive diagnostic testing or blood testing, routine intravenous fluids, the administration of antibiotics, or a pharmacologic or electric cardioversion for AF, AFL or AT.

8.5 Procedure, Device and COVID-19 Relatedness

The causality of all AEs in relation to 3 types of potential causes – the investigational devices, a protocol-stipulated procedure or a confirmed COVID-19 infection – will be determined according to four different levels of causality:

1. **Definitely Not Related:** An AE for which sufficient information exists to determine that it is unrelated to the potential cause.
2. **Unlikely Related:** An AE that occurs during or after device use, study procedure or COVID-19 infection that could also have been produced by other disease states or therapies. The Investigator determines after review of available clinical data that the AE is unlikely to have been related to the potential cause.
3. **Likely Related:** An AE that occurs during or after device use, study procedure or COVID-19 infection that could also have been produced by other disease states or therapies. The Investigator determines after review of the clinical data that the AE is likely to have been related to the potential cause.

4. **Definitely Related:** An AE that occurs during or after device use, study procedure or COVID-19 infection, is known to be a complication of device use, study procedure or COVID-19 infection and for which no other reasonable explanation can be determined.

For the determination of device, procedure and COVID-19 relatedness for this study's outcome measures, "Likely related" and "Definitely related" AEs will be deemed "related" and "Definitely not related" and "Unlikely related" AEs will be deemed "unrelated." A listing of all AEs including their relatedness and seriousness will be included in the final Clinical Study Report.

8.6 Device Effects

8.6.1 Adverse Device Effects

An Adverse Device Effect (ADE) is an AE related to the use of an investigational medical device.

NOTE 1: This definition includes AEs 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 use error or from intentional misuse of the investigational medical device.

NOTE 3: "Related to the uses of an investigational medical device" shall be defined for this protocol as a determination that the effects were likely or definitely related to an investigational device.

8.6.2 Serious Adverse Device Effects

A Serious Adverse Device Effect (SADE) is an ADE that has resulted in any of the consequences characteristic of an SAE.

8.6.3 Unanticipated Adverse Device Effects

An Unanticipated Adverse Device Effect (UADE) is an SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report as embodied in **Section 8.1**.

NOTE 1: An anticipated ADE / SADE is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report or included in **Section 8.1**.

NOTE 2: If an SAE is determined to be likely or definitely related to the device and has not been previously anticipated, the clinical finding would be classified as an unanticipated adverse device effect (UADE).

8.7 Device Deficiencies

A Device Deficiency is an inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

8.8 Use Errors

A "Use Error" is an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

NOTE 1: Use error includes slips, lapses and mistakes.
NOTE 2: An unexpected physiological response of the subject does not in itself constitute a use error.

8.9 Malfunctions

A Malfunction is a failure of an investigational medical device to perform in accordance with its design specifications and intended purpose when used in accordance with the instructions for use or this protocol.

8.10 Event Management and Reporting

8.10.1 Adverse Events

All AEs, including all SAEs, will be monitored from the time of the Index Procedure through study exit.

All AEs and SAEs must be documented in the subject chart and recorded in the appropriate CRF. A description of the event, including the start date, resolution date, action taken, and the outcome shall be provided along with the Investigator's assessment of the seriousness of the event and the relationship between the AE and the study devices and/or procedures.

All AEs should be followed until the event is resolved, judged to be chronically stable or 12-month study follow-up has been completed, whichever occurs first. The investigational site will provide relevant follow-up information to the Sponsor or designee upon request.

Any SAE will be reported to CRO within 24 hours of the site becoming aware of the event.

8.10.2 Adverse Device Effects

The Investigator shall record an ADE or SADE on the appropriate CRF as an aspect of reporting the associated AE.

An ADE will be reported promptly to the CRO.

A UADE will be reported to the CRO within 24 hours of the site becoming aware of the event.

8.10.3 Device Deficiency and Malfunctions

The Investigator shall record a Device Deficiency / Malfunction on the appropriate CRF.

A Device Deficiency or Malfunction that was associated with an SAE, or that could have contributed to an SAE, will be reported to the CRO within 24 hours of the site becoming aware of the event.

A Device Deficiency or Malfunction that did not contribute and would not likely contribute to an SAE, will be reported to the CRO within 7 days of the site becoming aware of the event.

8.10.4 Other Assessment and Reporting Requirements

The Sponsor's Quality Assurance function shall ensure an assessment is completed for each reported Device Deficiency / Malfunction. Such information shall be summarized in the final Clinical Study Report. Depending on the local requirements or following agreement between both parties, the Sponsor, its designated representative (CRO) or the Principal Investigator will be responsible for performing safety reporting to the IRB according to the relevant local regulatory requirements. The Sponsor or designated representative (CRO) will be responsible for reporting to the FDA according to the relevant reporting guidelines.

8.10.5 Reporting AEs, ADEs and Device Deficiencies

The following Table summarizes the various reporting requirements for events defined in this section.

Table 6 Reporting AEs, ADEs and Device Deficiencies

Type of Event	Process
Unanticipated adverse device effect (UADE)	**Submit within 24 hours** after study site personnel first learn of the event and to the IRB within the IRB required timeframe.
Serious adverse events, Serious Adverse Device Effects (SAE, SADE)	
Device deficiencies / malfunctions that contributed to or could contribute to an SAE	
Device deficiencies / malfunctions that did not contribute to or are unlikely to contribute to an SAE	**Submit within 7 days** after study site personnel first learn of the event and to the IRB (if required) within the IRB required timeframe.
Non-serious adverse device effect (ADE)	Submit to the CRO as soon as possible after Investigator has become aware of the event and to the IRB (if required) within the IRB required timeframe.

Documents should be sent electronically to:

CRO:	Medpace **Email: Medpace-safetynotification@medpace.com**

Return of Subject Device:

The device involved in the AE, SAE, Device Deficiency and/or Malfunction as described above is to be returned to the Sponsor or Sponsor's designee for analysis and investigation, as appropriate. The Study Coordinator shall contact the Sponsor for instructions on returning the device.

9. Statistical Procedures and Reporting

A separate Statistical Analysis Plan (SAP) governs the analysis and reporting of the data from this investigation. This section summarizes the essential elements of that plan.

9.1 General Statistical Considerations

This study is designed using Bayesian statistical methods, with non-informative prior distributions for all parameters. The appropriate sample size is determined adaptively via a Goldilocks design[36], in which the adequacy of the sample size is assessed at several pre-specified enrollment milestones. All primary and secondary objectives will be analyzed using Bayesian methods, though frequentist methods may be used for selected analyses such as baseline comparisons, poolability and sensitivity analyses and a subset of the pre-specified Additional Analyses.

When descriptive statistics are used, continuous variables will be summarized using standard quantitative statistics: number of available observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations will also be reported. Categorical variables will be summarized using classical frequency statistics: number of available observations and percentages by categories. Percentages will be calculated on the number of available observations. The number of missing observations will also be specified.

A full data listing will be prepared. Data will be pooled from all study sites.

All related and resulting reports, documents and data will be produced and maintained in such a way as to ensure their control and the protection of subject privacy. Data files and analytic reports will be archived according to requisite regulatory standards.

