A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation

The ADVANTAGE AF Study

92836802
PF106

CLINICAL INVESTIGATION PLAN

G220079

NCT 05443594

Sponsored By

Boston Scientific Corporation

Sponsored By
Boston Scientific Corporation
4100 Hamline Ave N.
St. Paul, MN 55112

and

Boston Scientific International S.A.
Le Val Saint-Quentin
2 rue René Caudron
78960 Voisins le Bretonneux, France

Contact Information

Role	Contact
Boston Scientific Corporation (BSC) Clinical Contact	[redacted] Boston Scientific Corporation 4100 Hamline Ave N. St. Paul, MN 55112 USA [redacted] [redacted] Boston Scientific Corporation 4100 Hamline Ave N. St. Paul, MN 55112 USA [redacted] [redacted] Green Square Lambroekstraat 5D 1831 Diegem (Brussels) Belgium [redacted]
Coordinating Principal Investigator(s)	Vivek Reddy, MD, Principal Investigator Mount Sinai Hospital [redacted]
Executive Steering Committee	Edward Gerstenfeld, MD Moussa Mansour, MD Andreas Metzner, MD Devi Nair, MD Andrea Natale, MD Walid Saliba, MD Boris Schmidt, MD Philipp Sommer, MD Atul Verma, MD
Vendors / Labs / External Organizations	A list of vendors / laboratories / external organizations involved in the trial is maintained by the Sponsor.

Original Release: February 24, 2022

Current Version: August 20, 2024

Revision Version	Protocol Date	Template # Version	Section(s) Modified	Summary of Changes	Justification for Modification
A	**February 24, 2022**	**90702637, Version AP**	**N/A**	**Original issue**	**N/A**
B	**May 10, 2022**	**90702637, Version AQ**	**Throughout**	Modifications according to initial FDA IDE review, application # G220079, 8 April 2022	Modifications according to initial FDA IDE review, application # G220079, 8 April 2022
C	**June 28, 2022**	**90702637, Version AQ**	**Sections 1, 2.2, 7.6.2.5, 17.1, 17.4 and 17.6**	Modifications according to G220079/A001 Interactive request, June 21, 2022 and follow-up FDA teleconference June 23, 2022	Modifications according to G220079/A001 Interactive request, June 21, 2022 and follow-up FDA teleconference June 23, 2022.
D	**July 28, 2022**	**90702637, Version AQ**	**Throughout**	Modification to reflect the FARASTAR Generator supplement	A specific investigational generator compatible for both FARAWAVE and FARAPOINT will be used for the study.
D	**July 28, 2022**	**90702637, Version AQ**	**Throughout**	Modifications to allow a commercially available RF catheter to be used for CTI ablation and increase the total study and Roll-In Subject sample size	Flexibility to conduct the study and treat the targeted arrhythmia for the study without a dependency on the FARAPOINT PFA Catheter but allow the option to add the catheter later
E	**November 10, 2022**	**90702637, Version AQ**	**Throughout**	Modifications to remove FARAPOINT,associated components and associated endpoints	Modification according to FDA IDE Supplement, application #G220079, Nov 2022
E	**November 10, 2022**	**90702637, Version AQ**	**Section 2**	Modifications to reflect the systems used in the different geographies	Commercial system will be used under the study specific IFUs in

Revision Version	Protocol Date	Template # Version	Section(s) Modified	Summary of Changes	Justification for Modification
					geographies where the system is approved, Investigational system will be used in North America
E	**November 10, 2022**	**90702637, Version AQ**	**Sections 8.1**	Modification to primary safety endpoint performance goal and sample size : increase from 219 Subjects to 258 treatment subjects – increase in stie number from 40 to 53	Answer to Study Design Consideration 1. From FDA correspondence, 24 Jun 2022
F	**August 9, 2023**	**90702637, Version AR**	**Throughout**	Updated reference to Phase 1 of the trial in Protocol synopsis; Added Appendix A for ADVANTAGE AF Phase 2 protocol	Modifications to incorporate ADVANTAGE Phase 2
F	**August 9, 2023**	**90702637, Version AR**	7.6.2.2, 7.6.2.3	Administrative corrections	Reference errors corrected
G	**August 18, 2023**	**90702637, Version AR**	Appendix A	Corrected indications for use statement in Appendix A, Section 2.1	Administrative corrections
H	**Aug 2024**	**90702637 Version AU**	Appendix A	Modification to definitions (Section 23.2) for AF, AFL, and AT Burden, Detectable AF, AFL, or AT, and BeatLogic; modification to the primary effectiveness endpoint justification, sample size, and statistical methods (Section 8.1.2), updates, and additions to additional effectiveness endpoints (Section 3.5.2), and added sensitivity analyses (Section 8.3.3).	Answer to Study Design Considerations: G220079/S012, from FDA Correspondence 08 Sep 2023, G220079/S016 from FDA correspondence 09 Feb 2024, and G220079/S018, from FDA Correspondence 21 Jun 2024.
H	**Aug 2024**	**90702637 Version AU**	Appendix B	Addition of Appendix B – LUX-Dx long term follow-up sub-study.	Allow for additional data collection up to 3 years post-procedure to

Revision Version	Protocol Date	Template # Version	Section(s) Modified	Summary of Changes	Justification for Modification
					characterize arrhythmia recurrence using LUX-Dx only.
H	**Aug 2024**	**90702637 Version AU**	Throughout	Updated to BSC protocol template version AU	Administrative updates

Protocol Synopsis: ADVANTAGE AF Study Phase 1

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation **The ADVANTAGE AF Study – Phase 1**	
STUDY OBJECTIVE(S)	The objective of the ADVANTAGE AF Study is to establish the safety and effectiveness of the FARAPULSE Pulsed Field Ablation System (FARAPULSE PFA System) for treatment of drug resistant, symptomatic persistent atrial fibrillation (PersAF).
INDICATION(S) FOR USE	The FARAPULSE™ Pulsed Field Ablation System is indicated for the treatment of drug resistant, symptomatic persistent atrial fibrillation. The FARAWAVE Catheter is indicated for the isolation of pulmonary veins and posterior wall in the ablation of drug resistant, symptomatic persistent atrial fibrillation.
DEVICES UNDER STUDY (TEST DEVICE)	The investigational devices comprise the FARAPULSE™ Pulsed Field Ablation (PFA) System • FARAWAVE™ Pulsed Field Ablation (PFA) Catheter • FARASTAR™ Catheter Connection Cable • FARASTAR™ Pulsed Field Ablation (PFA) Generator and associated cables • FARASTAR™ Recording System Module and associated cables • FARADRIVE™ Steerable Sheath
STUDY DESIGN	The FARAPULSE ADVANTAGE AF Study is a prospective, single arm, open label, multi-center IDE pivotal study utilizing the FARAPULSE PFA System in the treatment of patients with PersAF. After ablative isolation of the pulmonary veins (PVs), the left atrial posterior wall (PW) and if warranted the cavotricuspid isthmus (CTI), subjects will be followed at Pre-Discharge, Day 7, Day 30, Day 90, Day 180, and Day 360. The Blanking Period will include Days 0 through 90, after which subjects will be monitored twice per month plus symptom-driven event monitoring, as well as Day 180 and Day 360 24-hour Holter monitoring.

The ADVANTAGE AF Study – Phase 1	

INTERVENTIONS DURING INDEX PROCEDURE	**Pulmonary Vein Isolation (PVI):** PVI will be achieved in target veins using the FARAWAVE PFA Catheter.
	
	Posterior Wall Isolation (PWI): PWI will be achieved in the left atrial posterior wall between the PVs using the FARAWAVE PFA Catheter.
	
	CTI: Ablation of the CTI will be performed using a commercially available BSCRF catheter in the following situations:
	• Required: For subjects with a history of CTI-mediated (typical) AFL and
	  o Who have not had a CTI ablation procedure, or
	  o Who have had a CTI ablation procedure but have recurrent CTI conduction.
	• Required: subjects who manifest CTI-mediated AFL (spontaneous or induced) during the Index Procedure, or
	• At Investigator discretion: subject welfare indicates that CTI ablation should be performed.
	
	Other Ablation: When the Investigator determines that subject welfare requires intervention for either an accessory pathway, AVNRT or spontaneously occurring treatment-emergent AFL or AT, ablation for these arrhythmias may be performed using any commercially available RF ablation catheter. These permitted ablations and the associated data will be documented in the CRF and do not constitute Persistent AF Acute Procedural Failure.
	
	Ablation for an arrhythmia that is provoked only by catheter manipulation or is only inducible by pacing or pharmacologic stimulation is not permitted.

PLANNED NUMBER OF SUBJECTS	Approximately 417 treated subjects will be enrolled in this study (up to 159 Roll-In Subjects and approximately 258 Treatment Subjects). Roll-In Subjects (up to 159): The first subject enrolled by each ablating Investigator at each site will be treated with the investigational catheter(s) as part of Investigator preparation, up to a maximum of 159 subjects across 53 investigational sites. Roll-In procedures may be adapted based on prior experience, or additional subjects may be required as described in **Section 4.3**. Treatment Subjects (258): A planned 258 Treatment Subjects will be enrolled to support the proposed primary study outcomes. No site may enroll more than ~13% of these planned subjects (n= 33 Treatment Subjects maximum). Subject enrollment will stop once approximately 258 Treatment Subjects are accrued.
INVESTIGATIONAL SITES / COUNTRIES	Up to 53 clinical sites globally, which may include North America, Europe, and Asia. At least 50% of study subjects will be enrolled in the United States, and at least 50% of study sites will be in the United States. The number of active ablating Investigators at any site is limited to a maximum of three (3).

<table>
<tr><th colspan="2">The ADVANTAGE AF Study – Phase 1</th></tr>
<tr><td>Primary Safety Endpoint</td><td>The primary safety endpoint (PSE) is the proportion of Treatment Subjects and Attempt Subjects with one or more of the following device or procedure-related Composite Serious Adverse Events (CSAEs) following the Index Procedure / Rescheduled Index Procedure or the First Re-Ablation Procedure within the Blanking Period, with an Onset Date following the procedure as specified in the Table below:
<table>
<tr><th>Composite Serious Adverse Events</th><th>Onset Date</th></tr>
<tr><td>• Death
• Myocardial infarction
• Stroke
• TIA
• Peripheral or organ thromboembolism
• Pulmonary edema
• Unresolved phrenic nerve palsy / paresis
• Vascular access complications
• Heart block
• Gastric motility / pyloric spasm disorders</td><td>Day 0 – Day 7</td></tr>
<tr><td>• Cardiac tamponade / perforation
• Pericarditis</td><td>Day 0 – Day 30</td></tr>
<tr><td>• PV stenosis
• Atrio-esophageal fistula</td><td>Day 0 –Day 360 Assessment</td></tr>
</table>
The CSAE components of the PSE are defined in Table 3.2-2.</td></tr>
<tr><td>Additional Safety Endpoints</td><td>• Composite Non-Serious Adverse Event
• Related AEs
• Any SAE
• Post-Blanking Arrhythmia Hospitalizations
• Post-Blanking Cardioversions</td></tr>
<tr><td>Primary Effectiveness Endpoint</td><td>The primary effectiveness endpoint (PEE) is the proportion of Treatment Subjects with Treatment Success through the Day 360 Assessment.
Treatment Success is defined as:
1. Persistent AF Acute Procedural Success AND
2. Persistent AF Chronic Success, defined as freedom from the following after the Blanking Period (excluding documented CTI-dependent flutter):
i. Arrhythmia: Occurrence of any Detectable AF, AFL or AT
ii. Re-ablation: Any re-ablation for AF, AFL or AT
iii. Cardioversion: Any electrical cardioversion for AF, AFL or AT
iv. AAD Use: Use of a Non-Failed Class I / III AAD or amiodarone</td></tr>
</table>

The ADVANTAGE AF Study – Phase 1	
ADDITIONAL EFFECTIVENESS ENDPOINTS	• Persistent AF Acute Procedural Success • Persistent AF Chronic Success • Single Procedure Treatment Success • Off Drug Treatment Success • Re-Ablation Rate
PROCEDURAL ASSESSMENTS	Assessments of procedure durations • Procedure Time • LA Dwell Time • PVI and PWI Ablation Time • Fluoroscopy Time Characterization of lesion sets • PVI Ablations • PWI Ablations • CTI Ablations • Other Ablations
QUALITY OF LIFE ASSESSMENTS	Between Baseline and Day 180, and between Baseline and Day 360 • The 3-level EuroQol standardized questionnaire of health states (EQ-5D-3L) • The Atrial Fibrillation Effect on Quality of Life (AFEQT) instrument for the measurement of health-related quality of life
METHOD OF ASSIGNING PATIENTS TO TREATMENT	The ADVANTAGE AF Study is a single arm study, and any subject that signs the Informed Consent Form and meets all study inclusion criteria, and no exclusion criteria, will be eligible for treatment either as a Roll-In Subject or a Treatment Subject.
FOLLOW-UP SCHEDULE	• **Baseline Assessments** • **Index Procedure / Rescheduled Index Procedure (Day 0):** Cardiac ablation • **Pre-Discharge Assessment** • **Day 7 Assessment (remote):** safety assessment (Window Day 7 to 11) • **Day 30 Assessment (remote):** safety assessment (Window Day 30 – 37) • **Day 90 Assessment (in person):** clinical assessment, begin twice per month and symptomatic event monitoring transmissions (Window Day 90 ± 14) • **Day 180 Assessment (remote):** clinical assessment, 24-hour Holter, QoL (Window Day 180 ± 30) • **Day 360 Assessment (in person):** clinical assessment, 24-hour Holter, QoL (Window Day 360 ± 30) • **Re-Ablation Procedure** • **Unscheduled Assessments**

The ADVANTAGE AF Study – Phase 1	
STUDY DURATION	Enrollment is expected to be completed in approximately 9 months, and subjects will be followed for 12 months. There will be an approximate 2-month period of site close-out visits, for an estimated first patient in until last patient last assessment duration of 23 months.
SUBJECT DURATION	The study duration for each subject will be approximately 13 ± 1 months to allow for screening, pre-procedural diagnostic procedures, treatment, and 12 ± 1 months of study follow-up.
INCLUSION CRITERIA	Study subjects are required to meet all the following inclusion criteria: 1. Age ≥ 18 years of age, or older if specified by local law 2. Subjects have symptomatic, documented, drug-resistant, Persistent AF, defined as: a. **Documented**: at a minimum a physician's note confirming the arrhythmia symptoms and durations AND, within 180 days of Enrollment Date, either: i. A 24-hour continuous ECG recording confirming continuous AF OR ii. Two ECGs from any regulatory cleared rhythm monitoring device showing continuous AF taken at least 7 days apart b. **Drug-resistant**: effectiveness failure of, intolerance to, or specific contraindication to at least one (1) AAD (Class I or III). c. **Persistent**: continuous AF for > 7 days and ≤ 365 days 3. Subjects who are willing and capable of providing informed consent 4. Subjects who are willing and capable of participating in all testing associated with this clinical investigation at an approved clinical investigational center
EXCLUSION CRITERIA **(CONTINUED NEXT PAGE)**	1. Any of the following atrial conditions: a. Left atrial anteroposterior diameter ≥ 5.5 cm, or if LA diameter not available, non-indexed volume >100 ml (by MRI, CT or TTE report or physician note) b. Any prior atrial endocardial, epicardial or surgical ablation procedure for arrhythmia, other than right sided cavotricuspid isthmus ablation or for right sided SVT c. Current atrial myxoma d. Any PV abnormality, stenosis, or stenting (common and middle PVs are admissible) e. Current left atrial thrombus 2. Cardiovascular exclusions – Any of the following CV conditions: a. History of sustained ventricular tachycardia or any ventricular fibrillation b. AF that is secondary to electrolyte imbalance, thyroid disease, alcohol, or other reversible / non-cardiac causes

The ADVANTAGE AF Study – Phase 1	
EXCLUSION CRITERIA	c. Current or anticipated pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices, interatrial baffle, closure device, patch, or patent foramen ovale occluder, LA appendage closure, device or occlusion, active implantable loop recorder or insertable cardiac monitor at the time of ablation[1] d. Valvular disease that is any of the following: i. Symptomatic ii. Causing or exacerbating congestive heart failure iii. Associated with abnormal LV function or hemodynamic measurements e. Hypertrophic cardiomyopathy f. Any prosthetic heart valve, ring or repair including balloon aortic valvuloplasty g. Any IVC filter, known inability to obtain vascular access or other contraindication to femoral access h. Rheumatic heart disease i. Congenital heart disease with any clinically significant residual anatomic or conduction abnormality j. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months 3. Any of the following conditions at baseline (**Section7.5**): a. Heart failure associated with NYHA Class III or IV b. LVEF < 40% c. Uncontrolled hypertension (SBP > 160 mmHg or DBP > 95 mmHg on two (2) BP measurements at baseline assessment 4. Any of the following events within 90 days of the Consent Date: a. Myocardial infarction (MI), unstable angina or coronary intervention b. Any cardiac surgery c. Heart failure hospitalization d. Pericarditis or symptomatic pericardial effusion e. Gastrointestinal bleeding f. Stroke, TIA, or intracranial bleeding g. Any non-neurologic thromboembolic event h. Carotid stenting or endarterectomy 5. Thrombocytosis, thrombocytopenia, disorder of blood clotting or bleeding diathesis 6. Contraindication to, or unwillingness to use, systemic anticoagulation 7. Patients who have not been on anticoagulation therapy for at least 4 weeks prior to the ablation procedure 8. 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
(CONTINUED NEXT PAGE)	

The ADVANTAGE AF Study – Phase 1	
EXCLUSION CRITERIA	9. Health conditions that in the investigator's medical opinion 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) > 42.0 b. Solid organ or hematologic transplant, or currently being evaluated for a transplant c. Any prior history or current evidence of hemi-diaphragmatic paralysis or paresis. d. Severe lung disease, pulmonary hypertension, or any lung disease involving abnormal blood gases or requiring supplemental oxygen e. Renal insufficiency if an estimated glomerular filtration rate (eGFR) is < 30 mL / min / 1.73 m^2, or with any history of renal dialysis or renal transplant f. Active malignancy or history of treated malignancy within 24 months of enrollment (other than cutaneous basal cell or squamous cell carcinoma) g. Clinically significant gastrointestinal problems involving the esophagus or stomach including severe or erosive esophagitis, uncontrolled gastric reflux, gastroparesis, esophageal candidiasis or active gastroduodenal ulceration h. Active systemic infection i. 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 j. Uncontrolled diabetes mellitus or a recorded HgbA1c > 8.0% in the 90 days prior to the Consent Date k. Untreated diagnosed obstructive sleep apnea with apnea hypopnea index classification of severe (>30 pauses per hour) 10. Predicted life expectancy less than one (1) year 11. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments; each instance must be brought to the attention of the Sponsor to determine eligibility
STATISTICAL METHODS	

[1] Subjects may be enrolled with an active implantable loop recorder or insertable cardiac monitor if deactivation or removal is planned per standard of care prior to obtaining vascular access for the index ablation procedure.