Data gathered regarding COVID-19 impacts – including missed, late or alternative assessments, COVID-19-related complications, subject withdrawals or Severe COVID-19 status – will be used as required to address potential biases or to perform sensitivity analyses related to the impact of COVID-19 on the study integrity or outcomes. A tabulation and listing of all subjects impacted by COVID-19 will be included, with a description of how that subject's participation and/or outcome may have been altered. COVID-19-related deviations to the schedule, type of assessment and assessment windows will be aggregated and reported.

9.2 Randomization

Subjects meeting all pre-randomization inclusion and exclusion criteria who sign an ICF will be randomized. The study staff will confirm documented inclusion / exclusion success prior to requesting randomization.

Randomization will be achieved by an interactive web-based or phone-based system. Randomization will be stratified by site and use a permuted block design with randomly varying block sizes.

Subjects who meet the inclusion and exclusion criteria will be randomized using a 1:1 allocation ratio.

Each site will utilize only one control modality – either RFA or CBA – and will use that modality for all subjects randomized to the Thermal Group. Site activation and enrollment will be monitored and when necessary controlled to maintain a minimum 40% proportion of Thermal Subjects in either the RFA or CBA modality.

9.3 Subject Disposition

The disposition of all subjects enrolled in the study will be described in tables and diagrams, including numbers screened, randomized, excluded, treated and assessed at each scheduled follow-up interval. Roll-In Subjects will be assessed separately. Severe COVID-19 Subjects will be noted and the potential impacts on the study results assessed in sensitivity analyses. Subjects who do not complete the study will be enumerated and the reason(s) for their discontinuation will be described.

9.4 Populations for Analysis

Study populations, including those for statistical analysis, are defined in **Section 3.4**.

9.5 Assessment of the Primary Safety Endpoint

The primary safety endpoint for this study is the CSE defined in Protocol **Section 7.1**.

The principal analysis population for the safety endpoints is the Safety Population. Analysis in the PP Population will also be conducted as a sensitivity analysis.

The analysis of the primary safety endpoint is a test of non-inferiority of the event rate at 12 months using a non-inferiority margin of 8%. The null and alternative hypotheses are presented below for primary safety:

$$H_0: Q_T \geq Q_C + 0.08 \text{ versus } H_A: Q_T < Q_C + 0.08$$

where Q_T is the CSE proportion in the Pulsed Field (Treatment) Group and Q_C is the CSE proportion in the Thermal (Control) Group. The differences in the proportion of subjects with 1 or more CSE events between the Pulsed Field Group and the Thermal Group will be tested with a Bayesian statistical method and the prior distributions for Q_T and Q_C in these calculations are Beta (0.5, 0.5), which is the Jeffreys non-informative prior. Q_T will be deemed to be non-inferior to Q_C if it can be established that the posterior probability $Pr(H_A \mid data) > \Psi_{saf}$, where Ψ_{saf} is a pre-specified threshold value that controls the one-sided type I error rate (under simulation) at level 0.05. In the absence of missing data, the posterior distributions for Q_T and Q_C would be conjugate Beta distributions. However, some missing data are expected. Therefore, Bayesian multiple imputation of 12-month outcomes will be employed in the principal analysis. The imputation model accounts for primary outcome information up through the time of censoring. Details on the modeling for this imputation are given in the SAP.

9.6 Assessment of the Primary Effectiveness Endpoint

The primary effectiveness endpoint for this study is Treatment Success defined at **Section 7.4**.

The principal analysis population for the primary effectiveness endpoint is the MITT Population. Analysis in the PP Population will also be conducted as a sensitivity analysis.

The primary effectiveness endpoint for this study is Treatment Success, which will be analyzed as a test of non-inferiority of the event rate at 12 months using a non-inferiority margin of 15%. The null and alternative hypotheses are:

$$H_0: P_T \leq P_C - 0.15 \text{ versus } H_A: P_T > P_C - 0.15$$

where P_T is the Treatment Success rate at 12 months in the Pulsed Field Group and P_C is the Treatment Success rate at 12 months in the Thermal (Control) Group.

This study is designed using Bayesian statistical techniques and the prior distributions for P_T and P_C in these calculations are Beta (0.5, 0.5), which is the Jeffreys non-informative prior. P_T will be deemed to be non-inferior to P_C if it can be established that the posterior probability $Pr(H_A \mid data) > \Psi_{eff}$, where Ψ_{eff} is a pre-specified threshold value that controls the one-sided type I error rate (under simulation) at level 0.05. In the absence of missing data, the posterior distributions for P_T and P_C would be conjugate Beta distributions. However, some missing data are expected. Therefore, Bayesian multiple imputation of 12-month outcomes will be employed in the principal analysis. The imputation model accounts for primary outcome information up through the time of censoring. Details on the modeling for this imputation are given in the SAP.

9.7 Sample Size Considerations

Please refer to the SAP for a full treatment of this topic.

Parameter selection: IDE pivotal studies for the treatment of drug-resistant symptomatic PAF are highly standardized and utilize nearly identical definitions of primary effectiveness and similar definitions of primary safety. Published IDE studies with available information comparing new devices with approved control devices have all used non-inferiority designs with one-sided alpha of 0.05 and 15% effectiveness margins and either 8% or 9% safety margins.

Peer-reviewed studies do not undergo the same scrutiny or utilize the rigor of FDA-supervised studies and therefore their estimates of effectiveness and safety are not entirely comparable to IDE studies. The consensus regarding high quality randomized comparisons between currently approved technologies is that none are superior to another. Perhaps the largest non-IDE study comparing RFA and CBA technologies (Fire and Ice[37]) found no difference between the two and also reported very similar primary outcomes to IDE studies.

Sample Size Requirements for Safety:

Although the pre-specified statistical analysis methods are Bayesian, standard frequentist considerations are used to guide sample size selection. The sample size for primary safety computed for a Farrington-Manning test with PASS 13 indicates that, for 1:1 randomization, 90% power, alpha=0.05 (one-sided), CSE rate in both Groups of 0.08 and non-inferiority margin of 0.08, the study requires a completed sample size of 214 subjects in each Group, for a total of 428. Assuming a 5% rate of loss-to-follow-up (LTFU), 450 subjects are needed.

There is uncertainty in the CSE rate, and this can have dramatic impact on sample size requirements. If the CSE rate is 0.07 in the Pulsed Field group but 0.08 in the Thermal

group, 326 subjects are required to achieve 90% power (344 after compensating for 5% LTFU). If the CSE rate is 0.10 in the Pulsed Field group but 0.08 in the Thermal group, 690 subjects are required to achieve 85% power (727 after compensating for 5% LTFU).

This uncertainty in the CSE rate motivates the use of a design wherein the sample size is adaptively determined, with possible sample sizes ranging from 350 to 750.