The ADVANTAGE AF Study – Phase 1	
PRIMARY SAFETY ENDPOINT: HYPOTHESIS AND METHOD	The analysis of the primary safety endpoint (PSE) is a test comparing the proportion of Treatment Subjects and Attempt Subjects with one or more CSAEs through the Day 360 Assessment (Treatment) or through the Day 30 Assessment (Attempt) to a performance goal (PG). The null and alternative hypotheses are: H_0: $P \geq PG$ versus H_A: $P < PG$ where P is the proportion of Treatment Subjects and Attempt Subjects with one or more CSAEs through the Day 360 Assessment (Treatment) or through the Day 30 Assessment (Attempt) and the PG is 12%. The proportion of Treatment Subjects and Attempt Subjects with one or more CSAEs will be estimated using the Kaplan-Meier method. The 97.5% one-sided upper confidence limit of the observed event rate will be compared to the performance goal of 12%. If the upper confidence limit is less than the performance goal, the null hypothesis will be rejected. The upper confidence limit will be calculated as the pointwise confidence limit using the log-log methodology. **Both the PSE and PEE must be met for study success.**
PRIMARY EFFECTIVENESS ENDPOINT: HYPOTHESIS AND METHOD	The analysis of the primary effectiveness endpoint (PEE) is a test comparing the proportion of Treatment Subjects with Treatment Success through the Day 360 Assessment to a PG. The null and alternative hypotheses are: H_0: $P \leq PG$ versus H_A: $P > PG$ where P is the proportion of Treatment Subjects with Treatment Success through the Day 360 Assessment and the PG is 40%. The proportion of Treatment Subjects with Treatment Success through the Day 360 Assessment will be estimated using the Kaplan-Meier method. The 97.5% one-sided lower confidence limit of the observed Treatments Success rate will be compared to the performance goal of 40%. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected. The confidence limit will be calculated as the pointwise confidence limit using the log-log methodology. **Both the PSE and PEE must be met for study success.**

The ADVANTAGE AF Study – Phase 1	
SAMPLE SIZE	The sample size estimate for each endpoint was obtained through Binomial exact methods, and the following assumptions were used in the sample size calculations for the primary endpoints.

Assumption	**PSE**	**PEE**
Expected rate	6%	55%
Performance goal	12%	40%
Attrition (per year)	10%	10%
Significance level (one-sided)	0.025	0.025
Power	86%	90%
Evaluable subjects	232	122
Subjects accounting for attrition	258	136

The overall sample size of 258 Treatment Subjects is driven by the analysis of the primary safety endpoint through the Day 360 Assessment.

Table of Contents

List of Figures

List of Tables

1 Introduction

Atrial Fibrillation

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] Among Medicare beneficiaries, AF incidence is common and increases as individuals age, with incidence rates per 1,000 person-years reported at ages 70-74 of 18.8, increasing to 28.8 for persons 75-79 and 38.3 for persons 80-84. Similarly, the overall prevalence among Medicare beneficiaries age 70-74 is about 6% increasing to over 13% for individuals 80 years of age and older. Age-adjusted population trending projects 16 million people in the United States will have AF by 2050.[5]

Atrial fibrillation remains a significant cause of morbidity and mortality in industrialized societies. The annual risk of AF related stroke is 5% per year and one of every six 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, 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 approximately USD 3200 or €3000.[7]

The Heart Rhythm Society (HRS) 2017 Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation[8] defines several different stages of AF based on its duration and include:

- Paroxysmal AF (PAF): AF that terminates spontaneously or with intervention within 7 days of onset
- Persistent AF (PersAF): continuous AF that is sustained beyond 7 days
- Long-standing PersAF: continuous AF of greater than 12 months' duration

Several studies have demonstrated that AF catheter ablation is a safe and superior alternative to anti-arrhythmic drugs (AADs) for maintenance of sinus rhythm and symptom improvement.[9-16] In particular, the isolation of the pulmonary veins (PVI), where the majority of arrhythmogenic triggers is found, has been shown to be a safe and effective technique to reduce arrhythmia recurrence and related symptoms. Over the last 20 years PVI has remained the cornerstone catheter ablation technique for AF ablation in subjects with recurrent and symptomatic PAF refractory or intolerant to AADs.[8,17] More recently, PVI for the treatment of PAF is increasingly being performed as first line therapy, and clinical evidence is accruing that this may well become an accepted first line treatment.[18]

Persistent Atrial Fibrillation Ablation

Persistent AF (PersAF) represents approximately 25% of all AF cases.[19] In comparison to patients with PAF, patients with PersAF are at a significantly greater risk for both cardiac mortality and all-cause mortality.[20] The recent update of the 2020 ESC Guidelines[17] for the diagnosis and management of atrial fibrillation AF supports catheter ablation for maintaining sinus rhythm in patients with both PAF and PersAF, with the eligibility to treat PersAF patients with ablation being weighted by additional elements, including risk factors for recurrence (left atrial [LA] size, AF duration, patient age, renal dysfunction, and substrate visualization by means of MRI), heart failure with reduced ejection fraction, and patient choice. This recommendation is currently reflected in practice as approximately one third of all catheter ablation cases are performed on either persistent or long-standing persistent patients.[21]

There are currently two catheters approved in the US to treat PersAF, supported by data obtained from the PRECEPT (Biosense Webster, Thermocool SmartTouch® SF catheter) and STOP Persistent AF trials (Medtronic, ArcticFront Advance® Cryoballoon), respectively.[22,23] These trials showed that safety and effectiveness profile of catheter ablation for PersAF is well-established, with slight variations in rates depending upon the patient population and technology utilized. Although the PVs have been identified as the main triggers responsible for AF, PVI alone for the treatment of PersAF is less effective than for PAF, and PersAF ablation may require additional lesion sets beyond the PVs to achieve greater success.[24]

PersAF ablation success is challenged by the heterogeneity of the underlying pathophysiologic mechanisms, and multiple ablation strategies have evolved in the attempt to improve long-term outcomes in this population. These include left atrial lines (roof, mitral isthmus), right atrial lines (superior vena cava, cavo-tricuspid isthmus) other techniques aimed at suppressing additional triggers outside the PV. To date, limited data from randomized trials exist on the effectiveness of these techniques compared to PVI alone.[25-28] However, recent studies[29-31] have suggested a benefit associated with PVI and concomitant isolation of the portion the left atrial posterior wall (LAPW) lying between the PVs. The rationale for this ablation technique stands in the common embryological origin of this anatomical area in the PVs and the peculiar electrophysiological and structural characteristics of this region that give rise to its arrhythmogenic potential.

Specifically, spontaneous triggers located in the LAPW have been reported in previous studies,[32-35] establishing ablation of this area in addition to PVI being a potential adjuvant strategy in ablation of PersAF. Several studies have been recently published adding a dedicated LAPW ablation strategy together with PVI, including different available energy sources for ablation.[36-41] A recent systematic review and meta-analysis[29] showed that LAPW isolation can be successfully achieved in a large proportion of patients and is associated with a low risk of major-procedure related complications.

Irreversible Electroporation

Al-Sakere 2007[42] 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.[43-46] IRE ablation typically spares the extracellular matrix, which facilitates rapid wound healing.[47-51]

With respect to cardiac tissue, multiple studies have been described reporting the effects of IRE in a porcine model. Across the studies, no stenosis was observed at 3-weeks and 3-months of follow-up, and the lesion depth was further characterized in the proximity of the phrenic nerve and coronary arteries, with no damage to the adjacent structures or tissues noted.[52-55] These animal studies suggest that IRE can safely create deep lesions in heart tissue without harming adjacent tissues.

FARAPULSE Pulsed Field Ablation System

Preclinical animal studies investigating the safety and efficacy of the FARAPULSE Pulsed Field Ablation (PFA) System have been performed to demonstrate that PFA using the FARAPULSE PFA Catheter 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, and importantly demonstrated no tissue injury with respect to the esophagus or phrenic nerve as well as no degree of narrowing or flow impairment of the pulmonary veins.[56-59]

Paroxysmal Atrial Fibrillation:

Initial safety and feasibility human clinical studies of the FARAWAVE PFA Catheter were conducted in Europe in a PAF population, including the IMPULSE, PEFCAT, and PEFCAT II trials.[60-62] All studies supported the safety and feasibility of the FARAPULSE PFA System using the FARAWAVE PFA Catheter 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 acute procedural success resulting in CE Mark approval for the treatment of PAF in early 2021.

The randomized ADVENT Trial (A Prospective Randomized Pivotal Trial of the FARAPULSE PFA System Compared with Standard of Care Ablation in Patients with Paroxysmal Atrial Fibrillation) is being conducted in the United States to establish the safety and effectiveness of the FARAPULSE PFA System using the FARAWAVE PFA Catheter in a drug refractory symptomatic PAF patient population. Subjects in the study are either randomized to catheter ablation with the FARAPULSE PFA system or conventional thermal ablation (radiofrequency or cryoballoon ablation). The data will be used to gain initial market approval of the FARAPULSE PFA System using the FARAWAVE PFA Catheter in the US for the PAF population.

Persistent Atrial Fibrillation:

Initial data on treatment of PersAF with the FARAPULSE PFA System using the FARAWAVE PFA Catheter has been collected in the PersAFOne feasibility study (Feasibility Study of the FARAPULSE Endocardial Multi Ablation System in the Treatment of Persistent Atrial Fibrillation). The objective of the PersAFOne Study is to demonstrate that the endocardial creation of electrically isolating lesions in cardiac tissue via PFA using the FARAPULSE PFA System is a feasible and safe treatment for PersAF. Patients in the PersAFOne study, after the isolation of the PVs, received an additional set of lesions along the posterior wall region between the PVs, performed with the same FARAWAVE PFA Catheter used for PVI during the ablation procedure.

Reliable and safe electrical isolation of the left atrial posterior wall was confirmed via electro-anatomical mapping. Reddy et al[63] reported 100% acute PV isolation, no primary safety events, and chronic isolation of the PVs (82 / 85) and LAPW (100% with the pentaspline catheter) after remapping at 82 days post-procedure in 25 subjects. The data collected in the study demonstrated that the approach proposed in the ADVANTAGE AF Study to ablate the left atrial posterior wall in addition to creating PVI using the FARAPULSE PFA System is feasible, leading to an acceptable safety and feasibility profile for the study device to date.

One of the acknowledged challenges to LAPW ablation is the risk of collateral damage to the esophagus, given the repeated and additional ablation applications in addition to the PVs that are delivered to an anatomical area close to the esophagus.[64] Using PFA for LAPW ablation has the potential to substantially mitigate this risk, given the marked reduced risk of collateral damage to adjacent structures with the energy source noted above.

Although AF and CTI-dependent atrial flutter (AFL) are different arrhythmias with their own mechanisms and electrophysiologic presentation, their interrelationship has long been recognized and they coexist in a significant percentage of patients.[67] The relationship is reciprocal since patients diagnosed with AFL may develop AF after CTI ablation and patients with AF often go on to develop AFL.[68-70] In particular, the presentation of AFL in the context of AF may be the sign of additional atria remodeling or the presence of non-PV triggers.[71]

Accordingly, a strategy that includes both PVI and CTI ablation has become an established practice in the percutaneous ablative treatment of patients with AF. The current guidelines for the management of AF indicate that CTI ablation may be beneficial during procedures of AF ablation, in particular for those patients with history of typical AFL and where AFL is induced at the time of AF ablation.[8] The

present IDE study incorporates the treatment strategy for PersAF ablation utilized in PersAFOne using the FARAWAVE PFA Catheter for electrical isolation of the PV and isolation of the LAPW region between the PVs; In the PersAFOne II study, LAPW ablation was performed using the FARAWAVE Catheter in the fully deployed configuration. Consistent with the proposed treatment, two applications at 2000V at each catheter location was performed, with approximately 50% overlap between adjacent catheter positions. These catheter positions along the posterior wall linked the PVI lesion to create a continuous lesion set encompassing the PVs and LAPW, between the superior and inferior insertions of the left and right PV pairs. As of the date of the PersAFOne II interim clinical study report, 17 subjects have returned for the invasive remapping procedure. Sixty-four of sixty-eight (94.2%) of PVs and sixteen of seventeen (94%) of LAPWs remained durably isolated. Again, two SAEs in two patients, both pericardial effusions, were reported, related to the required remapping procedure.

Expanding the indication of the FARAPULSE PFA System for approval to treat PersAF patients would fulfill a clinical need in a growing population of subjects indicated to receive a catheter ablation. The present single arm, prospective cohort IDE study has been designed to demonstrate safety and effectiveness of the FARAPULSE PFA System in treating symptomatic drug-refractory PersAF patients.

2 Device Description

2.1 Intended Use

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

The FARAWAVE Catheter is indicated for the isolation of pulmonary veins and posterior wall in the ablation of drug resistant, symptomatic persistent atrial fibrillation.

2.2 Investigational Devices

2.2.1 FARAPULSE Pulsed Field Ablation System

The FARAPULSE Pulsed Field Ablation (PFA) System is comprised of the following. The full list of components is provided in **Table 2.2-1**.

- FARAWAVE Pulsed Field Ablation Catheter (FARAWAVE PFA Catheter)
- FARASTAR Catheter Connection Cable
- FARASTAR Pulsed Field Ablation Generator and associated cables
- Recording System Module and associated cables
- FARADRIVE Steerable Sheath

The FARAPULSE Pulsed Field Ablation System is currently commercialized in Europe and indicated for the treatment of Paroxysmal Atrial Fibrillation. The commercial system will be used for the study outside of its CE Mark scope. The investigational systems used in North America and in Europe are functionally equivalent.

A copy of the device labeling and DFU/IFU will be provided in local language(s) as required per national regulations, as well as the Investigator Brochure.

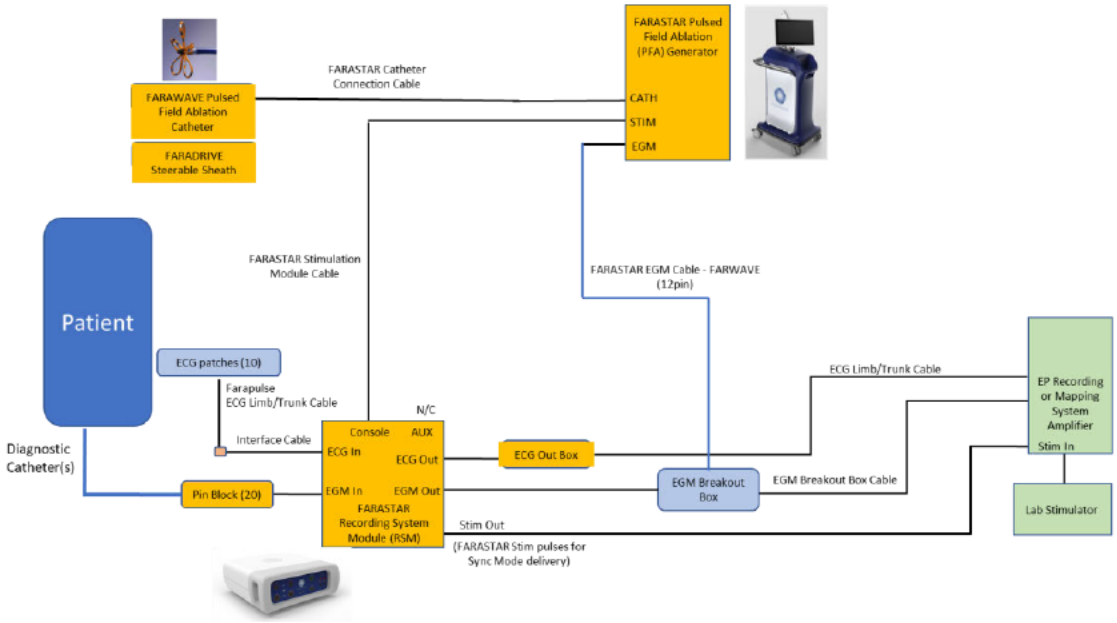
Table 2.2-1: Components of the FARAPULSE Pulsed Field Ablation System

Component	Subcomponents
FARAWAVE PFA Catheter	1. FARAWAVE Pulsed Field Ablation Catheters (31mm and 35mm) 2. FARASTAR Catheter Connection Cable
FARASTAR PFA Generator and Related Equipment	1. FARASTAR Pulsed Field Ablation Generator 2. FARASTAR Recording System Module <u>Sub-components of the FARASTAR Generator and RSM:*</u> 3. FARASTAR Stimulation Module Cable 4. FARASTAR Recording System Module Catheter Pin Cable 5. FARASTAR EGM Cable for FARAWAVE 6. FARASTAR Recording System Module ECG Trunk Cable 7. FARASTAR Recording System Module ECG Output Module 8. FARASTAR Recording System Module EGM Input Module 9. FARASTAR Cable Set • FARASTAR Stimulation Module Male Cable • FARASTAR Stimulation Module Female Cable • FARASTAR Stimulation Module Y-Cable – Long • FARASTAR Stimulation Module Y-Cable – Short
FARADRIVE Steerable Sheath	FARADRIVE Steerable Sheath

*Sub-components are not tracked for clinical device accountability

A diagram of the FARAPULSE Pulsed Field Ablation System set-up is provided in **Figure 2.2-1**.

Figure 2.2-1: Diagram of FARAPULSE Pulsed Field Ablation System Connections



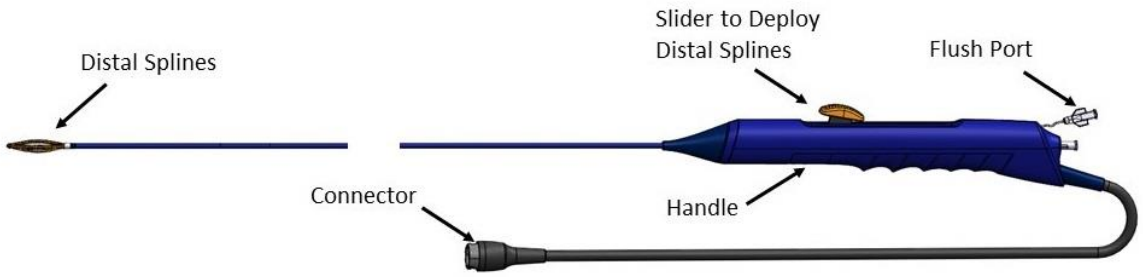
2.2.2 FARAWAVE Pulsed Field Ablation Catheter

The FARAWAVE PFA Catheter is a sterile, single use, over-the-wire, non-deflectable device that is used with the FARASTAR Catheter Connection Cable and FARASTAR Generator to enable delivery of Pulsed Field Ablation energy for irreversible electroporation.

The FARAWAVE PFA Catheter is offered in 2 different sizes (31 mm and 35 mm fully deployed diameters) to accommodate varying PV anatomy. Selection of either catheter will be at the Investigator's discretion.

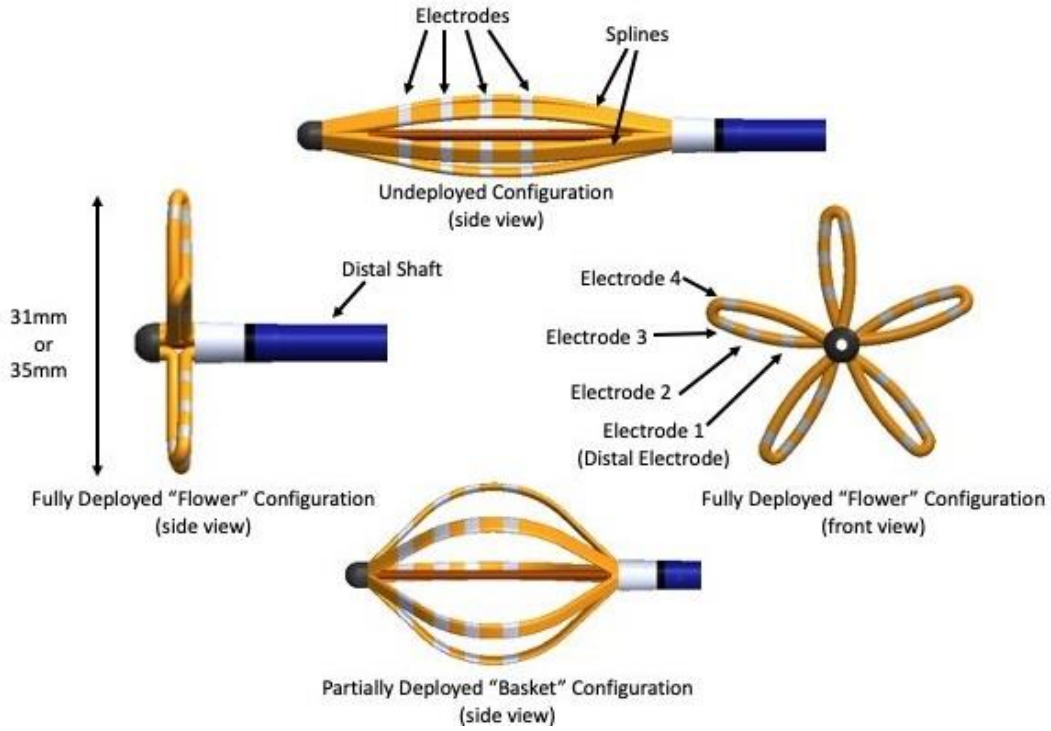
The FARAWAVE PFA Catheter is a multi-electrode catheter that connects electrically to the FARASTAR PFA Generator (**Figure 2.2-2**)**.** It consists of a distal section with electrodes arranged on splines, a shaft section, and a proximal handle with a manually operated deployment control.

Figure 2.2-2: FARAWAVE Pulsed Field Ablation Catheter



The FARAWAVE PFA 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 partially deployed ("basket-shaped") configuration to a fully deployed ("flower-shaped") configuration with five petals (**Figure 2.2-3**).

Figure 2.2-3: 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 PFA Generator. The Connection Cable is packaged sterile and is single-use only. The PFA energy is delivered from the FARASTAR PFA Generator over the set of ablation catheter electrodes.

In geographies where The FARAWAVE PFA Catheter is commercially available, the device will be used for the study under the investigational IFU and will then be handled according to **Section 13.2**

Additional important information is provided in the Investigational FARAWAVE PFA Catheter IFU regarding precautions, warnings, specific use instructions and procedural steps of the FARAWAVE PFA Catheter.

2.2.3 FARASTAR Catheter Connection Cable

The FARASTAR Catheter Connection Cable is a sterile, single-use device that is used to attach the FARAWAVE Catheter (31mm or 35mm) to the FARASTAR Generator

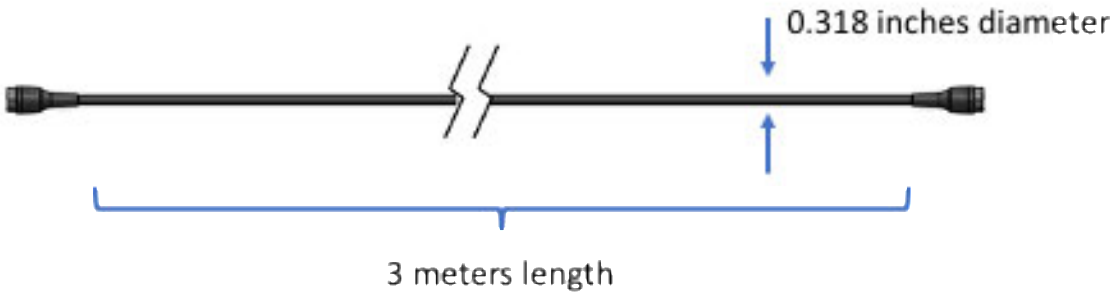


Figure 2.2-4 FARASTAR Catheter Connection Cable

It is 3 meters in length and terminated at both ends with auto-coupling connectors which contain alignment markers to facilitate connections to the FARASTAR Generator and FARAWAVE Catheter. The main cable diameter is approximately 0.318 inches at each end and is fitted with an over molded strain relief where the cable meets with the connectors.
The FARASTAR Catheter Connector Cable comes in two versions, GEN 1 and GEN 2.
The FARASTAR Connector Cable (GEN1) is investigational in North America. The FARASTAR Catheter Connector Cable (GEN1) is commercially available in Europe and approved for use with the FARAWAVE PFA Catheter. When used in Europe in conjunction with the FARAWAVE PFA Catheter, it will be handled according to **Section 13.2**.

The FARASTAR Catheter Connector Cable GEN 2 is investigational and will be used in geographies where the system is not commercially available.
Additional important information is provided in the FARASTAR Catheter Connection Cable IFU regarding precautions, warnings, specific use instructions and procedural steps.

2.2.4 FARASTAR Pulsed Field Ablation Generator

The FARASTAR PFA Generator is a 12-channel output unit that generates a pulsed voltage waveform that can be delivered to the FARAWAVE PFA Catheter. The user selectable voltage options for the FARAWAVE PFA Catheter are 1800V to 2000V in 100V increments. All versions of the FARASTAR PFA Generator consist of the components listed above in **Table 2.2-1**.

The generator utilized will be dependent upon regulatory approval in a specific geography. In geographies where The FARASTAR PFA Generator is commercially available, the commercial version of the generator will be used for the study under the investigational IFU and will then be handled according to **Section 13.2**.

Details regarding the generator are provided in the FARASTAR PFA Generator User Manual.

2.2.5 FARASTAR Recording System Module

The FARASTAR Recording System Module (RSM) is a system component to the FARASTAR Generator. The FARASTAR RSM is a filtering and protection unit meant to be placed in between a patient in the Electrophysiology Lab and other equipment such as a recording system for surface-lead signals (ECGs) and intra-cardiac electrograms (EGMs). The primary function of the FARASTAR RSM is to disconnect the inputs of the EP Lab Recording System from their connections to the patient during PFA delivery. The inputs include diagnostic catheters and surface ECGs. This action reduces the risk of interference to the Recording System inputs during an ablation. The secondary function of

the FARASTAR RSM is to provide Stimulation output connectors for Synchronous Mode PFA delivery.

Details regarding the Recording System Module are provided in the FARASTAR Recording System Module User Manual.

2.2.6 FARADRIVE Steerable Sheath

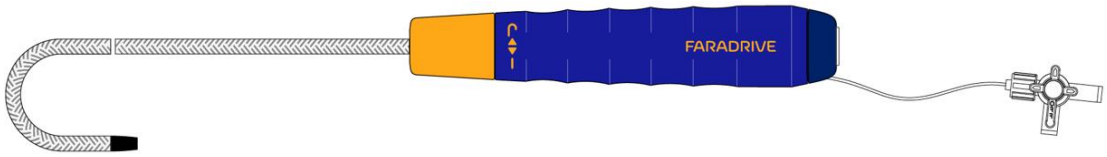
The FARAWAVE Catheter will be used with the FARADRIVE Steerable Sheath.

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 2.2-5**).

In geographies where the FARADRIVE Steerable Sheath is commercially available, the device will be used for the study under the investigational IFU and will then be handled according to **Section 13.2**.

Figure 2.2-5: FARADRIVE Steerable Sheath



Details regarding the sheath are provided in the FARADRIVE Steerable Sheath IFU.

3 Study Objectives and Endpoints

3.1 Study Objective

The objective of the ADVANTAGE AF Study is to establish the safety and effectiveness of the FARAPULSE Pulsed Field Ablation System for treatment of drug resistant, symptomatic persistent atrial fibrillation.

3.2 Primary Safety Endpoint

The primary safety endpoint (PSE) is the proportion of Treatment Subjects and Attempt Subjects with one or more of the following device or procedure-related Composite Serious Adverse Events (CSAEs) following the Index Procedure / Rescheduled Index Procedure or the Re-Ablation Procedure within the Blanking Period, with an Onset Date following the procedure as specified in **Table 3.2-1**:

Table 3.2-1: Primary Safety Endpoint Composite Serious Adverse Events

Composite Serious Adverse Events	Onset Date
• Death • Myocardial infarction • Stroke • TIA • Peripheral or organ thromboembolism • Pulmonary edema • Unresolved phrenic nerve palsy / paresis • Vascular access complications • Heart block • Gastric motility / pyloric spasm disorders	Day 0 – Day 7
• Cardiac tamponade / perforation • Pericarditis	Day 0 – Day 30
• PV stenosis • Atrio-esophageal fistula	Day 0 – Day 360 Assessment

For the analysis of the PSE, CSAEs are only defined for the following procedures that include the use of investigational devices:

- The Index Procedure / Rescheduled Index Procedure (**Section 7.6.1)**
- A Re-Ablation Procedure for AF, AFL or AT within the Blanking Period (**Section 7.13.1**)

Device or procedure-related SAEs related to any other ablation procedure that does not include an investigational device will not be included in the analysis of the PSE, including Other Re-ablation Procedures (**Section 7.13.2**).

3.2.1 Composite Serious Adverse Event Definitions

Each of the adverse events (AEs) comprising a PSE CSAE is specifically defined in **Table 3.2-2**:

Table 3.2-2: Composite Serious Adverse Event 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

Related SAE	Description / Criteria
Unresolved phrenic nerve palsy / paresis	A phrenic nerve palsy / paresis is defined as absent or reduced phrenic nerve function assessed as a change in the elevation of a hemi-diaphragm from baseline, that is: • Not resolved by the end of the procedure • Demonstrated radiographically by pacing, an inspiration / expiration chest X-ray or fluoroscopic sniff test • Not due to a demonstrable pulmonary process such as atelectasis or pleural disease. An unresolved phrenic nerve palsy or paresis is defined for this endpoint as not resolved at the time of the last in-person follow-up assessment.
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 Cardiac Imaging Core Laboratory (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

For the purposes of Clinical Event Committee (CEC) adjudication of trial outcomes and the associated analyses of safety endpoints:

- Procedures (such as cardioversion and endocardial ablation) are not adverse events.
- Pre-existing diseases or conditions (including AF, AFL, AT) will not be reported as adverse events unless there has been a substantial increase in severity or frequency of the problem as compared to the subject's baseline which cannot be attributed to the expected progression of the disease or condition
- AEs will be deemed serious according to the criteria and notes in **Section 17**.

3.3 Primary Effectiveness Endpoint

The primary effectiveness endpoint (PEE) is the proportion of Treatment Subjects with Treatment Success through the Day 360 Assessment. Treatment Success is defined as Persistent AF Acute Procedural Success AND Persistent AF Chronic Success.

3.3.1 Persistent AF Acute Procedural Success

Persistent AF Acute Procedural Success is defined as:

- The isolation of all attempted PVs as clinically assessed at the end of the procedure by entrance block performed with or without adenosine testing, AND
- The isolation of the left atrial PW as clinically assessed at the end of the procedure, performed with or without adenosine testing, via interrogation by multipolar diagnostic catheter or 3D electroanatomical mapping

Both PWI and PVI must be achieved using only the FARAWAVE Catheter to be classified as a Persistent AF Acute Procedural Success. If the Investigator determined that subject welfare required intervention for an accessory pathway, AVNRT or spontaneously occurring treatment-emergent AFL or AT, ablation for these arrhythmias may be performed using any commercially available RF ablation catheter, and these permitted ablations do not constitute Persistent AF Acute Procedural Failure.

3.3.2 Persistent AF Chronic Success

Persistent AF Chronic Success is defined as freedom from any of the following through the Day 360 Assessment after the Blanking Period, excluding documented CTI-dependent AFL[2]:

a. **Arrhythmia:** Occurrence of any Detectable AF, AFL or AT
b. **Re-ablation:** Any re-ablation for AF, AFL or AT
c. **Cardioversion:** Any electrical cardioversion for AF, AFL or AT
d. **AAD Use:** Use of a Non-Failed Class I / III AAD or amiodarone

Within the Blanking Period, recurrent arrhythmias can be managed with AADs, cardioversion or one re-ablation procedure with the FARAPULSE PFA System without constituting Persistent AF Chronic Failure. Titration of Class I/III antiarrhythmic medications are allowed during the Blanking Period. Subjects are allowed to remain on Class I/III antiarrhythmic medications at the historic maximum ineffective dose (prior to the ablation procedure) after the 90-day Blanking Period, except amiodarone. Subjects that undergo more than one re-ablation procedure within the Blanking Period will be classified as a Persistent AF Chronic Failure. Complete definitions of the endpoint terms (including Blanking Period, Detectable AF, AFL, or AT, Failed AAD and Non-Failed AAD), can be found in **Section 23.2**.

3.4 Additional Endpoints and Assessments

The following additional endpoints and assessments will be analyzed and reported for the ADVANTAGE AF Study.

3.4.1 Additional Safety Endpoints

The following endpoints will be descriptively analyzed through the Day 360 Assessment in Treatment Subjects and the Day 30 Assessment in Attempt Subjects:

- **Composite Non-Serious Adverse Events:**
  Defined as the proportion of subjects with one or more composite nonserious AEs otherwise as defined in **Table 3.2-2: Composite Serious Adverse Event Definitions**.
- **Related Adverse Events**
  Defined as the proportion of subjects with one or more device or procedure-related AEs
- **Any Serious Adverse Event**
  Defined as the proportion of subjects with one or more SAEs whether or not device or procedure-related
- **Post-Blanking Arrhythmia Hospitalizations**
  Defined as the proportion of Treatment subjects with one or more physician-directed admission to an inpatient hospital facility for at least two consecutive calendar days for the primary purpose of diagnosing or treating AF, AFL or AT beginning after Day 90
- **Post-Blanking Cardioversions**
  Defined as the proportion of Treatment subjects with one or more electrical cardioversions for AF, AFL or AT after Day 90

3.4.2 Additional Effectiveness Endpoints

The following endpoints will be descriptively analyzed in Treatment Subjects at the indicated time points:

[2] Post-blanking CTI-dependent AFL or re-ablation or cardioversion for CTI-dependent AFL does not constitute Treatment Failure.

- **Persistent AF Acute Procedural Success**
  Defined in **Section 3.3.1** at the conclusion of the Index Procedure / Rescheduled Index Procedure
- **Persistent AF Chronic Success**
  Defined in **Section 3.3.2** through the Day 360 assessment
- **Single Procedure Treatment Success**
  Treatment Success as defined in **Section 3.3.1** but counting subjects with any re-ablation for AT, AFL, or AT as Treatment Failures
- **Off Drug Treatment Success**
  Treatment Success as defined in **Section 3.3.1** but counting subjects treated with any Class I / III AAD after Day 90 as Treatment Failures
- **Re-Ablation Rate**
  Defined as the proportion of subjects who receive one or more re-ablations during study follow-up for AF, AFL, or AT, at any time during follow-up, and subdivided by re-ablation during Days 0 – 90 and by Days 91 and thereafter.

3.4.3 Procedural Assessments

The following assessments will be descriptively analyzed at the completion of the Index Procedure / Rescheduled Index Procedure:

Assessments of procedure durations (recorded and rounded to the nearest minute)

- **Procedure Time**
  Defined as the recorded time of initiation of venous access to the recorded time of venous access closure completion
- **LA Dwell Time**
  Defined as the recorded time between the insertion of the first device into the LA and the removal of the last device from the LA
- **PVI and PWI Ablation Time**
  Defined as the recorded time from the first FARAWAVE PFA Catheter application to the last FARAWAVE PFA Catheter application.
- **Fluoroscopy Time**
  Defined as the recorded total duration of exposure to fluoroscopic imaging

Characterization of lesion sets

- **PVI Ablations**
  Defined as the number of applications in each attempted vein
- **PWI Ablations**
  Defined as the number of applications during ablation of the LA posterior wall
- **CTI Ablations**
  Defined as the number of applications during CTI ablation
- **Other Ablations**
  For subjects undergoing welfare-required ablations for an accessory pathway, AVNRT, left-sided AFL or incessant AT a listing and descriptive summary of ablation lesions delivered.

3.4.4 Quality of Life Assessments

The following assessments will be descriptively analyzed between Baseline and Day 180, and between Baseline and Day 360.

- The 3-level EuroQol standardized questionnaire of health states (EQ-5D-3L)

- The Atrial Fibrillation Effect on Quality of Life (AFEQT) instrument for the measurement of health-related quality of life

3.5 Summary of Study Endpoints

Each of the ADVANTAGE AF Study endpoints corresponds to one or more specific objectives which are listed and justified in the following table.

Table 3.5-1: Primary Endpoint Objectives and Justification

OBJECTIVES	ENDPOINTS	JUSTIFICATION
Primary		
Establish the safety of the FARAPULSE PFA System	Composite of 7-day, 30-day, and Day 360 study-specific CSAEs as defined in **Section 3.2**	Composite list of CSAEs includes those AEs typically associated with catheter ablation of AF, consistent with other IDE Trial definitions. Performance goal and expected rates calculated from a meta-analysis of controlled and IDE clinical studies on PersAF ablation
Establish the effectiveness of the FARAPULSE PFA System	Treatment Success through 360 days as defined in **Section 3.3**	Definition of Treatment Success is consistent with from other IDE Trial definitions. Performance goal and expected rates calculated from a meta-analysis of controlled and IDE clinical studies on PersAF ablation.
Secondary		
There are no secondary endpoints for the ADVANTAGE AF Study.		
Additional		
Safety characterization	Composite non-serious adverse events	It is useful to demonstrate a more generalized safety profile
Safety characterization	Device or procedure-related adverse events	It is useful to demonstrate a more generalized safety profile
Safety characterization	Any SAE	It is useful to demonstrate a more generalized safety profile
Safety and economic impact demonstration	Post-blanking hospitalizations for AF, AFL, or AT	An important patient and economic impact

OBJECTIVES	ENDPOINTS	JUSTIFICATION
Safety and economic impact demonstration	Post-blanking electrical cardioversions for AF, AFL, or AT	An important patient and economic impact
Demonstrate acute effectiveness	Acute Procedural Success	Component of primary effectiveness endpoint
Demonstrate chronic effectiveness	Chronic Success	Component of primary effectiveness endpoint
Demonstrate single procedure effectiveness	Single Procedure Treatment Success	Important clinical measure for physicians
Demonstrate off-drug effectiveness	Off Drug Treatment Success	Important clinical measure for physicians
Report the rate of repeat procedures	Re-ablation rate	Important clinical measure for physicians
Report key procedural durations	Assessments of procedure durations (procedure, LA dwell, PVI / PWI ablation, and fluoroscopy times)	Important procedural parameters for physicians
Characterize ablative intervention	Characterization of lesion sets (PVI, PWI, CTI and Other)	Important procedural parameter for physicians
Characterize change in subjects' self-reported health status	The EuroQol (EQ-5D-3L) and AFEQT instruments	Important patient reported outcome measures for health status changes

4 Study Design

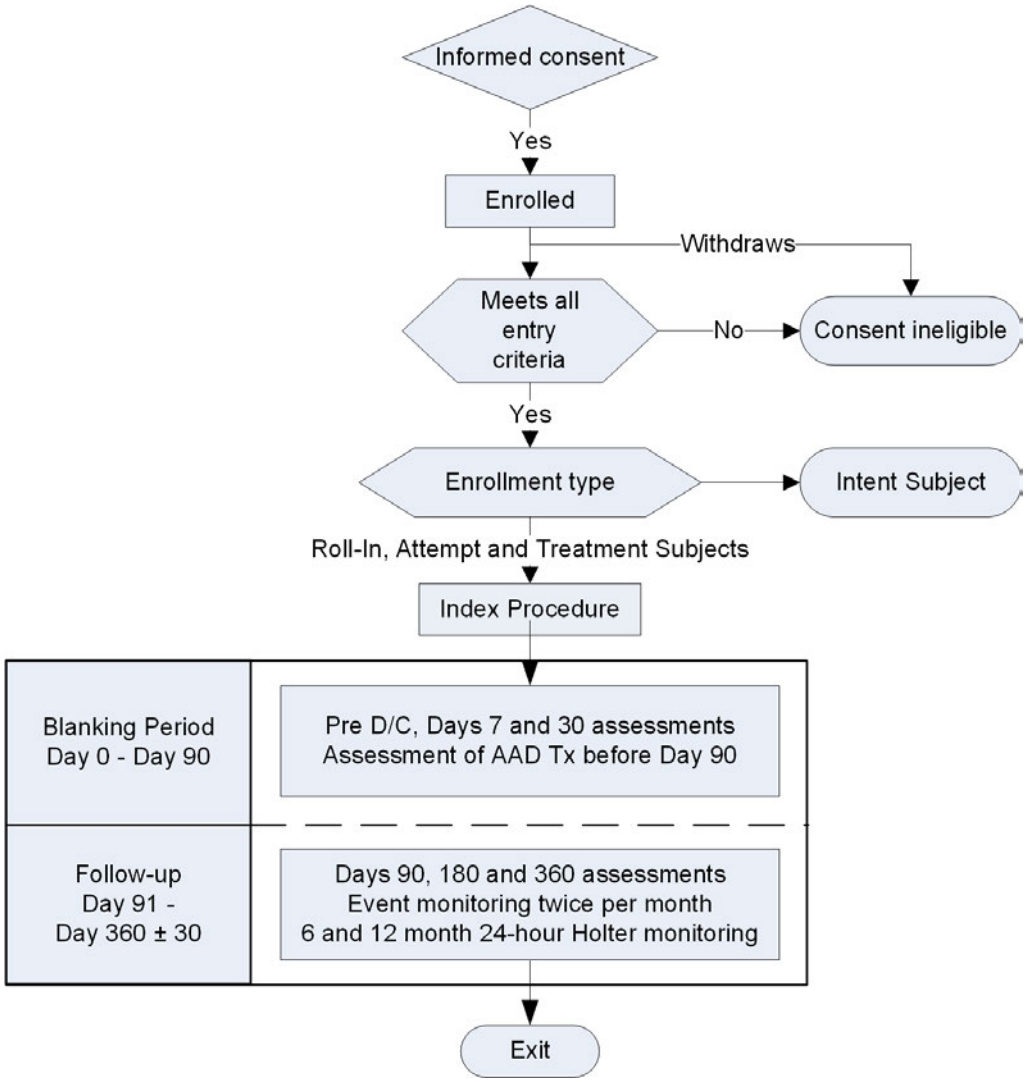
4.1 Overview of the ADVANTAGE AF Study Design

The ADVANTAGE AF Study is a prospective, single arm, open label, multi-center IDE pivotal study utilizing the FARAPULSE PFA System in the treatment of patients with PersAF.