Sample Size Requirements for Effectiveness:

Although the pre-specified statistical methods are Bayesian, standard frequentist considerations are used to guide sample size selection. The sample size required for the primary effectiveness endpoint obtained by PASS 13 for 1:1 randomization, 90% power, alpha=0.05 (one-sided), success rates in each group of 0.65 and non-inferiority margin δ=0.15 is 172 subjects in each arm, for a total of 344 subjects. Similar to the safety objective, there is uncertainty in the success rates, especially in the Pulsed Field group. If the success rate in the Pulsed Field group is 0.625 but 0.65 in the Thermal group, 502 subjects are required to achieve 90% power (558 after compensating for up to 10% missing data). If the success rate in the Pulsed Field group is 0.70 but 0.65 in the Thermal group, only 186 subjects are required to achieve 90% power (207 after compensating for missing data).

This uncertainty in the Treatment Success rate motivates the use of a design wherein the sample size is adaptively determined, with possible sample sizes ranging from 200 to 550.

Number of Enrolled Subjects:

The primary population for the analysis of effectiveness is the MITT Population. The Safety Population should be similar but will not be smaller. Considering the joint sample size needs of the primary safety and effectiveness objectives, the primary analysis population may range from a minimum of 350 to a maximum of 750.

To achieve a sample size of 750 MITT Subjects, up to 900 subjects may be enrolled consisting of 750 MITT and up to 105 Roll-In Subjects and up to 45 ITT Subjects (6%) who do not meet the criteria for the MITT Population.

9.8 Analysis Plan

This trial is designed using Bayesian statistical techniques. The appropriate sample size is determined adaptively via a Goldilocks design[38], with possible sample sizes of N=350, 450, 550, 650, and 750.

The sample size determination algorithm is as follows. At a pre-defined interim analysis point (e.g., when $N=N_i$ subjects have been accrued into the MITT population; N_i = 350, 450, 550 and 650), four predictive probabilities are calculated:

$PP_{int,saf}$ = Predictive probability that the trial will establish non-inferiority for safety, once the current sample (N_i) is followed to 12 months.

$PP_{max,saf}$ = Predictive probability that the trial will establish non-inferiority for safety, assuming the maximum sample size (750) is attained and followed to 12 months.

$PP_{int,eff}$ = Predictive probability that the trial will establish non-inferiority for effectiveness, once the current sample (N_i) is followed to 12 months.

$PP_{max,eff}$ = Predictive probability that the trial will establish non-inferiority for effectiveness, assuming the maximum sample size (750) is attained and followed to 12 months.

If $PP_{int,saf}$ exceeds a suitably high threshold $W_{saf,i}$, **and** if $PP_{int,eff}$ exceeds a suitably high threshold $W_{eff,i}$, subject accrual will stop because final success looks probable with the current sample. On the other hand, if $PP_{max,saf}$ is less than a suitably low threshold $F_{saf,i}$, **or** if $PP_{max,eff}$ is less than a suitably low threshold $F_{eff,i}$, subject accrual will stop because final success is unlikely. In either case, follow-up continues to 12 months for all subjects, at which time the final analysis will occur. If neither of these conditions obtains, enrollment will continue to the next larger sample size (subject to the maximum of 750). These analyses are termed "Interim Sample Size Looks." Further details on the calculation of these predictive probabilities and specification of the thresholds $\{W_{eff,i}, F_{eff,i}, W_{saf,i}, F_{saf,i}\}$ are provided in the SAP.

Once subject accrual has stopped, all accrued subjects will be followed to 12 months, and then the inferential tests of non-inferiority will occur as described in **Sections 9.5 and 9.6**. This is the only time that non-inferiority is tested.

9.9 Assessment of the Secondary Safety Endpoint

One endpoint – Aggregate PV Cross-Sectional Area (Section 7.2) – will be formally tested as a secondary safety endpoint.

The paired comparison of change in the Aggregate PV Cross-Sectional Area between baseline and 3 months will be compared between Pulsed Field Subjects and Thermal Subjects, testing whether the reduction in Aggregate PV Cross-Sectional Area is significantly less in the Pulsed Field Subjects. Within-subject changes in Aggregate PV Cross-sectional Area (3-month minus baseline) will be compared between Pulsed Field and Thermal groups via a Bayesian version of a t-test. The null and alternative hypotheses are:

$$H_0: \mu_T - \mu_C = 0 \text{ versus } H_A: \mu_T - \mu_C > 0,$$

where μ_T represents the change (3 months minus baseline) in area in the treatment (Pulsed Field) group, and μ_C represents the corresponding change in area in the control (Thermal) group. The null hypothesis will be rejected if the posterior probability $P(H_A \mid \text{data})$ exceeds a threshold value $\Psi_{PV} = 0.975$, corresponding to a one-sided significance level of 0.025.

The population for analysis will be MITT Subjects with pre- and post-procedure PV dimensional data related to one or more protocol-specified ablation lesions. Supplemental analyses will be performed using MITT single procedure subjects and the PP population.

9.10 Assessment of the Secondary Effectiveness Endpoint

The secondary effectiveness endpoint is Treatment Superiority, which is Treatment Success (**Section 7.4**) tested for superiority between the Pulsed Field and Thermal Groups.

The principal analysis population for the secondary effectiveness endpoint is the MITT Population. Analysis in the PP population will also be conducted as a sensitivity analysis.

The null and alternative hypotheses are provided below.

H_0: $P_T \leq P_C$ versus H_A: $P_T > P_C$

where P_T is the Treatment Success rate at 12 months in the Pulsed Field Group, and P_C is the Treatment Success rate at 12 months in the Thermal Group. Modeling will be identical to the test of non-inferiority, and superiority will be concluded if the posterior probability $Pr(H_A \mid data) > \Psi_{eff,sup}$, where the threshold $\Psi_{eff,sup}$ is a pre-specified threshold value that controls the one-sided type I error rate (under simulation) at level 0.025. In the absence of missing data, the posterior distributions for P_T and P_C would be conjugate Beta distributions. However, some missing data are expected, and especially so at the interim analysis. Therefore, Bayesian multiple imputation of 12-month outcomes will be employed in the principal analysis. The imputation model accounts for primary outcome information up through the time of censoring. More detail on this imputation is given in the Statistical Analysis Plan.

9.11 Assessment of Subject Blinding

Subjects will complete a survey regarding their opinion as to which study group they were assigned to at the time of Index Procedure / Rescheduled Index Procedure discharge and at the 12-month follow-up visit. Self-assessment of treatment status will be formally assessed according to the procedures defined by Bang 2004[39] and James 1996.[40]

10. Core Laboratories

10.1 Arrhythmia Core Laboratory

A qualified ACL will be established to receive, review and assess all protocol-stipulated ECGs, EMs and Holter monitors.

10.1.1 Procedures

Documented procedures will be established for the provision of equipment, the training of study subjects, the receipt of outputs, the assessment of arrhythmia and the transmission of results for inclusion in the study dataset.

10.1.2 Event Monitors

Each subject:

- Will be introduced to the use and importance of EMs at the Baseline visit
- Will be fully instructed on the use of an EM at the Day 60 EM training.

Either the ACL or the site will provide the subject with an EM not later than the Day 60 EM training to be used beginning at the time of the Day 90 Assessment and weekly thereafter and also for any symptomatic episodes throughout the remainder of the 12-month study follow-up.

Careful monitoring and subject follow-up will be implemented to ensure compliance with the required weekly scheduled and ad hoc symptomatic utilization and transmission of the EMs. Individual missed weekly transmissions will not be counted as protocol deviations, but a subject with less than 80% of weeks covered by at least one transmission at the end of follow-up will be considered a protocol deviation.

The EM will be returned to the ACL or the site at the time of the subject's exit from the study. ECG data from the EM will be analyzed by the ACL.

10.1.3 Holter Monitors

Each subject:

- Will be introduced to the use and importance of the Holter monitoring at the Baseline visit and the use of the EM hardware for this purpose.
- Will be fully instructed on the use of a 72-hour continuous ECG (Holter) monitor prior to the 6-Month and 12-Month Holter monitoring.

Careful monitoring and subject follow-up will be implemented to ensure that the device will be utilized by the subject for the nominal 72-hour period for both the Month 6 and Month 12 Assessments.

The 12-Month Holter monitor should be performed prior to the completion of the Month 12 Assessment.

ECG data from the Holter monitor will be analyzed by the ACL.

10.1.4 Arrhythmia Data Review and Transmission

The ACL will analyze all protocol-stipulated ECG, EM and Holter data and will make available the primary data for review and transmit the rhythm analyses of each monitoring study to the CRO for inclusion in the study dataset.

10.1.5 CEC Over-Reads of Potential Endpoints

Any ECG, EM or Holter result that is reported by the ACL to contain a first post-Blanking Period occurrence of AF, AFL or AT will be reviewed by the CEC to establish the presence or absence of a primary effectiveness endpoint event. Such adjudications will be repeated to the extent necessary to confirm the date, duration and rhythm of any potential Detectable AF, AFL or AT that will determine a post-Blanking Period Treatment Failure.

The CEC's determination regarding Detectable AF, AFL or AT is final.

10.2 Cardiac Imaging Core Laboratory

A qualified CICL will be established to receive, review and assess all protocol-stipulated cardiac MRIs and CTs.

10.2.1 Procedures

Documented procedures will be established for the performance of cardiac imaging, the receipt of outputs, the assessment of images – most importantly changes in PV dimensions – and the transmission of results for inclusion in the study dataset.

10.2.2 Pulmonary Vein Dimensions

Each treated vein will have pre-ablation and 3-month post-ablation assessments of standardized diameters (**Section 6.3.14)**. Subjects with documented 3-month PVS will have a protocol-mandated 12-month post-ablation assessment.

10.2.3 Cardiac Imaging Data Review and Transmission

The CICL will analyze all PV dimensions, calculate changes in dimensions, make available the primary data for review and transmit the PV dimensional analyses of each imaging study to the CRO for inclusion in the study dataset.

10.2.4 CEC Review of Pulmonary Vein Stenosis Results

Any cardiac imaging report that is determined by the CICL to contain a PVS will be reviewed by the CEC to confirm the finding of a primary effectiveness endpoint event. The CEC may request a review of the finding but will not review the images. A proposed change in the CICL finding will require consent from the CICL.

10.3 Brain Imaging Core Laboratory

A qualified BICL will be established to receive, review and assess all protocol-stipulated brain MRIs for NAS Subjects.

10.3.1 Procedures

Documented procedures will be established for the performance of brain imaging in NAS Subjects to allow assessment of SCEs and SCLs, the receipt of outputs, the assessment of images – most importantly SCEs and SCLs – and the transmission of results for inclusion in the study dataset.

10.3.2 SCE and SCL Assessment

Each post-procedural brain MRI in NAS Subjects will be assessed according to standardized parameters for SCE and SCL findings.

10.3.3 Brain Imaging Data Review and Transmission

The BICL will analyze all diffusion weighted and FLAIR findings in NAS Subjects, make available the primary data for review and transmit the brain lesion analyses of each imaging study to the CRO for inclusion in the study dataset.

The CEC will not review brain imaging findings for determination of SCE and SCL findings in NAS Subjects.

11. Monitoring

11.1 Monitors

Clinical and medical monitors, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the study in accordance with a study monitoring plan.

11.2 Clinical Monitoring Activities

The monitors will evaluate compliance with the protocol, any specific recommendations made by the site's IRB and the signed Investigator Agreement. Phone contacts and site visits will be conducted to ensure that the protocol is being followed and that any protocol deviations are properly documented. Clinical monitoring will include a verification that the ICF was properly obtained for all enrolled study participants, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results and a review of source documents. The clinical monitor will verify that the CRFs agree with the source documentation and other records. The Investigator will make available to the monitor for review as requested ICFs, completed CRFs, source documentation and other relevant records for enrolled study subjects.

If a deficiency is noted during an on-site monitoring visit or at any other time during the study, the monitor is required to discuss the situation with the Investigator and the Sponsor to ensure compliance.

11.3 Monitoring Responsibility and Data Verification

The Sponsor or its designated representative, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the study. The accuracy of all (100%) collected data will be verified for:

- Eligibility criteria
- Baseline characteristics
- Primary safety and effectiveness endpoints
- Secondary endpoints
- AEs (including SAEs) and Device Deficiencies / Malfunction Reporting

Verification will utilize source documents including, but not limited to, medical records, office/ clinic notes, procedure reports, laboratory results, and physician and nursing progress notes. Verification and quality of data, monitoring of clinical study progress and Investigator compliance with the approved protocol will be conducted by the Sponsor or its designated representative.

11.4 Site Visits

The Sponsor or its designated representative must be allowed to visit the clinical site and have direct access to all study records throughout the duration of the study. Where this is not possible due to COVID-19-related disruption, every effort will be made by Sponsor and site personnel to achieve monitoring goals remotely. Study procedures for remote monitoring will be consistent with FDA Guidance Documents.

Specific monitoring requirements are detailed in the study-specific Monitoring Plan maintained in the FARAPULSE and CRO clinical study project files. The Investigator and / or institution will provide direct access to source data / documents for study-related monitoring, audits and regulatory review and inspection.

It is important that the Investigator and other relevant site personnel, including the research study coordinator, are available for consultation with the monitors during the monitoring visits and that sufficient time is devoted at the site for the monitoring process.

Additionally, telephone, email contact, and onsite visits 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 study.

If a deficiency is noted during the study, the monitor is required to discuss the situation with the site and the Sponsor (if required) to secure compliance. A Monitoring Site Visit Report will be issued to the Sponsor.

12. Study Management

The Sponsor has overall responsibility for the conduct of the study according to Good Clinical Practice Guidelines (ICH E6 Consolidated Guidance to Good Clinical Practice) as well as any conditions imposed by local and national regulatory authorities.

For this investigation, the Sponsor may have certain direct responsibilities and will otherwise delegate in writing responsibilities to appropriate and qualified consultants, contractors and / or CROs. Together, the Sponsor, consultants and CRO will ensure that the study is conducted according to the approved Clinical Investigation Plan (CIP), IRB-approved ICF and all applicable governing regulations. All personnel participating in the conduct of this clinical study will be qualified by education and/or experience to perform their tasks.

12.1 Ethical Considerations

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The Sponsor and the Investigator shall avoid improper influence or inducement of the subject, monitor, other Investigator or other parties participating in or contributing to the clinical investigation.