Subjects requiring ablative intervention for PersAF meeting study entry criteria will undergo percutaneous ablative pulmonary vein isolation (PVI) and left atrial posterior wall isolation (PWI) using the FARAWAVE PFA Catheter. Subjects meeting protocol criteria will undergo ablative interruption of the cavo-tricuspid isthmus (CTI) using a commercially available BSC RF catheter.

Subjects will be followed at Pre-Discharge, Day 7, Day 30, Day 90, Day 180, and Day 360. The Blanking Period will include Days 0 through 90, after which subjects will be monitored twice per month plus symptom-driven event monitoring, as well as Day 180 and Day 360 24-hour Holter monitoring.

Figure 4.1-1: ADVANTAGE AF Study Design



4.2 Scale and Duration

4.2.1 Number of Subjects

Approximately 417 treated subjects will be enrolled in this study (up to 159 Roll-In Subjects and approximately 258 Treatment Subjects).

Roll-In Subjects (up to 159): The first subject enrolled by each ablating Investigator at each site will be treated with the investigational device(s) as part of Investigator preparation, up to a maximum of 159 subjects across 53 investigational sites. Roll-In procedures may be adapted based on prior experience, or additional subjects may be required as described in **Section 4.3**.

Treatment Subjects (258): A planned 258 Treatment Subjects will be enrolled to support the proposed primary study outcomes. No site may enroll more than 33 Treatment Subjects(13% of those planned). Subject enrollment will stop once approximately 258 Treatment Subjects are accrued.

4.2.2 Investigational Sites / Countries

Up to 53 clinical sites globally, including North America, Europe, and Asia.

At least 50% of study subjects will be enrolled in the United States, and at least 50% of study sites will be in the United States.

The number of active ablating Investigators at any site is limited to a maximum of three (3).

4.2.3 Study Duration

Enrollment is expected to be completed in approximately 9 months, and subjects will be followed for 12 months. There will be an approximate 2-month period of site close-out visits, for an estimated first patient in until last patient last assessment duration of 23 months.

4.2.4 Subject Duration

The study duration for each subject will be approximately 13 ± 1 months to allow for screening, pre-procedural diagnostic procedures, treatment, and 12 ± 1 months of study follow-up.

4.3 Treatment Assignment

The first subject enrolled by each Investigator at each site will be classified as a Roll-In Subject and will be treated with the FARAPULSE PFA System as part of Investigator preparation. Roll-In Subjects are further defined in **Section 6.6.2**.

The number of Roll-In Subjects for each investigator will be determined by BSC depending on prior experience. Sites with more than one (1) active investigator may utilize available Roll-In Subjects jointly as required. Each site will be allocated a maximum of 3 Roll-In Subjects total.

After an individual investigator has completed the Roll-In Subject requirements, BSC will provide the investigator with authorization to proceed with the enrollment of Treatment Subjects.

4.4 Justification for the Study Design

BSC believes that a prospective, single arm, open label IDE trial with the FARAPULSE PFA System as the treatment device and powered for standard safety and effectiveness performance goals is a reasonable method to generate valid scientific evidence regarding the safety and effectiveness of, and obtain approval for, the FARAPULSE PFA System for the treatment of persistent atrial fibrillation.

The rationale for a single arm trial comparing outcomes to performance goals includes the single arm, performance goal IDE study “Pulsed Field Ablation to Irreversibly Electroporate Tissue and Treat AF” (ClinicalTrials.gov Identifier: NCT04198701) utilizing endocardial pulsed field ablation to treat PersAF.

Additionally, the current understanding in the field of catheter ablation of PersAF, ongoing IDE investigations, and the presence of additional products approved by the FDA for the ablation of PersAF indication from two different manufacturers (Biosense Webster P030031 S100, Medtronic P100010 S098) suggests the field is mature enough to consider a single arm design adequate for this study.

Finally, the several clinical trials leading to CE Mark approval, the PersAFOne Trial and the post-market follow-up FARA-Freedom Trial in the EU using a substantially similar clinical investigation

plan will provide reviewers with additional relevant safety information related to the treatment of paroxysmal and persistent atrial fibrillation. The ongoing ADVENT IDE Trial (G200259) in the U.S. will provide safety information for the ablation of paroxysmal atrial fibrillation which will be compared with a prospectively randomized standard of care control population.

5 Subject Selection

5.1 Study Population and Eligibility

Study eligibility criteria are described in **Section 5.2** and **Section 5.3** below. No vulnerable populations will be enrolled in this study. See **Section 23.2** for the definition of a vulnerable subject.

Study eligibility criteria are determined at the time of study entry based on currently available information. If testing is required, it must take place within the various intervals specified for the Baseline Assessment in **Section 7.5**

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, a protocol deviation exists, but this does not change the enrolled status of the subject or the inclusion of their data in study analyses.

5.2 Inclusion Criteria

Subjects who meet all of the following inclusion criteria (**Table 5.2-1**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see **Section 5.3**) is met.

Table 5.2-1: Inclusion Criteria

Inclusion Category	Inclusion Definition
1. Age	≥ 18 years of age, or older if required by local law
2. Symptomatic, documented, drug-resistant, Persistent AF	
a. Documented	At a minimum a physician's note confirming the arrhythmia symptoms and durations AND within 180 days of the Enrollment Date, either: i. A 24-hour continuous ECG recording confirming continuous AF, OR ii. Two ECGs from any regulatory cleared rhythm monitoring device showing continuous AF taken at least 7 days apart
b. Drug-resistant	Effectiveness failure of, intolerance to, or specific contraindication to at least one (1) AAD (Class I or III) [3]
c. Persistent	Continuous AF for > 7 days and ≤ 365 days

[3] All AADs previously failed for ineffectiveness or intolerance ("Failed AADs"), as well as those deemed contraindicated, must be recorded. For Failed AADs, the maximum daily dose associated with effectiveness or intolerance failure must also be recorded. See **Sections 7.4 Antiarrhythmic Drugs,** and **23.2 Definitions**.

Inclusion Category	Inclusion Definition
3. Informed consent	Willing and capable of providing informed consent
4. Full participation	Willing and capable of participating in all follow-up assessments and testing associated with this clinical investigation at an approved clinical investigational center

5.3 Exclusion Criteria

Subjects who meet any one of the following criteria (**Table 5.3-1**) cannot be included in this study or will be excluded from this clinical study. Exclusion criteria that are remediated and are no longer present prior to the Index Procedure / Rescheduled Index Procedure do not preclude enrollment once resolved, including but not limited to the presence of left atrial thrombus, noncompliant pre-procedural systemic anticoagulation, COVID-19, risk of unplanned pregnancy or the presence of an active implantable loop recorder.

Table 5.3-1: Exclusion Criteria

Exclusion Category	Exclusion Definition
1. Atrial exclusions – Any of the following atrial conditions:	
a. Atrial size	Left atrial anteroposterior diameter ≥ 5.5 cm, or if LA diameter not available, non-indexed volume >100 ml (by MRI, CT or TTE report or physician note)
b. Prior atrial ablation	Any prior atrial endocardial, epicardial or surgical ablation procedure for arrhythmia, other than right sided cavotricuspid isthmus ablation or for right sided SVT
c. Atrial myxoma	Current atrial myxoma
d. Pulmonary veins	Any PV abnormality, stenosis, or stenting (common and middle PVs are admissible)
e. Atrial thrombus	Current left atrial thrombus
2. Cardiovascular exclusions – Any of the following CV conditions:	
a. Ventricular arrhythmia	History of sustained ventricular tachycardia or any ventricular fibrillation
b. Secondary AF	AF that is secondary to electrolyte imbalance, thyroid disease, alcohol, or other reversible / non-cardiac causes
c. Cardiac devices and implants	Current or anticipated pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices, interatrial baffle, closure device, patch, or patent foramen ovale occluder, LA appendage closure, device or occlusion, active implantable loop recorder or insertable cardiac monitor at the time of ablation[4]

[4] Subjects may be enrolled with an active implantable loop recorder or insertable cardiac monitor if deactivation or removal is planned per standard of care prior to obtaining vascular access for the index ablation procedure.

Exclusion Category	Exclusion Definition
d. Clinically significant valvular disease	Valvular disease that is any of the following: i. Symptomatic ii. Causing or exacerbating congestive heart failure iii. Associated with abnormal LV function or hemodynamic measurements
e. Cardiomyopathy	Hypertrophic cardiomyopathy
f. Valve prostheses	Any prosthetic heart valve, ring or repair including balloon aortic valvuloplasty
g. Access issues	Any IVC filter, known inability to obtain vascular access or other contraindication to femoral access
h. Rheumatic disease	Rheumatic heart disease
i. Congenital disease	Congenital heart disease with any clinically significant residual anatomic or conduction abnormality
j. Anticipated cardiac surgery	Awaiting cardiac transplantation or other cardiac surgery within the next 12 months
3. Any of the following conditions at baseline (**Section 7.5**):	
a. Heart failure NYHA	Heart failure associated with NYHA Class III or IV
b. Ejection fraction	LVEF < 40%
c. Uncontrolled hypertension	Uncontrolled hypertension (SBP > 160 mmHg or DBP > 95 mmHg on two (2) BP measurements at baseline assessment
4. Any of the following events within 90 Days of the Consent Date:	
a. Coronary disease	Myocardial infarction (MI), unstable angina or coronary intervention
b. Cardiac surgery	Any cardiac surgery
c. Heart failure hospitalization	Heart failure hospitalization
d. Pericardium	Pericarditis or symptomatic pericardial effusion
e. GI bleeding	Gastrointestinal bleeding
f. Neurovascular event	Stroke, TIA, or intracranial bleeding
g. Thromboembolism	Any non-neurologic thromboembolic event
h. Carotid intervention	Carotid stenting or endarterectomy
5. Bleeding diathesis	Thrombocytosis, thrombocytopenia, disorder of blood clotting or bleeding diathesis
6. Contraindication to anticoagulation	Contraindication to, or unwillingness to use, systemic anticoagulation
7. Pre-ablation anticoagulation	Patients who have not been on anticoagulation therapy for at least 4 weeks prior to the ablation procedure

Exclusion Category	Exclusion Definition
8. Pregnancy	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
9. Health conditions that in the investigator's medical opinion 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. Obesity	Body Mass Index (BMI) > 42.0
b. Transplantation	Solid organ or hematologic transplant, or currently being evaluated for a transplant
c. Diaphragmatic abnormality	Any prior history or current evidence of hemi-diaphragmatic paralysis or paresis
d. Pulmonary	Severe lung disease, pulmonary hypertension, or any lung disease involving abnormal blood gases or requiring supplemental oxygen
e. Renal	Renal insufficiency if an estimated glomerular filtration rate (eGFR) is < 30 mL / min / 1.73 m^2, or with any history of renal dialysis or renal transplant
f. Malignancy	Active malignancy or history of treated malignancy within 24 months of enrollment (other than cutaneous basal cell or squamous cell carcinoma)
g. Gastrointestinal	Clinically significant gastrointestinal problems involving the esophagus or stomach including severe or erosive esophagitis, uncontrolled gastric reflux, gastroparesis, esophageal candidiasis or active gastroduodenal ulceration
h. Infections	Active systemic infection
i. 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[5]
j. Diabetes	Uncontrolled diabetes mellitus or a recorded HgbA1c > 8.0% in the 90 days prior to the Consent Date
k. Sleep apnea	Untreated diagnosed obstructive sleep apnea with apnea hypopnea index classification of severe (>30 pauses per hour)
10. Life expectancy	Predicted life expectancy less than one (1) year
11. Participation in another trial	Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments; each instance must be brought to the attention of the Sponsor to determine eligibility

[5] Clinical resolution of COVID-19 disease is to be determined by the investigator, based on signs and symptoms of current active viral infection, not long-term sequelae of the disease such as anosmia or chronic fatigue.

6 Subject Enrollment and Accountability

6.1 Screening

6.1.1 Study Candidate Screening

Investigators are responsible for screening all potential subjects and selecting those who are appropriate for study inclusion. The subjects selected for participation should be from the Investigator's general patient population. The Investigator is expected to follow standard of care testing to diagnose and screen subjects for inclusion in the study.

6.1.2 Screening and Enrollment Log

A Screening and Enrollment Log will be maintained at the investigational site to document select information about candidates who sign an Informed Consent Form (ICF) and then fail to meet the general and specific selection criteria, including those enrolled in the study and classified either as Consent Ineligible, Intent, Attempt or Treatment subjects.

6.1.3 Informed Consent

In order to determine eligibility of a subject, the Investigator or designee needs to implement the consent process and verify and document the subject meets the inclusion / exclusion criteria. Informed consent is required for all subjects prior to their participation in the study. No study-specific procedures can be conducted prior to consent.

The subject will be given ample time to consider participation and ask questions if necessary. An approved ICF shall be personally signed and dated by the subject. The date the subject signs the ICF is the Consent Date. The original, signed document is to be kept with the subject's file and a copy must be provided to the subject.

The Index Procedure must be initiated within 30 days following the Consent Date. If at the Index Procedure the subject is found to have inadequate pre-procedural anticoagulation, a current atrial thrombus, or other resolvable exclusion criteria as determined by the Investigator, then the Rescheduled Index Procedure must be scheduled within 45 days of the Index Procedure.

If the Index Procedure / Rescheduled Index Procedure has not been performed within these time periods, the subject will be classified as an Intent or Consent Ineligible Subject (see **Section 6.6.1 and Section 6.6.3**), depending on the circumstances. **An Intent Subject or Consent Ineligible Subject cannot be considered for re-enrollment.** The site will ensure that originally signed ICFs and documentation of the ICF signature process are filed in subject's file and that the subject's participation into the study is documented per hospital process (e.g.in the medical file). Originally signed ICFs and the ICF process will be made available for review at Interim Monitoring Visits (IMVs).

For additional information regarding the informed consent process, refer to **Section 18**.

6.2 Point of Enrollment

Subjects who have signed and dated the Informed Consent Form are considered enrolled in the study.

Adverse events will be captured beginning on the Consent Date. Adverse events occurring prior to the Index Procedure / Rescheduled Index Procedure will be analyzed and listed separately and will not otherwise be part of the outcome analyses specified in this protocol.

Screening tests that are part of standard-of-care (SOC) can be used to determine pre-eligibility, but no study-related activities, testing, procedures, etc. can take place until the ICF is signed and dated by the subject. Study data from exams performed prior to consent / enrollment (e.g., transthoracic echocardiography [TTE]) will be collected as medical history data after the subject is consented / enrolled in the study.

6.3 Enrollment Controls

Subject study-specific identification (ID) will be generated through the Electronic Data Capture (EDC) system used for this study. This database will also be utilized to provide the sites with subject classification assignments (including Roll-In Subjects) once a subject has provided written informed consent. Enrollment controls will be put in place to ensure no more than 33 (13% of the estimated 258 Treatment Subjects) will occur at a single site. In addition, BSC will communicate the process that will be followed for enrolling subjects as the enrollment ceiling of 258 Treatment Subjects is approached.

6.4 Withdrawal

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the Investigator shall ask for the subject's documented permission to follow his / her status / condition outside of the clinical study.

Reasons for withdrawal may include physician discretion, subject choice to withdraw, lost to follow-up, or death. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. In the event a subject does decide to withdraw from the study, every effort should be made to obtain full information on any on-going reportable adverse events up to the point of withdrawal. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his / her consent, for whatever reason. Data collected up to the point of subject withdrawal may be used, unless any local regulations apply which require removal of the data.

If the withdrawal is due to the Investigator's discretion, the Investigator is obligated to follow all open reportable adverse events until they can be considered as resolved or not resolved.

The outcome of all open reportable adverse events should be documented. If the withdrawal is due to problems related to device safety or performance, the Investigator shall ask for the subject's documented permission to follow his / her status / condition.

Withdrawn subjects will not be replaced.

All applicable electronic case report forms (eCRFs) up to the point of subject withdrawal / lost to follow up and an "End of Study" eCRF must be completed.

6.5 Lost to Follow-Up

A subject will be considered lost to follow-up if he or she fails to return after documented attempts to attend a scheduled assessment and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to participate in a required study assessment:

- The site will attempt to contact the subject to reschedule the missed assessment and counsel the subject on the importance of maintaining the assigned assessment schedule and ascertain if the subject wishes to and / or should continue in the study.
- Before a subject is deemed lost to follow-up, the Investigator or designee will make every effort to regain contact with the subject (at minimum 3 telephone calls and a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts must be documented in the subject's medical record or study file.
- Should the subject continue to be unreachable, he or she will be considered lost to follow-up from the study.

All applicable eCRFs up to the point of subject withdrawal / lost to follow up and an "End of Study" eCRF must be completed.

6.6 Subject Status and Classification

As subjects are evaluated, enrolled, and treated in the study, they will be grouped into one of the following categories. Categorization will determine follow-up, data, and analysis requirements.

Investigational sites will list all Consent Ineligible (screening failure), Intent, Attempt and Treatment subjects in the Screening and Enrollment Log.

6.6.1 Consent Ineligible (Screening Failures)

A subject who has signed informed consent but is found ultimately not to meet eligibility criteria will be classified as "Consent Ineligible".[6] There are no follow-up reporting requirements for consent ineligible subjects. Subjects determined to be Consent Ineligible do not count towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the center's patient file. A subject ID will be assigned in the EDC system.

For consent ineligible subjects the following forms must be completed:

- Enrollment and End of Study eCRF must be completed
- Adverse Event CRFs for any reportable event, as defined in **Section 17** for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal

6.6.2 Roll-In Subjects

The first subject enrolled by each Investigator at each site will be treated with the FARAPULSE Pulsed Ablation System as part of Investigator preparation (**Section 4.2.1**) and be enrolled into the study as a Roll-In Subject.
Roll-In Subjects will:

- Be consented using the approved ICF
- Count against the Roll-In Subject enrollment ceiling
- Follow the Index Procedures as specified in **Section 7.6**
- Have all study data gathered as specified in **Section 7**
- Be followed for 12 months post-ablation, completing Day 7, Day 30, Day 90, Day 180, and Day 360 Assessments identically with Treatment / Attempt Subjects
- Be analyzed and reported separately from the Treatment / Attempt Subjects.

[6] See **Section 5.3** regarding the acceptability of exclusion criteria that can be remediated and thus do not constitute an ultimate failure of eligibility criteria.

6.6.3 Intent Subjects

Intent Subjects include the following types of subjects:

- Any subject who signs informed consent, meets eligibility criteria, but does not have any study investigational devices inserted into the body.
- Any subject that is enrolled in the study but does not undergo the Index Procedure within 30 days from the Consent Date or a Rescheduled Index Procedure within 45 days of the Index Procedure. These subjects will be withdrawn from the study as of the end of the above disqualifying interval.

Intent Subjects:

- Do not count towards the Treatment Subject enrollment ceiling
- Have no follow-up requirements once classified as an Intent Subject
- Will not be used for analysis of any study endpoints
- Will not be allowed to re-enroll in the study

For Intent Subjects, at a minimum the following forms must be completed:

- Enrollment and baseline CRFs such as, but not limited to, informed consent, enrollment information and other related CRFs
- End of Study CRF
- Adverse Event CRFs for any reportable event as defined in **Section 17.1** for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal

The original signed Informed Consent must be maintained in the investigation site's patient file. A subject ID will be assigned in the EDC system.

6.6.4 Attempt Subjects

An Attempt Subject is a subject who signs informed consent, meets eligibility criteria, and has any investigational device inserted into the body but does not receive any pulsed field ablation application.

Attempt Subjects:

- Do not count towards the Treatment Subject enrollment ceiling.
- Will be followed up to the Day 30 assessment with all applicable CRFs completed
- Will be used for analysis of the study safety outcomes
- Will not be used for analysis of the study effectiveness outcomes including subgroup, multivariable, and center pooling analyses.
- Will not be allowed to re-enroll in the study.

For Attempt Subjects, at a minimum the following forms must be completed:

- Enrollment and baseline CRFs such as, but not limited to, informed consent, enrollment information and other related CRFs
- End of Study CRF
- Adverse Event CRFs for any reportable event as defined in **Section 17.1** for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal

The original signed Informed Consent for each Attempt Subject must be maintained in the investigational site's patient file. A subject ID will be assigned in the EDC system.

6.6.5 Treatment Subjects

Any subject that signs the Consent Form, meets eligibility criteria, has an investigational device inserted into the body and receives at least one pulsed field ablation application will be classified as a Treatment Subject.

Treatment Subjects:

- Count towards the Treatment Subject enrollment ceiling.
- Will be followed up to the 360 Day Assessment with all applicable CRFs completed
- Will be included in all study analyses.

The original signed Informed Consent and any relevant documentation must be maintained in the investigational site's patient file. A subject ID will be assigned in the EDC system.

6.7 End-of-Study Definition

A clinical trial is considered completed when subjects are no longer being examined or the last subject's last study assessment has occurred. The end of the study is defined as completion of the last assessment or procedure shown in the Data Collection Schedule in the trial globally.

7 Study Methods

7.1 Overview of Study Interactions

Each Treatment subject will undergo the following formal study interactions:

- Baseline Assessment
- Index Procedure / Rescheduled Index Procedure (Day 0)
- Pre-Discharge Assessment (immediately prior to discharge after the Index Procedure)
- Day 7 Safety Assessment (window Day 7 – 11, remote)
- Day 30 Safety Assessment (window Day 30-37, remote)
- Day 90 Assessment (window 90 ± 14 days, in-person)
- Day 180 Assessment (window 180 ± 30 days, remote)
- Day 360 Assessment (window 360 ± 30 days, in-person)

In addition, the following events may also occur for some study subjects:

- Re-ablation Procedure: Re-ablations for AF, AFL and AT will be captured in the EDC database using the Re-Ablation Procedure CRF
- Unscheduled Assessments: Any unscheduled cardiovascular assessments will be captured in the EDC database using the Unscheduled Assessment CRF

The data collection schedule for these various interactions is shown in **Table 7.2-1**.

7.2 Data Collection Schedule

Table 7.2-1: Data Collection Schedule

Assessment	Screen / Baseline[1] (In-person)	Index Procedure Day 0 (In-person)	Pre-Discharge (In-person)	Day 7 (7-11 days) (Remote[2])	Day 30 (30-37 days) (Remote[2])	Re-Ablation within Blanking[10] (In-person)	Day 90 (90 ± 14 days) (In-person)	Day 180 (180 ± 30 days) (Remote[2])	Day 360 (360 ± 30 days) (In-person)	Unscheduled CV (In-person / Remote[2])
Informed consent, eligibility, baseline assessments (incl. NYHA Class)	X[3]	--	--	--	--	--	--	--	--	--
Laboratory testing[4]	X	--	X	--	--		--	--	--	--
AAD and anticoagulant medications	X	--	X	X	X	X	X	X	X	X
Recurrent arrhythmia, cardioversions, ablations, hospital admissions	--	--	X	X	X	X	X	X	X	X
12-lead ECG	X	--	X	--	--	X	X	--	X	X
Transthoracic echocardiogram (TTE)	X[5]	--	--	--	--	--	--	--	--	--
Cardiac CT / MRI	X[6]	--	--	--	--	X[6]	X[6]	--	X[6]	X[6]
Ablation procedure data	--	X	--	--	--	--	--	--	--	--
Event monitors	Introduction	--	--	--	--	--	Training Day 90, then twice per month / Sx			X
24-Hour continuous ECG (Holter)	Introduction	--	--	--	--	--	--	X	X	--
TEE / CT / ICE to exclude LA thrombus	--	X[7]	--	--	--	X[7]	--	--	--	--
Radiologic examination of diaphragm	--	X	--	--	--	X	X[8]	--	X[8]	--
EQ-5D-3L & AFEQT assessments	X	--	--	--	--	--	--	X	X	--
Pre / post NIHSS	X	--	X	--	--	X	--	--	--	--
Neuro assessment	--	--	X[9]	--	--	X[9]	--	--	--	--
Adverse events	--	X	X	X	X	X	X	X	X	X

[1] Baseline Assessments must be generated in the window beginning 30 days (within 180 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 7.5**.
[4] Laboratory tests include hematocrit, hemoglobin, electrolytes, blood urea nitrogen, creatinine and if applicable a pregnancy test at baseline, or for the Index or Re-ablation procedure (if baseline pregnancy test done more than 30 days prior to Index Procedure/re-scheduled procedure)
[5] Within 180 days of Consent Date.
[6] MRI / CT cardiac imaging at baseline within 180 days of Consent Date; subsequently only if required if there is a clinical suspicion of PV stenosis
[7] Performed within 48 hours prior to (TEE or CT) or at the procedure prior to transeptal puncture (TEE or ICE).
[8] Only if resolution of phrenic nerve palsy has not yet been demonstrated.
[9] 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 DW-MRI scan.
[10] Re-ablation post-Blanking Period procedure data collection will only include adverse events, gaps identified and ablated and number of applications required

7.3 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[72] relating to this issue.

With the exception of substantial compliance with 4 weeks of anticoagulation prior to the Index / Rescheduled Index Procedure (**Section 7.6.2.1**), adjustments in anticoagulation therapy 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.
- DOACs 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 4 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 DOAC should have either uninterrupted treatment (if receiving rivaroxaban) or a single dose interruption in DOAC with a restart shortly after the procedure, at Investigator discretion.
- A heparin bolus will be delivered prior to or immediately following transseptal puncture according to institutional standard of care. Procedural activated clotting times (ACTs) will be sampled regularly throughout the procedure according to institutional standard of care and maintained at a minimum of 300 seconds at least until all devices are withdrawn from the left atrium.

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 guidelines referenced in this section.

7.4 Antiarrhythmic Drugs

Use of Class I / III AADs during the ADVANTAGE AF Study must be managed carefully.

The terms “Antiarrhythmic Drugs, Class I and III”, “Blanking Period”, “Failed AAD” and “Non-Failed AAD” are defined specifically in **Section 23.2**.

Failed AADs

At the Baseline Assessment, **Section 7.5**, all Class I and III AADs previously used by the subject must be defined as Failed AADs or Non-Failed AADs in the CRF, including for any Failed AADs the maximum failed dose (see **Section 23.2**).

Amiodarone

- May not be used after the Blanking Period or the subject becomes a Treatment Failure.
- If subjects are prescribed Amiodarone, treatment should be stopped within 30 days following the Index Procedure.

Managing AADs During the Blanking Period

During the Blanking Period the subject should be assessed for AAD continuation. Titration of Class I / III AADs is allowed during the Blanking Period.

To account for the hard cutoff of the Blanking Period at 90 days and given the permitted visit window for the Day 90 Assessment (90 ± 14 days), AADs that are taken during the Blanking Period but are stopped at the time of a within-window Day 90 visit (up to and including Day 104) will not be counted as potential Treatment Failures to allow the necessary physician evaluation.

Managing AADs After the Blanking Period

If indicated, subjects may remain on Class I / III AADs following the Blanking Period, preferably those established as Failed AADs (see **Section 23.2**) at or below the maximum failed dose so as not to create a post-Blanking Period Treatment Failure.

Use of a Non-Failed AAD after the Day 90 Assessment constitutes a Treatment Failure for the primary effectiveness endpoint.

AAD Monitoring

At all subsequent follow-up assessments, subject compliance with, and changes in drugs and daily doses for any Class I / III AAD, will be elicited and recorded.

7.5 Baseline Assessment

Type of Assessment: In-person at investigational site
The completion of the Baseline Assessment requires an in-person assessment. 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 but is not limited to:

- Demographics including gender, height, and weight, race and ethnicity, in accordance with local requirements[7]
- Pertinent medical and cardiovascular history
- AAD history to establish Failed AAD and Non-Failed AAD status
- 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 according to investigation site requirements. The following information is not required if it is not a site requirement, but if available the data should be recorded:
    - A negative PCR for SARS-CoV-2 virus or equivalent testing, or
    - Confirmation of vaccination with a commercially available vaccine

[7] With a goal of achieving an unbiased estimate of treatment effect in the general population, Boston Scientific seeks to enroll a diverse population including representative proportions of relevant age, racial, and ethnic subgroups, which are consistent with the intended use population of the device. Case Report Forms will collect data on age, race and ethnicity in order to achieve this goal, in accordance with local regulations.

- 12-lead ECG
- Imaging (within the window beginning 180 days prior to the Consent Date and ending on the date of the Index Procedure)
  - TTE or Cardiac CT/ MRI for LA dimensions
  - TTE for LVEF
  - Cardiac CT or MRI establishing cardiac anatomy for mapping and PV dimensions
- NYHA Classification
- National Institutes of Health Stroke Scale (NIHSS) score by NIHSS-certified site personnel
- CHA_2DS_2-VASc score
- Quality of Life Measures:
  - The 3-level EuroQol standardized questionnaire of health states (EQ-5D-3L)
  - The Atrial Fibrillation Effect on QualiTy-of-Life Questionnaire (AFEQT) quality of life assessments

Introduction to the Rhythm Monitoring: At the Baseline Assessment, the subject will receive an introduction to event and Holter monitoring (rhythm monitoring) and how this will be performed during the follow-up period. The importance of compliance with these critical assessments will be stressed.

7.6 Index Procedure / Rescheduled Index Procedure

7.6.1 Index Procedure / Rescheduled Index Procedure Data Collection

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 assessment. The Index Procedure / Rescheduled Index Procedure must be deferred if this is not possible.

Procedural data will be collected including but not limited to:

- The results of transesophageal echocardiography (TEE) or volumetric CT within 48 hours prior to procedure, or intracardiac echocardiography (ICE) prior to transseptal puncture, utilized for exclusion of LA thrombus.
- Pregnancy test (all women of childbearing potential if the baseline pregnancy test was obtained more than 30 days prior to the Index Procedure / Rescheduled Index Procedure)
- Documentation of PVI for each attempted vein, of PWI, and if performed, of CTI BDB
- Post-ablation electroanatomical maps, if performed with Rhythmia
- The functional status of both phrenic nerves will be assessed radiographically pre and post ablation.
- Method of sedation or anesthesia
- Whether adenosine was used to confirm PVI and / or PWI
- Whether a post-procedure cardioversion was performed
- Adverse events
- For the 3D mapping system: Manufacturer and model, when applicable
- Procedural times
- Ablation data

- Procedural anticoagulation data:
  - For subjects on a DOAC whether DOAC therapy was interrupted for procedure
  - For subjects on warfarin, a pre-ablation international normalized ratio (INR) value
  - Procedural heparin administration and timing
- Device deficiencies and malfunctions

7.6.2 Index Procedure Workflow

This section contains important information regarding the procedures for cardiac ablations specified in the ADVANTAGE AF Study. Investigators and staff should refer to training materials and the IFU documents as applicable per device and study region.

Ablation under this protocol will generally follow the order below. However, the Investigator may alter the ablation sequence if necessary for subject welfare.

Unless otherwise directed by Sponsor, at the conclusion of the procedure, all single-use components of the FARAPULSE PFA System should be returned to the Sponsor.

7.6.2.1 Preparation

Subjects must be screened for substantial compliance with 4 weeks of systemic anticoagulation prior to the Index Procedure and, if in the opinion of the Investigator, this condition has not been met, the subject will be rescheduled as defined in **Section 7.6.3**.

TEE or volumetric CT 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 as defined in **Section 7.6.3**.

Phrenic nerve function will be assessed prior to ablation per Investigator standard of care, preferably by a pre-sedation fluoroscopic sniff test. 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 aseptically under ultrasound guidance.

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

A heparin bolus will be delivered prior to or immediately after transseptal puncture. Procedural ACTs will be monitored according to the investigational site's standard of care and maintained at a minimum of 300 seconds at least until all devices are withdrawn from the left atrium.

7.6.2.2 Pulmonary Vein Isolation

Ablation of the PVs will be performed according to the IFU and institutional practice.

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

The use of ICE is recommended but not required for Pulsed Field Ablation procedures.

All catheter exchanges should be carefully performed to avoid introducing air bubbles into the FARADRIVE Steerable Sheath.

Esophageal temperature monitoring, esophageal cooling and esophageal deviation are unnecessary during PVI and PWI ablation with the FARAWAVE PFA Catheter and should not be utilized.

7.6.2.3 Posterior Wall Isolation

Following PVI ablation, LAPW ablation will be performed according to the IFU and institutional practice.

LAPW ablation will be performed in the area below the superior aspect of the superior PVs, above the inferior aspect of the inferior veins, and between the insertions of the left sided and right sided PVs. In the event the PW is found to be electrically isolated following PVI, LAPW ablation will still be performed using the same anatomically guided approach until there is sufficient overlap between PFA application sites. No ablation in other locations, including the left atrial appendage, is permitted.

LAPW ablation should be guided by electroanatomical mapping, ICE and / or fluoroscopy to ensure the entire area of LAPW is ablated with the appropriate amount of overlap between PFA application sites.

All catheter exchanges should be carefully performed to avoid introducing air bubbles into the FARADRIVE Steerable Sheath.

Esophageal temperature monitoring, esophageal cooling and esophageal deviation are unnecessary during PVI and LAPW ablation with the FARAWAVE PFA Catheter and should not be utilized.

7.6.2.4 Assessment of Isolation and Phrenic Nerve Function

Assessment of Isolation

After the completion of the planned PV and LAPW ablations, isolation will be assessed as:

- The isolation of all attempted PVs at least 20 minutes following the last PFA application in each respective vein by entrance block performed with or without adenosine testing, AND
- The isolation of the LAPW at the end of the LAPW ablation, performed with or without adenosine testing, via interrogation by multipolar diagnostic catheter or 3D electroanatomical mapping. If electroanatomical mapping is used, electrograms demonstrating PWI are required per **Section 7.17**. At the Investigator's discretion, exit block pacing of the PW may be performed to detect any epicardial exit pathways.

Additional PV and LAPW ablation as described above may be performed as needed at any time to achieve complete PVI and PWI. Alternative dosing or fewer applications may be performed as needed for subject welfare, technical difficulties, or anatomical challenges and will not constitute a Treatment Failure if electrical isolation is still confirmed as required. In the event that touch-ups are performed after the initial isolation assessment, further waiting periods are not required.

Assessment of Phrenic Nerve Function

Once all PV and LAPW ablation is completed and isolation is confirmed, the functional status of both phrenic nerves will be assessed per Investigator standard of care (e.g. radiographically either by pacing, fluoroscopy, or a sniff test.[8])

7.6.2.5 CTI Ablation

The following subjects will undergo CTI ablation:

- Required: For subjects with a history of CTI-mediated (typical) AFL and
  - Who have not had a CTI ablation procedure, or
  - Who have had a CTI ablation procedure but have recurrent CTI conduction.
- Required: Subjects who manifest CTI-mediated AFL (spontaneous or induced) during the Index Procedure
- At Investigator discretion: Subject welfare indicates that CTI ablation should be performed.

Ablation of the CTI will be performed using, a commercially available BSC RF catheter. If performed, CTI ablation should occur following PV and LAPW ablation. FARAWAVE usage is not allowed to complete any CTI lesion.

After CTI ablation is completed in these subjects, BDB will be assessed, and if necessary, additional applications may be performed until BDB is confirmed. The CTI ablation data will be documented in the CRF and does not constitute a Persistent AF Acute Procedural Failure.

7.6.2.6 Other Ablation

When the Investigator determines that subject welfare requires intervention for either an accessory pathway, AVNRT or spontaneously occurring treatment-emergent AFL or AT, ablation for these arrhythmias may be performed using any commercially available RF ablation catheter. Such ablations should be performed after all ablation with the FARAPULSE PFA System is complete. These permitted ablations and the associated data will be documented in the CRF and do not constitute Persistent AF Acute Procedural Failure. FARAWAVE usage is not allowed to complete any lesion outside of the PVs and LAPW, as described in the IFU.

Ablation for an arrhythmia that is provoked only by catheter manipulation or is only inducible by pacing or pharmacologic stimulation is not permitted.

7.6.3 Rescheduled Index Procedure

If, at the Index Procedure, the subject is found to have inadequate pre-procedural anticoagulation, a current atrial thrombus, COVID-19, or other temporarily disqualifying condition, the subject may have their Index Procedure rescheduled not later than 45 days later. The Rescheduled Index Procedure will otherwise follow the data and procedural requirements of **Section 7.6.1**.

The Rescheduled Index Procedure must be scheduled within 45 days of the Index Procedure, and only one Rescheduled Index Procedure may be allowed; otherwise, the subject will be exited from the study as an Intent Subject.

This rescheduling is permissible and does not create an Acute Procedural Failure. The subject remains a potential Treatment Subject.

[8] If anesthesia necessitates, a pre-discharge fluoroscopic sniff test or inspiration / expiration CXR may be acceptable. See **Section 7.7**.

References to "Index Procedure" in this protocol should be assumed when appropriate to include "Rescheduled Index Procedure" as well if not otherwise specified.

7.7 Pre-Discharge Assessment

Subjects should be prescribed a form of systemic anticoagulation treatment for at least two months following the ablation procedure. See **Section 7.3** regarding post-ablation anticoagulation requirements.

Type of Assessment: In-person at investigational site

Prior to hospital discharge, study data will be collected including but not limited to:

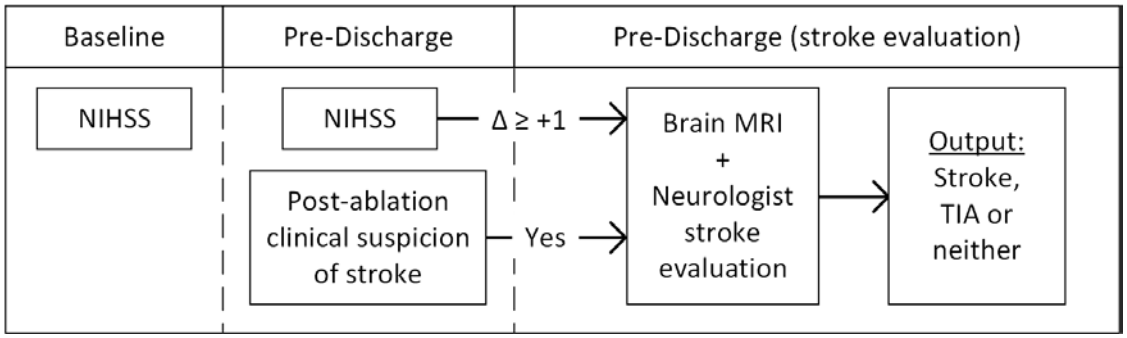
- Adverse events
- Hematocrit, hemoglobin, electrolytes, BUN, creatinine
- 12-lead ECG to document the subject's rhythm and if any new conduction disturbances are observed.
    - A 12-lead ECG collected at the end of the Index Procedure / Rescheduled Index Procedure after all ablation was complete is also acceptable.
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs.
- Occurrence, date, indication and outcome of any post-procedure cardioversion(s)
- Phrenic nerve assessment, as only applicable:
    - If the function of both phrenic nerves could not be confirmed at the end of the Index Procedure / Rescheduled Index Procedure, a radiologic examination of the diaphragm (fluoroscopic sniff test or inspiration / expiration CXR)
    - If the post-Index Procedure / Rescheduled Index Procedure fluoroscopy indicated diminished phrenic nerve response and resolution has not been previously demonstrated, a radiologic examination of the diaphragm

Pre-Discharge Stroke Evaluation:

- NIHSS score by NIHSS-certified site personnel after the effects of anesthesia have fully resolved.
- 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 DW-MRI scan. This assessment will be sufficient to determine with reasonable certainty whether a stroke, TIA or neither have occurred, using the definitions in **Table 3.2-2**. Please refer to **Figure 7.7-1**.