12.1.1 Study Conduct

The study will be performed in accordance with the relevant parts of the Code of Federal Regulations, ICH Guidelines for Good Clinical Practices and ethical principles consistent with the Declaration of Helsinki. The clinical investigation shall not begin until the required approval has been obtained from the FDA and the local IRB. Any additional requirements imposed by the regulatory authority or IRB shall be followed. These principles shall be understood, observed and applied at every step in this clinical investigation.

12.1.2 Ethics Review

Before any subject can be enrolled in this study, the local, central or national IRB and the FDA must review and approve the CIP and the ICF to be used. A subject cannot be asked to sign the ICF until the study has been fully approved by the institution's IRB and by the FDA. The Sponsor or their designated CRO will require a copy of any IRB correspondence, as well as the final IRB approval letter and the final IRB-approved ICF and approvals for the CIP and ICF revisions on amendments from the IRB. The Sponsor or their designated CRO will keep all the FDA correspondence as well as the FDA approval letter.

12.1.3 Informed Consent

Subjects will not sign the ICF until the study has been fully approved by the institution's IRB and the Sponsor or their designated CRO has received and reviewed the specific IRB-approved ICF. When the Investigator has determined the eligibility of a specific subject to enter the study, the ICF must be completed. The ICF must be read and understood by the subject, the subject's questions answered, and the form

signed by the subject before any study-related procedures can be performed. All subjects are to receive copies of their signed ICF.

12.1.4 Confidentiality

Confidentiality of subjects will be maintained throughout the study. A unique identification code will be assigned to each subject participating in this study. Any data that may be published in abstracts, scientific journals or presented at medical meetings will reference a unique subject code and will not reveal the subject's identity. The Sponsor, CRO, Investigators and site personnel will make every reasonable effort to protect the confidentiality of all subjects participating in the study.

12.2 Key Contributors

12.2.1 Sponsor

Clinical Affairs, Regulatory Affairs and Quality Assurance
FARAPULSE, Inc.
3715 Haven Ave. Suite 110
Menlo Park, CA 94025
USA

John Allison, Vice President
Tel: +1.650.422.3633
Email: jallison@farapulse.com

12.2.2 Contract Research Organization

Medpace Medical Device
3787 95th Ave NE
Suite 100
Blaine, MN 55014
USA

Patricia Bobzin, Director, Medical Devices
Tel: +1.612.234.8500
Fax: +1.513.527.0368
Email: p.bobzin@medpace.com

12.2.3 Arrhythmia Core Laboratory

HeartcoR Solutions LLC
2403 Harnish Drive, Suite 201
Algonquin, IL 60102
USA

12.2.4 Clinical Events Committee

The Sponsor or CRO will establish an external group of expert physicians to serve as the CEC. This group will consist of a panel of 3 experienced, independent physicians

who are not Investigators and will be supported by one or more Medical Monitors and staff as required. The CEC will develop a Charter, which will establish committee procedures.

The CEC will convene regularly during the study to review, classify and/or adjudicate AEs reported in this investigation as well as primary and secondary study outcomes. The CEC will be provided with case summaries, relevant source documents and any other information required to evaluate and adjudicate the AEs and study outcomes.

12.2.5 Data and Safety Monitoring Board

The Sponsor will establish an external group of physicians and an independent statistician to serve as the DSMB. This group will include at least 2 experienced, independent physicians who are not Investigators and an independent statistician not involved in the routine operation of the study. The DSMB will develop a Charter, which will establish committee procedures.

The DSMB will convene regularly during the study to assess overall event rates to ensure the integrity of the clinical study and the rights, safety and welfare of study subjects. The DSMB will also review the results of the interim analyses.

Should any protocol changes be necessitated by the findings of the DSMB during its deliberations, or by the impact of externalities such as the COVID-19 pandemic, the DSMB may propose such changes to the Sponsor. The Sponsor will review these changes with the DSMB and upon consensus submit such changes to the FDA.

12.3 Sponsor Responsibilities

Sponsor has the overall responsibility for the study and will perform the following, either directly or by documented delegation to qualified contractors:

- Select qualified Investigators and study sites.
- Select qualified monitors.
- Provide the CIP and any subsequent amendments.
- Provide appropriate information and investigational system training to the Investigator and study site staff.
- Ensure that all deviations from the CIP are reviewed with the appropriate Investigator(s) and reported on the CRFs and the final clinical report and that any necessary preventative or corrective action is taken.
- Ensure that all AEs and all ADEs are reported and reviewed with the Investigator(s) and where appropriate, that all SAEs and all SADEs are appropriately reported.
- Ensure that all Device Deficiencies / Malfunctions are reviewed by the Sponsor, and properly assessed and investigated, as appropriate.
- Promptly inform the Investigator and where applicable, any regulatory authorities, if the study is prematurely terminated or suspended and the reason for the termination or suspension.
- Ensure proper device usage, uniform data collection and protocol compliance.
- Provide comprehensive initial and remedial training throughout the study, including site initiation training regarding the FARAPULSE Pulsed Field

Ablation System, the IFU, the CIP, CRF instructions, CRFs, AE/SAE/Device Deficiency reporting and requirements for obtaining informed consent.

- Provide the FARAPULSE Pulsed Field Ablation System to the participating study site, in quantities adequate to support study activities.
- Coordinate ongoing communication with CROs, consultants and study site to resolve any problems concerning the protocol or data collection.
- Ensure compliance with the protocol. Where repeated efforts have failed to correct serious compliance issues, the Sponsor may pause or terminate a site's further enrollment in the study; see **Section 12.12**.
- Retain ownership of all clinical data generated in this study and control the use of the data for purposes of regulatory submissions.
- Protect subject confidentiality.

12.4 Monitor Responsibilities

Clinical monitors, qualified by training and experience, supervised and coordinated by qualified managers, and supplied with appropriate data and instructions, will be responsible for monitoring and overseeing the conduct of the study.

Site Initiation Visit: Sponsor personnel and / or clinical monitors will conduct site initiation visits at the investigational site – or if required via effective remote communication – to ensure that the Investigator and other investigational site personnel involved in the conduct of this investigation have received and understood the requirements and contents of this CIP, the Investigator's Brochure, the subject ICF, the CRFs, CRF Instructions, AE/SAE/Device Deficiency reporting requirements and the IFU and the Institution and / or Investigator Agreement.

Site Monitoring: The clinical monitors will conduct routine on-site monitoring visits in-person or when this cannot be achieved by effective remote communications in accordance with a study monitoring plan to evaluate compliance with the CIP, any specific recommendations made by the site's IRB and the signed Institution and/or Investigator Agreement and to ensure that the CIP is being followed and that any protocol deviations are properly documented on the respective CRF. Clinical monitoring will include a verification that informed consent was properly obtained and documented for all enrolled study participants, a review of clinical records and CRFs for accuracy and completeness, resolution of missing or inconsistent results and a review of source documents.

Clinical monitoring will include a review of all AEs, SAEs and Device Deficiencies / Malfunctions to ensure that all information has been reported to the Sponsor, IRB and regulatory authorities as required by the Clinical Investigational Plan and applicable standards and laws.

The clinical monitor will verify that the CRFs are complete and in agreement with the source documentation and other records. The clinical monitor will ensure that all CRFs have been signed and dated by the Investigator.