Figure 7.7-1: Pre-Discharge Stroke Evaluation



7.8 Day 7 Safety 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. Any subject who continues to be hospitalized at the time of the assessment will have their Day 7 assessment performed in-hospital.

Study data will be collected by interview, including but not limited to:

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

7.9 Day 30 Safety Assessment

Type of Assessment: Remote
Window: Days 30 – Day 37
The Day 30 Assessment is essential to establish the primary safety endpoint and every effort must be made to complete this assessment between Day 30 and Day 37.
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 30, or thereafter.
AAD Treatment: Between the Day 30 Assessment and the Day 90 Assessment – the subject should be assessed for AAD continuation. See Section 7.10.

Discharged subjects will be assessed remotely between Day 30 and Day 37 post-Index Procedure / Rescheduled Index Procedure. Any subject who is hospitalized at the time of the assessment will have their Day 30 assessment performed in-hospital.

Study data will be collected by interview including but not limited to:

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

7.10 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 assessment within window: • As much data as possible may be collected remotely. • 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. • If a radiologic 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.

Event Monitoring: Prior to or at the scheduled Day 90 Assessment, the subject will receive event monitor (EM) hardware and training regarding its use and the importance of event monitoring. The subject will be instructed to begin using the twice per month EM recordings starting at the time of the Day 90 Assessment and also for any symptomatic episodes experienced at any time throughout the remainder of study follow-up.

The subject will be reminded of the critical importance of full compliance with rhythm monitoring both for successful treatment of their arrhythmia and for the success of the study.

AAD Treatment: During the Blanking Period the subject should be assessed for AAD continuation.

At Investigator discretion, Class I / III AADs may be stopped to allow assessment of the subject's potential for off-drug freedom from recurrent AF, AFL, or AT.

Subjects who require continued AAD treatment may be continued; preferably with a Failed AAD. Using a Non-Failed AAD or amiodarone would create an unnecessary Treatment Failure. See **Section 7.4**.

Subjects will be assessed at Day 90 ± 14 days following the Index Procedure / Rescheduled Index Procedure. Study data will be collected at the Day 90 Assessment including but not limited to:

- Adverse events

- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs
- Recurrent arrhythmia, cardioversions, ablations, or hospital admissions since last assessment
- Cardiac rhythm as determined by a 12-lead ECG at the time of the assessment (in-person assessment only). All 12-lead ECGs will be provided to the Arrhythmia Core Laboratory (ACL).
- If the post-Index Procedure / Rescheduled Index Procedure fluoroscopy indicated diminished phrenic nerve response and resolution has not been previously demonstrated, a radiologic examination of the diaphragm
- If there is a clinical suspicion of PV stenosis, a cardiac CT or MRI scan of the same type as the baseline scan to assess the dimensions of the PVs.
- If data is collected remotely, the date, time and communication method(s) used to collect the data remotely.

7.11 Day 180 Assessment

Type of Assessment: Remote; In-person allowed
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 Day 180 ± 30 days following the Index Procedure / Rescheduled Index Procedure. Any subject who is hospitalized or seen in the office as standard of care at the time of the assessment may have their Day 180 assessment performed in-person.

Rhythm Monitoring

- **Holter Monitor:** Within the 180 ± 30-day window for this assessment, the subject will be contacted, receive remote training regarding the use of the Holter and complete a 24-hour monitoring session.
- **EM Review:** During this assessment, EM compliance will be reviewed for twice per month and ad hoc symptomatic monitoring, and retraining of the subject provided as needed.

Study data will be collected at the Day 180 Assessment including but not limited to:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs
- Recurrent arrhythmia, cardioversions, ablations, or hospital admissions since last assessment
- Quality of Life Measures:
    - The 3-level EuroQol standardized questionnaire of health states (EQ-5D-3L) The Atrial Fibrillation Effect on QualiTy-of-Life Questionnaire (AFEQT) quality of life assessments
- The date, time and communication method(s) used to collect the data remotely

7.12 Day 360 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. • If a radiologic 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.

Rhythm Monitoring: Within the 360 ± 30-day window for this assessment the subject will be contacted, receive remote training regarding the use of the Holter, complete a 24-hour monitoring session and return both the Holter and EM as instructed.

Study data will be collected at the Day 360 Assessment including but not limited to:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs
- Recurrent arrhythmia, cardioversions, ablations, or hospital admissions since last assessment
- If the post-Index Procedure / Rescheduled Index Procedure fluoroscopy indicated diminished phrenic nerve response and resolution has not been previously demonstrated, a radiologic examination of the diaphragm
- If there is a new clinical suspicion of PV stenosis, a cardiac CT or MRI scan of the same type as the baseline scan to assess the dimensions of the PVs.
- Cardiac rhythm as determined by a 12-lead ECG at the time of the assessment (in-person assessment only). All 12-lead ECGs will be provided to the ACL.
- Quality of Life Measures:
  - The 3-level EuroQol standardized questionnaire of health states (EQ-5D-3L)
  - The Atrial Fibrillation Effect on QualiTy-of-Life Questionnaire (AFEQT) quality of life assessments
- 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 Day 360 Assessment a Study Exit CRF will be completed.

7.13 Re-Ablation Procedures

7.13.1 Re-Ablation Procedure within the Blanking Period

For subjects undergoing a first re-ablation procedure within the Blanking Period for Detectable AF, AFL or AT, the procedure will be performed by the investigator under the procedures and data

requirements of **Section 7.6**, modified to assess and treat only those locations required, and including the pre- and post-procedure NIHSS.

Such re-ablation using the methods and devices described in **Section 7.6** does not constitute a Treatment Failure.

7.13.2 Other Re-Ablation Procedures

For a second re-ablation during the Blanking Period and for any re-ablation after the Blanking Period, any commercially available ablation catheter may be used for re-ablation.

The FARAPULSE Pulsed Field Ablation System is not permitted to be used for these procedures.

Such re-ablations constitute Treatment Failures, and therefore during such procedures other sites may be ablated at Investigator discretion.

The following data will be collected for these procedures:

- Adverse events
- During re-ablation procedures, a mapping procedure will be performed to characterize the reconnection status for each originally treated PV and the PW (if a left-sided re-ablation), and the CTI, to characterize lesion durability.
- Limited ablation data

7.14 Unscheduled Assessments

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

Any unscheduled follow-up assessments for cardiovascular events that occur throughout study follow-up will be documented. Study data will be collected including but not limited to:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs
- Recurrent arrhythmia, cardioversions, ablations, or hospital admissions since last assessment
- EM compliance will be reviewed for twice per month and ad hoc symptomatic monitoring and retraining of the subject provided as needed.
- Cardiac rhythm
  - At the investigational site: 12-lead ECGs will be collected and provided to the ACL.
  - At another health care site: a record of any ECG should be obtained if available.
  - Remote, not at a health care site: An EM submission should be requested.
- If there is a new clinical suspicion of PV stenosis, a cardiac CT or MRI scan of the same type as the baseline scan to assess the dimensions of the PVs.
- If data is collected remotely, the date, time and communication method(s) used to collect the data remotely

7.15 Unforeseen Circumstances

There may be unforeseen circumstances that occur during the course of the study, such as a natural disaster or a global pandemic (e.g., COVID-19) that prevents a subject from participating in study assessments during the required follow-up window. While every attempt should be made to avoid

disruptions in collecting study data, it is important to collect as much data as possible, by any available means and from any available resources. This may include obtaining records from an outside clinic, hospital or other healthcare facility that is not IRB / EC / REB approved.

In the event that study data must be collected remotely, every effort should be made to collect the data within the study assessment window. Critical data collected during the study includes any device or procedure-related adverse events, recurrence of any AF / AT / AFL, and a Cardiac CT or MRI (if PV stenosis is suspected). Event monitoring can be used to assess current heart rhythm. If a Cardiac CT or MRI is required because PV stenosis is suspected, the Cardiac CT or MRI – preferably using the baseline modality – may be performed at another healthcare facility and the window to conduct this test may be extended by up to one month (30 days) following the normal study assessment window.

When such unforeseen circumstances result in a deviation from the requirements of the protocol, the deviations will be distinguished from routine protocol deviations and reported separately.

7.16 Study Completion

Each Roll-In Subject and Treatment Subject will be followed until the Day 360 Assessment. Participation in the study is considered complete upon completion of the Day 360 Assessment or the completion of the Day 360 Holter monitoring, whichever comes later. Each Attempt Subject will be followed through the Day 30 Assessment following the Index Procedure / Rescheduled Index Procedure and then exited from the study. In case of premature termination of the study, please refer to **Section 20.1**.

Following termination or completion of the study, subjects will be managed according to local institution practice. Sites will need to document and complete the "End of Study" CRF to signify study completion.

7.17 Source Documents

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in **Table 7.17-1** below.

Table 7.17-1: Source Documentation Requirements

Requirement	Disposition
Screening and enrollment log	Retain at Center
Informed consent documentation process	Retain at Center
Medical history documents pertaining to eligibility criteria	Retain at Center
Documentation of demographics data	Retain at Center
Pregnancy testing, if applicable	Retain at Center
Required laboratory testing	Retain at Center
Cardiovascular / pulmonary examination	Retain at Center

Requirement	Disposition
AAD and Anticoagulation Medication Regimen and Changes	Retain at Center
Medical history	Retain at Center
Quality of Life Instruments (AFEQT and EQ-5D-3L)	Retain at Center
NIH Stroke Scale Assessments	Retain original at center and submit copies and copies of all associated source documents if an increase in scale is observed from baseline
If determined necessary, neurological consultation and brain MRI (DW-MRI)	Retain originals at center and submit copies of all source documents and copy of complete scan to BSC
Baseline cardiac imaging and any required follow-up imaging	Retain at Center
12-Lead ECGs data including ongoing rhythm	Retain at Center Submit copies of the ECGs collected at Day 90 and Day 360 Follow up and Unscheduled visits when applicable to the ACL.
Post-ablation electrograms showing entrance block for each treated PV	Retain at Center
Post-ablation electrogram documentation demonstrating PWI	Retain at Center (Submit to BSC if Rhythmia)
Post-ablation electrograms showing bidirectional isthmus block (CTI ablations only)	Retain at Center (Submit to BSC if Rhythmia)
Recording lab logs, showing PV entrance block, PW isolation and CTI BDB (if applicable)	Retain at Center
Signed Technical Source Form	Retain at Center
Printed EP Lab Procedure Report	Retain at Center
Adverse Events	Retain at Center, copy may be requested by BSC
In the event of a patient death: • Death narrative • Relevant medical records • Death Certificate • Autopsy report	Submit one copy to BSC, Retain one copy at center
For events adjudicated by CEC: • Relevant medical records	Submit one copy to BSC, Retain one copy at center

7.18 Local Laboratory Documentation

Normal values for the required blood tests for each participating laboratory will be collected for each study site. Appropriate certifications and documentation records are required to be maintained at the site for participating laboratories.

8 Statistical Considerations

8.1 Endpoints

The ADVANTAGE AF Study has primary endpoints designed to assess the safety and effectiveness of the FARAPULSE PFA System for the treatment of symptomatic, drug-refractory persistent atrial fibrillation. The ADVANTAGE AF Study will be considered successful if both the primary safety and effectiveness endpoints are passed.

8.1.1 Primary Safety Endpoint

The primary safety endpoint (PSE) is defined in **Section 3.2**.

The expected safety event rate for the PSE has been estimated by performing a meta-analysis on recently completed studies (see **Table 8.1-1**).

The selection of the studies eligible for the meta-analysis for safety was based on the following criteria:

- Prospective studies either single cohort or randomized trials with only large sample size (N>100), high quality, multi-center.
- Patients with PersAF: Studies with PAF or long-standing PersAF were excluded from the analysis. Also, studies with mixed population (i.e., including both PersAF and other forms of AF) were excluded if the safety results were not presented for PersAF subset only.
- Patients undergoing transcatheter ablation of AF, with approved energy source (e.g., radiofrequency, cryoballoon, laser). Studies that included any other concomitant treatment, surgical or trans-catheter (e.g., LAA closure, surgical ablation) were excluded.
- Collection of procedure-related serious adverse events had to be identified as an endpoint in the study (indicated as primary, secondary, or additional in the methods section of the paper, into SSED or supplementary material) and adequately reporting all the components of the safety endpoint were included in the ADVANTAGE-AF protocol (i.e.: Death, Myocardial infarction, Stroke, TIA, Peripheral or organ thromboembolism, Pulmonary edema, Unresolved phrenic nerve palsy / paresis, Vascular access complications , Heart block, Gastric motility / pyloric spasm disorders, Cardiac tamponade / perforation, pericarditis, PV stenosis and Atrio-esophageal fistula). Timeframe of reporting had to be at least 7 days post-procedure (i.e., peri-procedural events).

The analysis included 6 studies: event rates and their 95% confidence intervals were estimated from SSED, primary publications or results disclosed on clinicaltrials.gov and calculated based on the occurrence of the events that constitute the PSE defined in this protocol.

Table 8.1-1: Meta-Analysis to Determine Primary Safety Endpoint Parameters

Study	Design Info.	Technology	Event / Total	Rate (%)	95% CI
PRECEPT Trial	IDE, Prospective, multicenter, PersAF	RF with THERMOCOOL SMARTTOUCH SF catheter (PVI)	18/344	5.23	(3.13, 8.14)
CRYO4PERSISTENT AF	Prospective, multicenter, single arm, PersAF	Arctic Front Advance Cryo (PVI)	4/101	3.96	(1.09, 9.83)
Schmidt et al., 2017	Randomized, multicenter, PersAF	Laser Balloon vs. RF (PVI WACA)	7/134	5.22	(2.13, 10.47)
Wynn et al., 2016, SWAN-PAF	Prospective, multicenter, randomized, PersAF + sustained PAF	PVI vs. PVI + lines	8/124	6.45	(2.83, 12.32)
REAFFIRM Trial	Randomized, PersAF	RF (PVI vs. PVI+ FIRM)	25/350	7.14	(4.68, 10.36)
STOP Persistent AF Trial	IDE Prospective, PersAF	Cryo (PVI)	5/165	3.03	(0.99, 6.93)
*PersAF - Persistent AF, CFS- Contact Force-Sensing, PVI -pulmonary vein isolation					
Overall				**5.41**	**(4.21, 6.75)**
* Overall Rate, 95% CI calculated using a binary random effects model					

The overall safety event rate from this meta-analysis is 5.41%. We conservatively chose the expected rate of 6% based on potential unknown factors:

(1) ablation includes both the posterior ablation wall and PVI ablation, a technique not commonly utilized in the studies listed above.
(2) the FARAPULSE PFA System is different from those of listed studies in which either Cryoballoon ablation or RF ablation or other ablation systems were utilized.

The PSE performance goal of 12% was chosen based on the approximate upper limit of each individual study from the above analysis and deemed reasonable with an absolute difference of 6% from the expected rate 6%. The absolute difference is comparable to meaningful clinical difference of 8% used in both IDE single arm trials ((STOP Persistent AF trial[23] with performance goal 13% and (PRECEPT Trial[22] with performance goal 16%).

8.1.1.1 Hypotheses

Let P be the proportion of Treatment Subjects and Attempt Subjects with one or more CSAEs through the Day 360 Assessment (Treatment) or Day 30 Assessment (Attempt) and PG be the performance goal, the following hypothesis will be tested in a one-sided test at 0.025 significance level.

- H_0: $P \geq PG$
- H_A: $P < PG$

Where PG = 12%.

8.1.1.2 Sample Size

The sample size estimate was obtained using the binomial exact method. The following assumptions were used in the sample size calculation:

Table 8.1-2: Assumptions for the Primary Safety Endpoint Sample Size Estimate

Assumptions	Primary Safety Endpoint
Expected rate	6%
Performance goal	12%
Attrition (per year)	10%
Significance level (one-sided)	0.025
Power	86%
Evaluable subjects	232
Subjects accounting for attrition	258

Under the method and assumption outlined above, the required sample size for this endpoint after attrition is 232, so a minimum of 258 Treatment Subjects are required for the analysis of primary safety endpoint. In addition, all Attempt Subjects will be included in the primary safety endpoint analysis.

8.1.1.3 Statistical Methods

The proportion of Treatment Subjects and Attempt Subjects with one or more CSAEs will be estimated using the Kaplan-Meier method. The 97.5% one-sided upper confidence limit of the observed event rate will be compared to the performance goal of 12%. If the upper confidence limit is less than the performance goal, the null hypothesis will be rejected. The upper confidence limit will be calculated as the pointwise confidence limit using the log-log methodology.

Subjects who withdraw from the study prior to the Assessment Day (Day 360 Assessment for Treatment, Day 30 Assessment for Attempt) without experiencing a primary endpoint event will be censored on the date of withdrawal. Subjects who undergo a second re-ablation procedure or a re-ablation procedure following the Blanking Period without experiencing a primary endpoint event will be censored as of the date of that re-ablation procedure. Subjects who are determined to be Severe COVID-19 Subjects during trial participation without experiencing a primary endpoint event will be censored as of the Onset Date of the condition.

8.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint (PEE) is defined in **Section 3.3**.

In order to determine the expected Treatment Success rate for the PEE, ten (10) recently conducted PersAF trials with similar primary effectiveness endpoint definitions were evaluated. The selection of the studies eligible for the meta-analysis for the PEE was based on the following criteria:

- Prospective studies either single cohort or randomized trials.
- At least 12 months of follow up
- Patients with PersAF: Studies with PAF or long-standing PersAF were excluded from the analysis. Also, studies with mixed population (i.e., including both PersAF and other forms of AF) were excluded if the safety results were not presented for PersAF subset only.

- Patients undergoing transcatheter ablation of AF, with any energy source (e.g., radiofrequency, Cryoballoon, laser). Studies that included any other concomitant treatment, surgical or trans-catheter (e.g., LAA closure, surgical ablation) were excluded.
- Effectiveness outcome / endpoint identified in the study according to *HRS Consensus Statement for AF ablation* and including at minimum:
    - Presence of a 3-month blanking period, inclusive of a follow up at three months. During the blanking period treatment with AADs could be applied per standard of care, and any arrhythmia occurring during this period was not counted as an effectiveness failure.
    - Endpoint was identified at least as freedom from recurrence of arrhythmias inclusive of AF, AFL and AT between 3 and 12 months of follow up.
    - Presence of periodic follow ups at 3, 6 and 12 months,
    - Monitoring of arrhythmia recurrence performed with ECG during the assessments, Holter monitoring (at least 12 month) and arrhythmia monitoring via remote event monitor in the timeframe between 3 and 12 months.

The table below shows the meta-analysis results, with expected rate 67.23% [62.87%, 71.46%] from the random effect model. There are differences in methods when comparing these trials: these include different AAD management after blanking period (patients off AAD or under stable dose of previous AAD) or different methods for monitoring of recurrences (Holter monitoring frequency and duration, frequency of reporting from EMs). A selection of studies with a strictly uniform set of methods would lead to too few data to analyze in the meta-analysis. Accordingly, a conservative approach has been applied and a value of 55% has been selected for the expected rate of the PEE, to acknowledge the methods differences and multiple variance sources. This is justified by the following aspects: (1) Acute Procedural Success is considered both as successful isolation of the PV and the LAPW and all studies analyzed do not consider LAPW isolation success as part of the endpoint (2) the FARAPULSE PFA System is different from those of listed studies in which either Cryoballoon ablation or RF ablation or other ablation systems were utilized.

Table 8.1-3: Meta-Analysis to Determine Primary Effectiveness Endpoint Parameters

Study	Design Info.	Ablation Technology	Event /Total	Rate (%)	95% CI
PRECEPT Trial	IDE, Prospective, multicenter, PersAF	RF with THERMOCOOL SMARTTOUCH SF catheter (PVI)	234/333	70.27	(65.05, 75.13)
Schmidt et al., 2017	Randomized, multicenter, drug-refractory PersAF	Laser Balloon vs. RF (PVI WACA)	96/134	71.64	(63.21, 79.09)
Adiyaman et al., 2018	Prospective, randomized, early PersAF	RF vs. Surgical	14/26	53.85	(33.37, 73.41)
Chauhan et al., 2021 (pvi)	Randomized, single-center, high-burden PAF or PersAF	CFS catheter Smart-Touch SF (PVI)	20/40	50.00	(33.80, 66.20)
Chauhan et al., 2021 (pvi+)	Randomized, single-center, high-burden PAF or PersAF	CFS catheter Smart-Touch SF (PVI + FaST mapping/ablation)	28/38	73.68	(56.90, 86.60)
Mortsell 2019	Prospective, randomized, PersAF	Arctic Front Advance (Cryo)	51/62	82.26	(70.47, 90.80)
Wynn et al., 2016	Prospective, multicenter, randomized, PersAF + sustained PAF	PVI vs. PVI + lines	81/122	66.39	(57.28, 74.69)
Dong 2015	Prosepective, randomized, single center, PersAF	RF (PVI +)	93/146	63.70	(55.34, 71.49)
REAFFIRM Trial	Randomized, PersAF	RF (PVI vs. PVI+ FIRM)	239/350	68.29	(63.13, 73.13)
STOP Persistent AF Trial	IDE Prospective, PersAF	Cryo (PVI)	114/186	61.29	(53.89, 68.33)
*PersAF - Persistent AF, PAF - Paroxysmal AF, CFS - Contact Force-Sensing, PVI - Pulmonary Vein Isolation					
Overall				**67.23**	**(62.87, 71.46)**
* Overall Rate, 95% CI calculated using a binary random effects model					

A PEE performance goal of 40% has been chosen based on the minimum chronic acceptable success rate for PersAF at 12-month follow-up defined in the 2017 HRS / EHRA / ECAS Expert Consensus document.[8] The recommendation for evaluating the effectiveness of a treatment for PersAF described as:

> "If minimum chronic success rate is selected as an objective effectiveness endpoint for a clinical trial, we recommend that the minimum chronic acceptable success rate for PersAF at 12-month follow-up is 40%."

8.1.2.1 Hypotheses

Let P be the proportion of Treatment Subjects with Treatment Success through the Day 360 Assessment and PG be the performance goal, the following hypothesis will be tested in a one-sided test at 0.025 significance level.

- H_0: $P \leq PG$
- H_A: $P > PG$

Where PG = 40%.

8.1.2.2 Sample Size

The sample size estimate was obtained using the binomial exact method. The following assumptions were used in the sample size calculation:

Table 8.1-4: Assumptions for the Primary Effectiveness Endpoint Sample Size Estimate

Assumptions	Primary Effectiveness Endpoint
Expected rate	55%
Performance goal	40%
Attrition (per year)	10%
Significance level (one-sided)	0.025
Power	90%
Evaluable subjects	122
Subjects accounting for attrition	136

Under the methods and assumptions outlined above, the required sample size for this endpoint after attrition is 122, therefore a minimum of 136 Treatment Subjects are required for the analysis of primary effectiveness endpoint.

8.1.2.3 Statistical Methods

The proportion of Treatment Subjects with Treatment Success through the Day 360 Assessment will be estimated using the Kaplan-Meier method. The 97.5% one-sided lower confidence limit of the observed Treatment Success rate will be compared to the performance goal of 40%. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected. The confidence limit will be calculated as the pointwise confidence limit using the log-log methodology.

Each Treatment subject will be classified as Treatment Success (event-free) or Treatment Failure (primary effectiveness endpoint event). Subjects who withdraw or die from the study prior to the Day 360 Assessment, without experiencing a primary effectiveness endpoint event, will be censored on the date of withdrawal or death. Subjects who are determined to be Severe COVID-19 Subjects during trial participation without experiencing a primary endpoint event will be censored as of the Onset Date of the condition.

8.1.3 Other Endpoints and Assessments

The following analyses will also be performed as defined in the referenced sections using descriptive statistics:

- Additional Safety Endpoints (**Section 3.4.1**)
- Additional Effectiveness Endpoints (**Section 3.4.2**)
- Procedural Assessments (**Section 3.4.3**)
- Quality of Life Assessments (**Section 3.4.4**)

8.2 General Statistical Methods

8.2.1 Analysis Sets

While each primary endpoint was individually powered, each endpoint analysis will use all available data: Attempt and Treatment Subjects will be used for persistent AF safety endpoint analyses unless otherwise clarified, and Treatment Subjects will be used for persistent AF effectiveness endpoint analyses.

Roll-In Subjects: Endpoint data will be summarized separately. Roll-In subjects will not be used in the main primary endpoint analyses.

8.2.2 Control of Systematic Error / Bias

Control and reduction of potential bias associated with a single-arm study design have been addressed by a series of measures including but not limited to:

- Patients meeting the eligibility criteria and signing the ICF will be eligible for sequential enrollment in the study.
- ECG, Holter monitoring, and event monitoring data will be evaluated by a third-party Arrhythmia Core Laboratory according to standardized protocols.
- Cardiac MRI / CT images utilized for assessing potential PV stenosis will be evaluated by a third-party Cardiac Imaging Core Laboratory according to standardized protocols.
- The use of a comprehensive set of study procedures as defined in the protocol which ensure consistent patient management.
- Comprehensive site and data monitoring to ensure accurate and complete recording of study data.
- The use of an independent Clinical Events Committee (**Section 19.2**) will review and adjudicate all potential SAEs and primary safety outcomes.
- Creation of a complete Clinical Study Report and full dataset to allow scientific and clinical reviewers to independently assess potential error and bias.

To avoid any center effect and bias, no center will be authorized to enroll more than 33 Treatment Subjects (13% of the total planned enrollment of 258 Treatment Subjects).

8.2.3 Study Success and Control of Type I Error

Both the primary endpoints must pass in order to achieve study success. Each primary endpoint will be tested at a significance level of 2.5% while still maintaining the overall Type I error level at no greater than 2.5%. This follows the methodology of the Intersection-Union Test (IUT).

8.3 Data Analyses

8.3.1 Roll-In Subject Analyses

The stipulated analyses for Roll-In Subjects will be summarized with descriptive statistics. Endpoint data for Roll-In Subjects will be summarized but no hypothesis testing will be performed.

8.3.2 Interim Analyses

No formal interim analyses are planned for the purpose of stopping the study early for declaring success or futility. Analysis of each endpoint will be performed for regulatory submission when all applicable data for that endpoint has been collected,[9] dependent on specific geographic requirements where applicable. The ADVANTAGE AF Study may be used to satisfy the requirements of multiple regulatory bodies. Details on these analyses will be included in the ADVANTAGE AF SAP when available.

8.3.3 Subgroup Analyses

An analysis will be performed to evaluate whether any significantly different effects exist in the primary endpoints within subgroups of subjects. The list of covariates (with applicable subgroups in parentheses) will include at least the following:

[9] Additional data analysis and reporting may be performed after a sub-set of subjects have completed their Assessment for regulatory submission outside of the United States.

- Subject demographics (e.g., age-[e.g. age >=65 vs. <65, Medicare eligible], gender)
- Subject baseline characteristics (e.g., LVEF, cardioversion history, BMI, and LA diameter)
- Index Procedure lesion sets
  - PV + LAPW ablation alone versus PV + LAPW plus additional ablations
  - CTI ablation versus no CTI ablation
- Geography
- FARAPULSE PFA System used (Investigational vs. Commercial)

Each subgroup covariate will be included as a single independent variable in a logistic regression model with the primary endpoint outcome as the dependent variable and a test for significance at the 15% level will be performed**.**

In addition to subgroup analyses, descriptive statistics of subject demographic and baseline characteristics will be presented for each subgroup listed in this section.

8.3.4 Center Pooling Analysis

Center-to-center heterogeneity will be assessed for the primary endpoints by performing a Chi-square test, treating site as a fixed effect. Descriptive statistics for each site will be presented. Small sites (sites enrolling less than five subjects) will be combined to form "supercenters". Small centers will be combined until the newly created supercenter has five enrollments and then a new super center will be created. If sites are not deemed poolable in the initial Chi-square analysis, the poolability analysis will be reperformed by treating site as a random effect. A significance level of 15% will be used for each test.

8.3.5 Multivariable Analyses

For each primary endpoint, univariable analyses of the following covariates will be performed, and any found to be significantly associated with the outcome at the 0.15 alpha level will be included as covariates in a multivariable regression model. Backward selection with 0.15 alpha level stay criterion will be used to determine the final multivariable model.

The list of baseline covariates includes, but is not necessarily limited to:

- Subject demographics (e.g., age, gender)
- Subject baseline characteristics (e.g., LVEF, cardioversion history, BMI, and LA diameter)
- Index Procedure lesion sets
  - PVI + LAPW ablation alone versus PVI + LAPW plus additional ablations
  - CTI ablation versus no CTI ablation
- Geography
- FARAPULSE PFA System used (Investigational vs. Commercial)

8.3.6 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

9 Health Economics Outcomes

A formal health economics analysis may be completed as part of this trial study, given meaningful clinical results are obtained. This will take into consideration complication rates, quality of life, and

resource utilization. The EQ-5D-3L, a generic quality of life measure, will be used to assess health utilities. Costs associated with the health care utilization measures may be estimated at all sites. These inputs may be used in health economics analysis performed.

10 Data Management

10.1 Data Collection, Processing, and Review

Subject data will be recorded in a limited access secure electronic data capture (EDC) system. The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the Sponsor or its representative(s). The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his / her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the Sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and / or electronic data review will be performed to identify possible data discrepancies. Manual and / or automatic queries will be created in the EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database. Data transfers from other systems including the ACL, the CICL, CEC records and electronic questionnaires will be coordinated by BSC. CRF Completion Guidelines will be created by BSC and provided to all sites.

10.2 Data Retention

The Principal Investigator or his / her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his / her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his / her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform BSC in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

10.3 Technical Source Forms

The Technical Source Form (TSF) is the Sponsor-approved document to capture protocol-required data elements that are not duplicated in any other source documents. This form when completed requires review and approval by the Investigator and may be used as a source document.

Collection and completion of all information on the TSF is the responsibility of the appropriately delegated site personnel. If available, the protocol trained BSC representative will provide the delegated site personnel with the study related data collected during the case directly from the console.

Data collected on any site created worksheets must not be attributable to the Boston Scientific representative. The Boston Scientific representative providing technical support is not part of the site study team.
General TSF documentation considerations for the protocol trained Boston Scientific representative are as follows:

- Data that is collected as part of a clinical study must be attributable to the individual collecting/providing the data, and must include the individual's name, signature, and date of signature.
- Boston Scientific Representative involvement with data collection/providing source documentation should be minimized.
- Any source data collected to capture protocol required data elements by a Boston Scientific representative must be provided to a member of the study team at the conclusion of the visit and retained at the site.
- The Boston Scientific representative and Research Coordinator must make arrangements in advance as to how the clinical trial data will be transferred from the Boston Scientific representative to a member of the study team.
- The Boston Scientific representative completes the sections of the TSF that are appropriate to his/her role only (e.g., technical sections.)
- The Boston Scientific representative signs and dates completed sections of the TSF applicable to the Boston Scientific representative role.
- The Boston Scientific representative may assist in obtaining the signature and date of the Investigator or clinical research site staff delegated by the Investigator to oversee the study activity.

At the conclusion of the procedure, the completed TSF should be signed (and initialed as needed) by the following people:

- Delegated Site Personnel completing the TSFs
- Delegated Investigator conducting and / or supervising the case
- Protocol trained BSC representative supporting the case

11 Core Laboratories

11.1 Arrhythmia Core Laboratory

Specified arrhythmic events will be analyzed by an ACL to determine if the episodes are associated with Detectable AF.

During the ADVANTAGE AF Study, more than one ACL may be utilized for either EM or Holter studies to optimize equipment availability, vendor capacity or other factors as determined by BSC. Each vendor utilized will be described in the final study report.

11.1.1 Event Monitors

The ACL will provide the investigational site and / or subject as applicable all necessary instructions and materials related to the use of the EM.

All Roll-In Subjects and Treatment Subjects:

- Will be introduced to the use and importance of EMs at the Baseline Assessment

- Will receive a device and be fully instructed by either the ACL or the study site on the use of an EM prior to or at the scheduled Day 90 Assessment
- Will be reminded that beginning on Day 90, they are to:
  - Record and transmit all symptomatic episodes potentially associated with cardiac arrhythmias (e.g., palpitations, lightheadedness, syncope, dyspnea) for detection and / or treatment of recurrences.
  - At a minimum, transmit at least two recordings (symptomatic or asymptomatic) every month.

Careful monitoring and subject follow-up will be implemented to ensure compliance with the required twice per month and ad hoc symptomatic utilization and transmission of the EMs.

Individual missed monthly transmissions will not be counted as protocol deviations, but a subject that misses > 20% of their total monthly required EM transmissions will be considered a protocol deviation.

All EMs must be returned to the ACL or investigational site upon completion of a subject's 12-month follow-up or withdrawal from the study.

ECG data from the EM will be analyzed by the ACL.

11.1.2 Holter Monitors

The ACL will provide the investigational site and / or subject as applicable all necessary instructions and materials related to the use of the Holter monitor.

Each subject:

- Will be introduced to the use and importance of the Holter monitoring at the Baseline assessment.
- Will receive a device and be fully instructed on the use of a 24-hour continuous ECG (Holter) monitor prior to the Day 180 and Day 360 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 24-hour period for both the Day 180 and Day 360 Assessments. The ACL will work with the investigational site to ensure compliance.

All Holter monitors must be returned to the ACL or investigational site upon completion of a subject's Day 360 Assessment or withdrawal from the study.

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

11.1.3 Study ECGs

To ensure objective assessment of rhythm monitoring data, the following 12-lead ECG tracings will be reviewed by the ACL and/or CEC and included as study data:

- ECGs obtained during the following assessments: Day 90 and Day 360
- ECGs submitted during monitoring and adjudication of adverse events
- ECGs submitted during the evaluation of potential arrhythmias during the effectiveness evaluation period

11.2 Cardiac Imaging Core Laboratory

A qualified CICL will be established to receive, review, and assess any cardiac MRIs and CTs obtained for the evaluation of potential PV stenosis.

Baseline cardiac MRIs and CTs will only be read by the CICL if subsequent events result in follow-up imaging for the assessment of potential PV stenosis.

Pulmonary Vein Dimensions

Treated veins to be assessed will have the baseline and post-ablation assessments of standardized diameters (See definition of PV Diameter in **Section 23.2**).

Cardiac Imaging Data Review and Transmission

The CICL will analyze 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 Sponsor for inclusion in the study dataset.

12 Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An Investigator shall notify the Sponsor, the reviewing IRB / EC / REB, and the regulatory authority if applicable of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical investigation. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the Sponsor using the eCRF. Sites may also be required to report deviations to the IRB / EC / REB, and the regulatory authority, per local guidelines and national / government regulations.

When unforeseen circumstances (See **Section 7.15**) result in a deviation from the requirements of the protocol, the deviations will be distinguished from routine protocol deviations and reported separately.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including IRB / EC / REB and any regulatory authority notification, site re-training, or site discontinuation / termination) will be put into place by the Sponsor.

The Sponsor will not approve any waivers to the requirements of this protocol or its supporting documentation that would affect the rights, safety or welfare of study subjects or the scientific validity of the study results.

13 Device Accountability

13.1 Investigationally-Labeled Test Devices

Table **13.1-1**below shows a list of FARAPULSE PFA System components for which device accountability is required by the investigational site.

Table 13.1-1 : Device Accountability for the FARAPULSE PFA System

Component	Subcomponents
FARAWAVE PFA Catheter	1. FARAWAVE Pulsed Field Ablation Catheters (31mm and 35mm) 2. FARASTAR Catheter Connection Cable
FARASTAR PFA Generator and Related Equipment	1. FARASTAR Pulsed Field Ablation Generator: 2. FARASTAR Recording System Module
FARADRIVE Steerable Sheath	FARADRIVE Steerable Sheath

The Sponsor shall keep records to document the physical location of all investigational devices from shipment from BSC or designated facility to the investigation sites until return or disposal.

The Investigator or an authorized designee shall do the following for device accountability:

- Securely maintain and control access to these items to ensure they are used only in this clinical study and only per the protocol and limit access to authorized site personnel at all times.
- Ensure the storage environment for these items is appropriate for maintaining conditions per the items' labeling (e.g., temperature, humidity, etc., as applicable)
- Maintain accurate and timely Device Accountability Records in a form specified by the Sponsor and provide copies of the record and any supporting documentation to the Sponsor upon request. Such records shall include the following content at a minimum:
  - Name(s) of person(s) who received, used, returned, or disposed of each item
  - Date of receipt
  - Identification and quantity of each item (examples of identification: batch number, serial number, or unique code)
  - Date or dates items were opened / used
  - Subject identification
  - Return or disposal date, identity, and quantity, as directed by Sponsor
- Return or dispose of devices as directed by Sponsor
  - Complaint / deficiency related items will be returned whenever possible
  - Opened non-complaint / non-deficiency related items should be returned or disposed as directed by Sponsor
  - Unopened items should be returned to the Sponsor or designee upon Sponsor request. Unopened items are expected to be returned in the condition in which they were provided, reasonable wear and tear expected.

13.2 Commercially-Labelled Devices Used Investigationally

This section applies to instances in which any component of the FARAPULSE PFA System is commercially available for other indications in the participating country. The system components may be supplied out of commercial inventory and utilized per this investigational protocol. *In this situation, the investigational nature of the FARAPULSE PFA System will start at the point of investigational use under this protocol.*

The Investigator or an authorized designee shall do the following for commercially-labeled devices:

- Maintain accurate and timely Device Accountability Records in a form specified by the Sponsor and provide copies of the record and any supporting documentation to the Sponsor upon request. Such records shall include the following content at a minimum:
    - Date or dates items were used investigationally for this study
    - Subject identification
    - Return or disposal date, identity, and quantity, as directed by Sponsor
- Return or dispose of devices used investigationally for this study, as directed by Sponsor
    - Complaint / deficiency related items should be returned whenever possible
    - Used non-complaint / non-deficiency related items should be returned or disposed as directed by Sponsor
    - Unopened items – not applicable, as the devices are not investigational until they are opened / used for the study

13.3 Non-Medical Devices, Components, and Commercially-Labelled Devices Used Within Approved Labeling

Investigational Device Accountability does not apply to components of the FARASTAR Generator, RSM (See **Table 2.2-1**) nor to commercially-labelled items that are used within their currently approved labeling. Unless otherwise directed by this protocol or other study-related materials, the tracking or special labeling of such items (if any) will be for logistical purposes only to facilitate study operations.

14 Compliance

14.1 Statement of Compliance

This clinical investigation is financed by the Sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the Sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the Investigator.

This study will be conducted in accordance with 21 CFR 812, 814.20, Part 50, Part 54, and Part 56; European Medical Device Regulation; EN ISO 14155 Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice; ethical principles that have their origins in the Declaration of Helsinki; and applicable individual country laws and regulations.