The Investigator will make available to the clinical monitor for review upon request ICFs, CRFs, source documentation and other relevant records for Enrolled Subjects at the site. It is important that the Investigator and other relevant site personnel are

available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site for the monitoring process.

If a deficiency is noted during an on-site visit or at any other time during the course of the study, the clinical monitor is required to discuss the situation with the Investigator and the Sponsor and to subsequently monitor the implementation of corrective actions that are required to address the situation.

All monitoring activities will be documented by the clinical monitor in a monitoring report and will include, at a minimum, the date, investigational site visited, names of all personnel involved in the visit and a summary of all findings, facts, deviations, conclusions and recommended actions to be taken. Key findings will be reviewed with the Investigator.

Upon completion of the study, a study closeout visit will be conducted to ensure that all data collection and study requirements are complete.

Medical monitors qualified by training and experience will support clinical monitors and other study personnel by providing study-related medical judgment regarding such subjects as interpretation of eligibility criteria, reviewing and assessment of AEs and the review of monitoring and study reports.

12.5 Investigator Responsibilities

At a minimum, the following documents will be provided by the investigational site to the Sponsor prior to study start (consent of the first subject):

- Signed Clinical Trial Agreements
- Signed Financial Disclosure Form
- Signed CIP signature page
- Investigator and Sub-Investigator's current curriculum vitae
- Investigator and site personnel protocol and device training records
- Any other additional documents as required by the Sponsor

The Investigator is responsible for ensuring that the investigation is conducted according to all signed agreements, the CIP, governing regulations, data protection regulations, medical device laws, the Declaration of Helsinki and any other conditions imposed by the relevant regulatory authorities. The Investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically such as digital imaging). The Investigator will also maintain original source documents from which study-related data are derived.

The Investigator(s) shall be responsible for the day-to-day conduct of the investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation.

The Investigator(s) shall:

- Have the qualified and trained resources to conduct the investigation properly.
- Obtain from the Sponsor the information that the Investigator(s) judges essential about the device and be familiar with this information.

- Be well acquainted with the CIP before signing the signature page.
- Support the monitor and auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the CRF where inconsistencies or missing values are identified.
- Discuss with the Sponsor management any question of modification of the CIP.
- Make sure that the CIP is followed by all responsible for the conduct of the study at his/ her institution. Any deviation shall be documented and reported to the study Sponsor and CRO.
- Make the necessary arrangements to ensure the proper conduct and completion of the investigation.
- Make the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject.
- Ensure that appropriate IRB and FDA approvals are obtained prior to the start of the investigation.
- Inform Sponsor about AEs and Device Deficiencies / Malfunctions in a timely manner; document on applicable CRFs.
- Endeavor to ensure an adequate recruitment of subjects.
- Ensure that the subject has adequate information and time to provide informed consent.
- Ensure that informed consent is obtained and documented on the IRB-approved ICF.
- Ensure that clinical records are clearly marked to indicate that the subject is enrolled in this study.
- Provide subjects with well-defined procedures for any emergency situation and safeguard the subject's interest. Under these circumstances, deviations from the CIP shall not require the prior approval of the Sponsor or the national and local regulatory authorities. Such deviations shall not be considered as a breach of agreement but shall be documented and reported to Sponsor.
- Ensure that information which becomes available as a result of the clinical investigation which may be of importance to the health of a subject and the continuation of the investigation shall be made known to the Sponsor and, if pertinent to the safety or well-being of the subject and the private clinician.
- Inform the subject and/ or the subject's physician about any premature termination or suspension of the investigation with a rationale for study termination.
- Have primary responsibility for the accuracy, legibility and security of all investigation data, documents and subject records both during and after the investigation.
- Sign each subject's CRF, as applicable.
- Be responsible for the supervision and assignment of duties at his/ her clinical center. The Investigator must maintain a Delegation of Authority Form of appropriately qualified persons to whom the Investigator has delegated significant study related duties.

- Ensure that all investigational devices are kept in a secure location and that all Systems are accounted for on the Device Accountability Form (number of devices used, discarded and returned to Sponsor).

12.6 Investigator and Site Staff Training

The participating Investigator and the relevant staff members at each investigational site will be trained in the use of the FARAPULSE Pulsed Field Ablation System prior to participating in the study. Device training will be conducted by the Sponsor or its representatives. All device training will be documented in a training log that will be maintained in the Regulatory Site Binder.

12.7 Confidentiality and Publication Policy

This clinical study, its associated documentation and the study data are all confidential and should not be discussed or shared with persons outside of the study. Additionally, the information in this document and regarding this study contains trade secrets and commercially sensitive information that are confidential and may not be disclosed unless such disclosure is required by law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in the study who have a need to know, but all such persons must be instructed not to further disseminate this information to others. These restrictions of disclosure will apply equally to all future information that is indicated as confidential.

The data generated by this clinical study are the property of the Sponsor and may not be disclosed without the prior written permission of FARAPULSE, Inc. These data may be used by FARAPULSE, Inc. now and in the future for presentation or publication at FARAPULSE, Inc.'s discretion or for submission to governmental regulatory agencies. FARAPULSE, Inc. reserves the right of prior review of any publication or presentation of data from the subject investigation.

A final comprehensive Clinical Study Report including these analyses will be prepared at the conclusion of the study or at such time as the study may be prematurely terminated, regardless of outcome. Publication in the appropriate peer-reviewed medical literature of the pre-specified study results will be attempted, based on the Clinical Study Report. Copies of the final report will be provided to the Investigator and their IRB and to the FDA as applicable. Neither Investigators nor their staff will publicize any study results without written permission of the Sponsor.

12.8 Data Management

Data management procedures will be included in a data management plan.

eCRFs will be made available to the participating site. Investigators are responsible for the accurate completion of subject eCRFs during the study. The Investigator will ensure that complete, accurate and timely data in eCRFs are completed, that protocol requirements are followed and that complications, AEs and ADEs are correctly reported and investigated, as appropriate. The Investigator is expected to maintain all source documents as required by the CIP, including laboratory results, supporting medical records and signed ICFs. The source documents will be used during the regular monitoring visits to verify information against data contained in the completed eCRFs.

eCRF data will be reviewed to identify any inconsistent or missing data and any AEs. Any data issues are to be promptly addressed with the Investigator by the CRO.

After eCRF monitoring has been complete and deficiencies / discrepancies resolved, study data in the central database will be updated to reflect any changes.

12.9 Insurance

The Sponsor will maintain the appropriate and necessary insurance coverage for the duration of the study.

12.10 Audits and Inspections

The Investigator will allow representatives of the governing IRB and FDA, with appropriate notice, to inspect all study records, CRFs and corresponding portions of the subject's office and / or hospital medical records at intervals throughout the study. These inspections are for the purpose of verifying adherence to the CIP, completeness and exactness of the data being entered onto the CRFs and compliance with regulatory agency regulations.

The Investigator will inform the Sponsor or the Sponsor's designee immediately upon notice that they are to be audited or inspected by any regulatory agencies. The Sponsor or the Sponsor's designee will also inform the site if they are made aware of a pending audit or inspection by a regulatory agency.

12.11 Study Suspension or Early Termination

The study can be discontinued at the discretion of the Sponsor for reasons including, but not limited to, the following:

- Occurrence of AEs unexpected as to their nature, severity, or duration, or the unexpected incidence of known AEs
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Data demonstrates a benefit to subjects who undergo percutaneous ablation with the FARAPULSE Pulsed Field Ablation System making treatment without the FARAPULSE Pulsed Field Ablation System unethical
- Insufficient recruitment of subjects
- UADEs presenting an unreasonable risk to subjects (Sponsor may terminate the study immediately)

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform the Investigators of the termination or suspension and the reason(s) for discontinuation / suspension. Regulatory authorities shall also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor. Subjects enrolled up to the date of suspension / termination will continue to be followed for safety through the 12-month timepoint.

12.12 Criteria for Suspending or Terminating a Study Site

Sponsor reserves the right to stop the screening of subjects at an individual study site at any time after the study initiation visit for reasons including the following:

- Absent or insufficient enrollment of study subjects
- Persistent non-compliance with the CIP or regulatory requirements
- Repeated failure to complete CRFs prior to scheduled monitoring visits
- Failure to obtain written informed consent using the IRB-approved ICF
- Failure to report SAEs/ UADEs to Sponsor within 24-hours of knowledge
- Loss of (or unaccounted for) investigational product inventory or repeated failure of device accountability.

12.13 Deviations from the Clinical Investigation Plan

Under emergency circumstances, deviations from the CIP to protect the rights, safety, and well-being of human subjects may proceed without prior approval of the Sponsor or IRB, including but not limited to those required to minimize or eliminate immediate hazards or to protect the life and well-being of research participants especially in relation to limiting exposure to COVID-19.

The Investigator must notify the Sponsor and the CRO of any deviation from the CIP and document the reason for the deviation in the eCRF.

The Investigator shall notify the Sponsor and the reviewing IRB of any deviation from the CIP to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than five (5) working days after the emergency occurred.

12.14 COVID-19 Pandemic Considerations

This clinical investigation has been designed with consideration given to the impact of COVID-19 on the safety of study participants, maintaining compliance with Good Clinical Practice (GCP) requirements and minimizing risks to study integrity. The design includes input from the HRS/ACC/AHA COVID-19 Task Force recommendations[41] and the relevant FDA Guidelines.[42, 43]

Specific areas of concern include availability of electrophysiology resources for non-urgent procedures, governmental limitations on travel or hospital utilization, hospital restrictions on procedures and personnel access, illness among study or site staff, provision of clinical, rhythm and/ or imaging assessment at locations other than the treating center, handling and reporting of protocol deviations, availability of investigational devices and analysis and reporting of COVID-19-related deviations and missing data.

Should unforeseen circumstances occur, study-related decision making will prioritize in the following order: the safety of study participants, maintaining compliance with GCP requirements and minimizing risks to study integrity.

13. Regulatory Considerations

13.1 Maintaining Records

The Sponsor and CRO will maintain copies of critical correspondence, regulatory approvals, Trial Master Files, clinical data, shipment of devices, AEs, SAEs, SADEs, UADEs and other records related to the clinical study.

Trial records will be maintained for a minimum of 3 years following the completion of research activities and closure of the study with IRBs, whichever is longer.

13.2 Data Handling and Record Keeping

13.2.1 Source Documents

The Investigator must maintain detailed source documents on all subjects who are enrolled or who undergo screening in the study. Source documents include but are not limited to, subject medical records, hospital charts, clinic charts, Investigator subject study files, as well as the results of diagnostic tests (e.g., laboratory tests, hemodynamic studies).

The following minimum information should be entered into the subject's medical record:

- The date the subject entered the study and the subject number.
- The CIP number and the name of the Sponsor.
- The date that informed consent was obtained and signed by the subject and Investigator.
- Evidence that the subject meets the study eligibility requirements (e.g., medical history, study procedures and/or evaluations).
- The dates of all study related subject visits.
- Evidence that required procedures and/or evaluations were completed.
- Use of any concurrent medications.
- Documentation of specific device used.
- Occurrence and status of any AEs or SAEs
- The date the subject exited the study and a notation as to whether the subject completed the study or was discontinued, including the reason for discontinuation.

13.2.2 Data Collection

The Investigator must maintain detailed records on all subjects who sign the ICF and begin the pre-procedure evaluation. Data for Enrolled Subjects are transcribed onto eCRFs provided by the Sponsor or designee. All data should be transcribed completely and promptly.

Study exit eCRF will be completed for all Enrolled Subjects, regardless of whether they did or did not complete the study (e.g., subject discontinuation, study termination). The Sponsor and investigational site will maintain all records pertaining to this study in accordance with local and national regulations. Prior to the destruction of study records the Investigator or his representative shall contact the Sponsor to

ensure that they no longer need to be retained. In addition, Sponsor shall be contacted if the Investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

13.3 Institutional Review Board and FDA Approval

Regulatory approvals must be obtained prior to enrollment of the first subject. The Sponsor is responsible for obtaining regulatory and local approvals for the study. The Sponsor or its designated representative will require a copy of any IRB and FDA correspondence as well as the final approval letter from the IRB.

An Investigator may not make CIP changes without prior approval by the Sponsor. All significant CIP changes that may affect the following must be submitted and approved by the IRB and FDA before initiating the change:

- Validity of the data or information resulting from the completion of the approved CIP
- Relationship of the likely subject risk to benefit relied upon to approve the CIP
- Scientific soundness of the CIP
- Rights, safety, or welfare of the human subjects involved in the investigation

The Sponsor will notify the investigational site of such changes to ensure the study continues to be conducted consistent with the approved CIP.

13.4 Procedure for Amending the CIP

The process of amending the CIP and/or related documents is the responsibility of the Sponsor. The procedure for amending the CIP shall be as follows:

- The Sponsor, Investigator, or other relevant party (e.g., IRB, FDA, CEC, DSMB) may recommend modification of the CIP.
- The Sponsor will then modify as necessary the CIP and any associated documents requiring amendment as a result of the modification(s).
- The Sponsor or designated CRO will then submit the revised CIP and any other affected documents to the IRB and FDA for approval.
- Once all required approvals are obtained, the site will be trained to the latest approved version of the CIP and any other affected documents.

13.5 Device Accountability

The Sponsor will only ship investigational devices to the site once evidence of required regulatory approval has been provided to the Sponsor or designee.

The Investigator must keep complete, current and accurate records of the receipt, use, or disposition of investigational devices (21 CFR 812.140 (a)(2)).

14. Bibliography

1 Page RL. Newly Diagnosed Atrial Fibrillation. *New England Journal of Medicine*, 351(23):2408–16, 2004.

2 Feinberg WM, Cornell ES, Nightingale SD, et al. Relationship between prothrombin activation fragment F1.2 and international normalized ratio in patients with atrial fibrillation. Stroke Prevention in Atrial Fibrillation Investigators. *Stroke.* 1997;28(6):1101-1106.

3 Fuster V, Rydén LE, Asinger, RW, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients With Atrial Fibrillation): developed in Collaboration With the North American Society of Pacing and Electrophysiology. ACC. *J Am Coll Cardiol*. 2001;38(4):1231-1266.

4 Go AS, Hylek EM, Phillips KA et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: The AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA*. 2001;285(18):2370-2375.

5 Miyasaka Y, Barnes ME, Gersh BJ, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation.* 2006;114(2):119-125.

6 Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991;22(8):983-988.

7 Le Heuzey JY, Paziaud O, Piot O, et al. Cost of care distribution in atrial fibrillation patients: the COCAF study. *Am Heart J* 2004;147:121- 126.

8 Calkins H, Hindricks G, Cappato R, et al. HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm.* 2017;14(10):e275-e444.

9 Al-Sakere B, AndréF, Bernat C, et al. Tumor ablation with irreversible electroporation. *PLoS One. 2007*;2(11): e1135.

10 Neumcke, B, Walz, D, Läuger, P. Nonlinear effects in lipid bilayer membranes. III. The dissociation field effect. *Biophys J*. 1970;10(2):172-182.

11 Benz R, Beckers F, Zimmermann U. Reversible electrical breakdown of lipid bilayer membranes: a charge-pulse relaxation study. J Membr Biol. 1979;48(2):181-204.

12 Chang, DC. Cell poration and cell fusion using an oscillating electric field. *Biophys J*. 1989;56(4):641-652.

13 Chang DC, Reese TS. Changes in membrane structure induced by electroporation as revealed by rapid-freezing electron microscopy. *Biophys J.* 1990;58(1):1-12.

14 Wendler JJ, Pech M, Blaschke S, et al. Angiography in the isolated perfused kidney: radiological evaluation of vascular protection in tissue ablation by nonthermal irreversible electroporation. *Cardiovasc Intervent Radiol. 2012;*35(2):383-390.

15 Gehl J, Skovsgaard T, Mir LM. Vascular reactions to in vivo electroporation: characterization and consequences for drug and gene delivery. *Biochim Biophys Acta*. 2002;1569(1-3):51-58.
16 Kingham TP, Karkar AM, D'Angelica MI et al. Ablation of perivascular hepatic malignant tumors with irreversible electroporation. *J Am Coll Surg.* 2012;215(3):379-387.
17 Olweny EO, Kapur P, Tan YK et al. Irreversible electroporation: evaluation of nonthermal and thermal ablative capabilities in the porcine kidney. *Urology. 2013*;81(3):679-684.
18 Maor E, Ivorra A, Leor J, et al. Irreversible electroporation attenuates neointimal formation after angioplasty. *IEEE Trans Biomed Eng*. 2008;55(9):2268-2274.
19 Thomson KR, Cheung W, Ellis SJ, et al. Investigation of the safety of irreversible electroporation in humans. *J Vasc Interv Radiol.* 2011;22(5):611-21.
20 Wittkampf FH1, van Driel VJ, van Wessel H, et al. Feasibility of electroporation for the creation of pulmonary vein ostial lesions. *J Cardiovasc Electrophysiol.* 2011;22(3):302-309.
21 van Driel VJ, Neven KG, van Wessel H, et al. Pulmonary vein stenosis after catheter ablation: electroporation versus radiofrequency. *Circ Arrhythm Electrophysiol*. 2014;7(4):734-738.
22 Neven K, van Driel V, van Wessel H, et al. Epicardial linear electroporation ablation and lesion size. *Heart Rhythm*. 2014;11(8):1465-1470.
23 van Driel V, Neven K, van Wessel H, et al. Low vulnerability of the right phrenic nerve to electroporation ablation. *Heart Rhythm*. 2015;12(8):1838-1844.
24 Op. cit.
25 Koruth JS, Kuroki K, Kawamura I, et al. Pulsed field ablation versus radiofrequency ablation: esophageal injury in a novel porcine model. *Circ Arrhythm Electrophysiol.* https://doi.org/10.1161/CIRCEP.119.008303.
26 Sponsor preclinical study, on file.
27 Sponsor preclinical study, on file.
28 Final Clinical Study Report, Document Number CS1009, Rev A. The IMPULSE Study: A Safety and Feasibility Study of the FARAPULSE™ Endocardial Ablation System in the Treatment of Paroxysmal Atrial Fibrillation. July 27, 2020.
29 Interim Clinical Study Report, Document Number CS1010, Rev A. PEFCAT: A Safety and Feasibility Study of the FARAPULSE™ Endocardial Ablation System to Treat Paroxysmal Atrial Fibrillation. July 28, 2020
30 Interim Clinical Study Report, Document Number CS1011, Rev A. PEFCAT II: Expanded Safety and Feasibility Study of the FARAPULSE™ Endocardial Multi Ablation System to Treat Paroxysmal Atrial Fibrillation. July 28, 2020.
31 Sponsor analysis of study data, on file.
32 Cochet H, Nakatani Y, Sridi-Cheniti S, Cheniti G, Ramirez D, Goujeau C, André C, Nakashima T, Eggert C, Schneider C, Viswanathan R, Derval N, Duchateau J, Pambrun T, Chauvel R, Reddy VY, Montaudon M, Laurent F, Sacher F, Hocini M, Haïssaguerre M, Jais P, Pulsed Field Ablation Selectively Spares the

Esophagus After Pulmonary Vein Isolation For Atrial Fibrillation. In Review, Journal of the American College of Cardiology: Electrophysiology.
33 Sponsor analysis of study data, on file.
34 Kuroki K, Whang W, Eggert C, et al. Ostial dimensional changes after pulmonary vein isolation: pulsed field ablation vs radiofrequency ablation. *Heart Rhythm*. https://doi.org/10.1016/j.hrthm.2020.04.040.
35 Dr. Hubert, Cochet, personal communication regarding analysis of PEFCAT and PEFCAT II subjects by brain MRI post-ablation.
36 January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Circulation. 2019;139.
37 Kuck KH, Brugada J, Fürnkranz A, et al. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. *N Engl J Med.* 2016;374(23):2235-2245.
38 Broglio KR, Connor JT, Berry SM., "Not too big, not too small: a Goldilocks approach to sample size selection," *J Biopharm Stat*. 2014;24(3):685-705.
39 Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. *Control Clin Trials*. 2004;25(2):143-156.
40 James KE, Bloch DA, Lee KK, et al. An index for assessing blindness in a multi-centre clinical trial: disulfiram for alcohol cessation--a VA cooperative study. *Stat Med*. 1996;15(13):1421-1434.
41 Lakkireddy D, Chung, M, Gopinathannair R, et al. Guidance for cardiac electrophysiology during the coronavirus (COVID-19) pandemic from the Heart Rhythm Society COVID-19 Task Force; Electrophysiology Section of the American College of Cardiology; and the Electrocardiography and Arrhythmias Committee of the Council on Clinical Cardiology, American Heart Association, *Heart Rhythm.* https://doi.org/10.1016/j.hrthm.2020.03.028.
42 FDA Guidance on conduct of clinical trials of medical products during COVID-19 public health emergency. Guidance for Industry, Investigators, and Institutional Review Boards., March 2020, updated on July 2, 2020, US Department of Health and Human Services, Food and Drug Administration.
43 Statistical considerations for clinical trials during the COVID-19 public health emergency. Guidance for Industry. June 2020, US Department of Health and Human Services, Food and Drug Administration.