The study shall not begin until

- The required approval / favorable opinion from the IRB / EC / REB and regulatory authority has been obtained, if appropriate.
- The issuance of the site Authorization to Enroll, as provided by the Sponsor.

Any additional requirements imposed by the IRB / EC / REB or regulatory authority shall be followed.

14.2 Investigator Responsibilities

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, ISO 14155 Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice, any conditions of approval imposed by the reviewing IRB / EC / REB, and prevailing local and / or country laws and / or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page (if applicable) and the Protocol Signature page documenting his / her agreement to conduct the study in accordance with the protocol.
- Provide his / her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation.
- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-investigation-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device / procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to Sponsor, per the protocol requirements, all reportable events.
- Report to the IRB / EC / REB and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential / USADE or UADE, if required by applicable laws or regulations or this protocol or by the IRB / EC / REB, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Maintain the Device Accountability Records and control of the device, ensuring that the investigational device is used only by authorized / designated users and in accordance with this protocol and instructions for use.
- Allow the Sponsor to perform monitoring and auditing activities and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the IRB / EC / REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB / EC / REB requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of study-related devices and equipment when they are used / operated by the subject.

- Inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study and make the necessary arrangements for emergency treatment.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical investigation are provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

All Investigators will provide their qualifications and experience to assume responsibility for their delegated tasks through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.

14.2.1 Delegation of Responsibility

When specific tasks are delegated by an Investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training to site staff, ensuring that staff are competent to perform the tasks they have been delegated and supervising those to whom tasks are delegated. Where there is a sub-Investigator at a site, the sub-Investigator should not be delegated the primary supervisory responsibility for the site. The Investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

14.3 Institutional Review Board / Ethics Committee / Research Ethics Board

The investigational site will obtain the written and dated approval / favorable opinion of the IRB / EC / REB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB / EC / REB and / or competent authority (CA) approval of the protocol (or permission to conduct the study) and ICF, must be received by the Sponsor before recruitment of subjects into the study and shipment of investigational product / equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the IRB / EC / REB before the changes are implemented to the study. All changes to the ICF will be IRB / EC / REB approved; a determination will be made regarding whether a new ICF needs to be obtained from subjects who provided consent, using a previously approved ICF. Annual IRB / EC / REB approval and renewals will be obtained throughout the duration of the study as required by applicable local / country laws or regulations or IRB / EC / REB requirements. Copies of the study reports and the IRB / EC / REB continuance of approval must be provided to the Sponsor.

14.4 Sponsor Responsibilities

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and / or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and / or other business purposes, such as overseeing and improving the performance of its device, new medical research, and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

14.5 Role of BSC Representatives

BSC personnel can provide technical support to the Investigator and other health care personnel (collectively HCP) as needed during ablation procedures, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment / devices (including generators, connection cables and boxes, and other support equipment).

At the request of the Investigator and while under Investigator supervision, BSC personnel may, where permitted by law and hospital procedures, operate equipment during ablation procedures, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities.

Typical tasks may include the following:

- Providing instructions for the safe return of investigational products. For potentially hazardous items, provide specialized instructions and materials, as applicable.
- Clarifying device behavior, operation or diagnostic output as requested by the Investigator or other health care personnel
- Entering technical data on technical source form as long as the responsible Investigator verifies and signs the completed form
- Providing technical expertise / support to subjects during office assessments and / or during teleconference calls / electronic communications with the Investigator or their delegated site staff and the subject.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following.

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

BSC personnel will not do the following.

- Practice medicine
- Provide medical diagnosis or treatment to subjects
- Discuss a subject's condition or treatment with a subject
- Independently collect critical study data (defined as primary or secondary endpoint data)
- Enter data in electronic data capture systems or on paper case report forms

If the situation necessitates, Boston Scientific personnel may use remote case support technology (e.g. video conferencing software) to establish a tele-mentoring communication stream/live stream to perform the applicable support tasks described above. The streaming will be in a secure and encrypted high-definition format and will not be recorded. The BSC personnel on the live stream will not have any direct contact with the subject.

14.6 Insurance

Where required by local / country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

15 Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, clinical research monitors will verify that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator and his or her institution guarantee direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The Sponsor will put a plan in place to document the specific monitoring requirements.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time as determined by the Sponsor is devoted to the process.

16 Potential Risks and Benefits

16.1 Anticipated Adverse Events

Subjects participating in this study are subject to the same risks shared by all patients undergoing an ablation procedure for the treatment of PersAF. Since the characteristics of the FARAPULSE PFA System are similar to those of other commercially available devices for AF ablation, it is anticipated that the rate of complications in this study will be similar to those reported from ablations performed with other commercially available catheter ablation systems. The protocol-required testing for this study uses standard techniques that are routinely used for the treatment and management of subjects with drug refractory PersAF.

Based upon the current literature and prior reports on adverse events with an ablation catheter, the list below includes an alphabetical list of the possible anticipated adverse events and possible adverse device effects associated with ablation with the FARAPULSE PFA System for the treatment of PersAF. Occurrence of any of the listed events could lead to harm, the need for intervention, or prolonged hospitalization for the subject.

These anticipated events may 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.

- Access site complications (e.g., hematoma, fistula, pseudo-aneurysm, laceration, bleeding) potentially requiring surgical intervention
- 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/impingement potentially requiring endovascular or surgical intervention
- Conduction system injury, either transient or permanent, potentially requiring pacemaker insertion
- Coronary artery or vein injury
- Damage to cardiac structure
- Death
- Esophageal injury, ulcer, or fistula
- Gastric motility / pyloric spasm disorders
- Harmful large muscular contraction
- Heart failure
- 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, and lung).
- Pericardial effusion
- Pericarditis
- Peritonitis
- Phrenic nerve injury with potential paralysis of the diaphragm and breathing impairment
- Pneumomediastinum
- Pneumopericardium
- Pneumoperitoneum
- Pneumothorax
- Procedural delay
- 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.
- Vessel obstruction due to thrombus, debris, introduction of gas, or vascular spasm

16.2 Risks Associated with the Study Device(s)

Benchtop studies, pre-clinical research and CE Mark clinical studies have demonstrated that the FARAPULSE PFA System is safe for human use. Potential risks have been evaluated and mitigation strategies have been implemented to reduce potential risks to acceptable levels.

16.3 Risks associated with Participation in the Clinical Study

There are no specific tests or procedures outside those recommended as standard practice for catheter ablation of PersAF required by this clinical study protocol. Therefore, there is no foreseen increased risk to subjects for participating in the ADVANTAGE AF Study.

16.4 Possible Interactions with Concomitant Medical Treatments

Anti-arrhythmic and anticoagulant medications included in ADVANTAGE AF procedures are all approved for their indicated uses in the relevant geography. Therefore, there is no foreseen increased risk to subjects for participating in the ADVANTAGE AF Study.

16.5 Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and / or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

16.6 Anticipated Benefits

Subjects may or may not receive any benefit from participating in the ADVANTAGE AF Study as compared to the current standard of care received for treatment of PersAF. Potential benefits of the FARAPULSE PFA System for the subject may include the following:

- Complete or partial reduction in symptoms related to PersAF
- Complete or partial reduction in the number of cardioversions, medications a subject is taking, and in the number of hospitalizations related to PersAF
- Treatment using an investigational device which has demonstrated the ability to isolate PVs and the PW 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.

16.7 Risk to Benefit Rationale

Risk management activities, including Hazard Analyses (HA) and Failure Mode Effects Analyses (FMEA), have been performed on the FARAPULSE PFA System and its components to identify and analyze known and foreseeable hazards (in both normal and fault conditions) and reasonably foreseeable sequences or combinations of events that could result from using this product and the risks associated with each hazard. Mitigations have been implemented in the design, processes, and / or labeling and directions for use of the product to reduce the residual risk of each hazard as necessary and practicable. The HA has been reviewed and approved and the remaining risks are acceptable when weighed against the anticipated benefits to the subject.

17 Safety Reporting

17.1 Reportable Events by Investigator to BSC

It is the responsibility of the Investigator to assess and report to BSC any event which occurs in any of following categories:

- All Serious Adverse Events
- All thromboembolic adverse events
- All study procedure-related adverse events
- All investigational device-related adverse events
- All study-related device deficiencies
- Unanticipated Adverse Device Effects / Unanticipated Serious Adverse Device Effects if not previously defined in the IFU or ICF
- The occurrence of any ventricular tachycardia or ventricular fibrillation (VT/VF) during ablation with the FARAPULSE PFA System.
- New findings / updates in relation to already reported events.

When possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and / or device deficiency.

Any reportable event, experienced by the study subject after informed consent and once considered enrolled in the study (as defined in study subject classification section), whether prior to, during or subsequent to the study procedure, must be recorded in the eCRF.

Underlying diseases and chronic conditions are not reported as AEs unless there is an increase in severity or frequency during the course of the investigation. Death should not be recorded as an AE but should only be reflected as an outcome of one (1) specific SAE (see **Table 17.2-1** for AE definitions).

Refer to **Section 16.1** for a listing of anticipated adverse events and **Section 16.2** for the known risks associated with the study device(s).

17.2 Classifications for Adverse Event Reporting

Adverse event definitions for the purpose of investigator assessment and reporting to BSC and subsequent regulatory reporting are provided in **Table 17.2-1** and **Table 17.3-1**. Administrative edits

for clarification purposes were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR Part 812, ISO 14155, and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations.

Table 17.2-1: Safety Definitions for Reporting Purposes

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users, or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the investigational medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of an investigational medical device[10] **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the 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**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases, or 3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) foetal distress, foetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.

[10] Including all adverse event related to the device or investigational procedure.

Term	Definition
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current risk assessment. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity, or outcome has been identified in the risk assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users, or other persons, and that requires prompt remedial action for other subjects, users, or other persons. **NOTE 1**: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety, or performance. **NOTE 1**: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g., medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g., subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g., procedure required by protocol)

Term	Definition
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

17.3 Relationship Determination for Device Reporting

The Investigator must assess the relationship of potentially reportable AEs to the study device(s) and study procedures. See the criteria for assessing relatedness for reporting purposes in **Table 17.3-1**.

Table 17.3-1: Criteria for Assessing Relatedness for Reporting Purposes

Classification	Description
Not Related *Ref: MDCG 2020-10/1*	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the investigational device, or the procedures related to the use of the investigational device; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ that cannot be affected by the device or procedure; - the serious event can be attributed to another cause (e.g., an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Possibly Related *Ref: MDCG 2020-10/1*	The relationship with the use of the investigational device or comparator, or the relationship with procedures is weak but cannot be ruled out completely. Alternative causes are also possible (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug, or treatment). Cases where relatedness cannot be assessed, or no information has been obtained, should also be classified as possible.
Probably Related *Ref: MDCG 2020-10/1*	The relationship with the use of the investigational device or comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.

Classification	Description
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the investigational device or comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that -the investigational device or procedures are applied to; -the investigational device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g., an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug, or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

17.4 Investigator Reporting Requirements

The communication requirements for reporting to BSC are as shown in **Table 17.4-1**. Adverse events and device deficiencies must always be reported through the eCRF system. In the event that an alternative method of reporting is necessary (i.e., the eCRF system is unavailable), please report the adverse event or device deficiency to BSC by sending the Event Notification Form via email to the following email address:

[redacted]

Table 17.4-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline Pre-Market Studies*
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of Sponsor.

Event Classification	Communication Method	Communication Timeline Pre-Market Studies*
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Immediately, but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event, as requested by Sponsor.	• Upon request of Sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Immediately, but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available
		• Upon request of Sponsor
VT/VF occurring during ablation with the FARAPULSE PFA System	Complete AE eCRF page with all available new and updated information, including the location and number of all PFA energy deliveries.	• Immediately, but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available
		• Upon request of Sponsor
Device Deficiencies (including but not limited to malfunctions, use errors and inadequacy in information supplied by the manufacturer, including labeling) Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, circumstances had been less fortunate is considered a reportable event.	Complete Device Deficiencies eCRF with all available new and updated information.	• Immediately, but not later than 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of Sponsor

Event Classification	Communication Method	Communication Timeline Pre-Market Studies*
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• Adverse Device Effects (or other key events of interest): In a timely manner but not later than 10 business days after becoming aware of the information • Adverse Events: In a timely manner but recommend within 10 business days after becoming aware of the information • Reporting required through end of study • Upon Sponsor request
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event, as requested by Sponsor.	

* Note that pre-market studies are clinical studies with investigational devices or with medical devices that bear regulatory approval but are not being used for an approved indication. (21 CFR Part 812, MDCG 2020-10/1)

17.5 Device Deficiencies

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by BSC) associated with the investigational devices will be documented and reported to BSC. If possible, the investigational device(s) should be returned to BSC for analysis. Instructions for returning the devices will be provided in the Site Initiation Visit slides. If it is not possible to return the device, the Investigator should document why the device was not returned and the final disposition of the device. Device failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, a reportable event that results from a device failure or malfunction, would be recorded as an adverse event on the appropriate eCRF.

For Device Deficiencies, the Investigator must assess and report if the device deficiency could have led to an SAE if:

- Suitable action had not been taken or
- Intervention had not been made or
- Circumstances had been less fortunate is considered a reportable event.

17.6 Reporting to Regulatory Authorities / IRBs / ECs / REBs / Investigators

BSC is responsible for reporting adverse event information to all participating Principal Investigators, IRBs / ECs / REBs and regulatory authorities, as applicable. Sponsor reporting to the FDA will adhere to applicable requirements, including 10 working days following Sponsor awareness for UADEs, or the occurrence of VT/VF during ablation with theFARAPULSE PFA System, and 5 working days following Sponsor awareness for failure to obtain informed consent by the investigator, withdrawal of IRB approval.

The Principal Investigator is responsible for informing the IRB / EC / REB, and regulatory authorities of UADEs and SAEs as required by local / regional regulations.

17.7 Subject Death Reporting

A subject death during the study should be reported to BSC as soon as possible and, in any event, within three (3) calendar days of site notification. The site's IRB / EC / REB must be notified of any deaths in accordance with that site's IRB / EC / REB policies and procedures.

Notification of death must include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death. A death narrative in the local language is acceptable, if accompanied by a translation in English. The details listed below should be addressed in the death narrative, in order for BSC to understand the circumstance surrounding the death:

- Date and time of death
- Place death occurred
- Immediate cause of death
- Rhythm at the time of death, if known (include any available documentation)
- Whether the death was related to the catheter, clinical investigation, procedure, or patient condition
- Whether or not the death was witnessed
- Whether the patient had worsening heart failure
- Any other circumstances surrounding the death
- Approximate time interval from the initiating event to death (temporal course) -items to consider include, but are not limited to information regarding last time subject was seen by Investigator, last office visit, etc.
- Investigator or sub-Investigator signature and date

Also submit the following documentation:

- If the patient expired in the hospital:
    - A copy of the medical records for that admission (e.g., H & P, consults, test results, operative reports, and / or progress notes from the hospital chart)
    - Death certificate (if available)
    - Autopsy report (if applicable)
- If the patient expired outside of the hospital (e.g., home):
    - A copy of the most recent clinic visit or study assessment (if not already submitted to BSC)
    - Death certificate (if available)

18 Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his / her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any investigational devices, study-required procedures and testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and / or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g., CRO), and approved by the site's IRB / EC / REB, or central IRB, if applicable.

BSC will provide a study-specific template of the ICF to Investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's IRB / EC / REB.

Any modification requires acceptance from BSC prior to use of the ICF. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated ICFs must also have IRB / EC / REB approval prior to their use. Privacy language shall be included in the body of the ICF or as a separate ICF as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations, and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his / her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations, and guidelines and by the Investigator and / or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his / her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated ICF and any other written information must be given to the person signing the ICF.

Failure to obtain informed consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the Sponsor and local regulatory authorities (e.g., IRB / EC / REB), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the IRB / EC / REB. The new version of the ICF must be approved by the IRB / EC / REB. Acceptance by BSC is required if changes to the revised ICF are requested by the site's IRB / EC / REB. The IRB / EC / REB will determine the subject population to be re-consented.

19 Committees

19.1 Safety Monitoring Operations Team

The BSC personnel from the Medical Safety and Safety Trial Operation Teams review safety data as it is reported by the sites throughout the duration of the study. During scheduled monitoring activities, clinical research monitors further support this review through their review of source documents and other data information. The BSC Medical Safety and Safety Trial Operations team include health care providers with expertise in electrophysiology and endocardial ablation of cardiac arrhythmias and

with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

19.2 Clinical Events Committee

A Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that will adjudicate events reported by study Investigators and their relationship toward potential primary endpoints.

- All deaths
- All Serious Adverse Events
- All adverse events included in the composite primary safety endpoint per **Section 3.2** of this protocol
- All adverse events that are potentially related to the procedure or any of the devices included in the FARAPULSE PFA System
- All unanticipated device effects.
- Other events at the discretion of BSC

Committee members will include practitioners of Electrophysiology (EP), and / or Cardiology, as well as other experts with the necessary therapeutic and subject matter expertise to adjudicate the event categories outlined above. A complete description of CEC responsibilities, qualifications, membership, and committee procedures will be outlined in the CEC charter.

The CEC will review a safety event dossier, prepared by BSC, which may include copies of subject source documents provided by study sites, core lab results and independent reviewer information as available for the above listed events. For purposes of determining inclusion into the primary safety endpoint, the CEC will adjudicate all the above listed events as to their level of seriousness and relation to the ablation procedure and / or catheter. All supporting source documentation provided by the center will be sent to the CEC for adjudication as defined in the CEC charter. The CEC's adjudication of study adverse event data is final.

19.3 Data Monitoring Committee

A Data Monitoring Committee (DMC) is responsible for the oversight review of all AEs. The DMC will include leading experts in Electrophysiology and Biostatistics who are not participating in the study and who have no affiliation with BSC. During the course of the study, the DMC will review accumulating safety data to monitor the incidence of AEs sent to the CEC and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and DMC procedures will be included in the DMC Charter.

Any DMC recommendation for study modification or termination due to concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to BSC and the study Principal Investigator for consideration and final decision. If the DMC at any time determines that a potentially serious risk exists to subjects in this study, the DMC chairman will immediately notify both BSC and the Principal Investigator.

19.4 Executive Steering Committee

A Steering Committee composed of the Sponsor's Clinical Management, the study Principal Investigator and other prominent Electrophysiologists from around the globe has been convened for this study. Responsibilities for the Committee include oversight of the overall conduct of the study with regards to protocol development, study progress, subject safety, overall data quality and

integrity, and first line review and final decision making of independent medical reviewer recommendations, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission.

20 Suspension or Termination

20.1 Premature Termination of the Study

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

20.1.1 Criteria for Premature Termination of the Study

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

- Suspicion of an unacceptable risk, including serious health threat. In this case, the Sponsor shall suspend the clinical investigation while the risk is assessed. The Sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB / EC / REB or regulatory authorities to suspend or terminate the clinical investigation.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of BSC to suspend or discontinue development of the device.

20.2 Termination of Study Participation by the Investigator or Withdrawal of IRB / EC / REB Approval

Any Investigator, or associated IRB / EC / REB or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to BSC. Investigators, associated IRBs / ECs / REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

20.3 Requirements for Documentation and Subject Follow-up

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

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

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another Investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by BSC.

The Principal Investigator or his / her designee must return all investigational product to BSC and, unless such action would jeopardize the rights, safety, or welfare of the subjects, must return all study-related documents.

20.4 Criteria for Suspending or Terminating a Study Site

BSC reserves the right to suspend or terminate the inclusion of subjects at a study site at any time for slow enrollment, or if the site has multiple or severe protocol violations / noncompliance without justification and / or fails to follow remedial actions.

In the event of termination of site participation, the site must return all investigational product and testing equipment to BSC and, unless such action would jeopardize the rights, safety, or welfare of the subjects, must return all study-related documents. The site must continue to allow BSC full access to study data and documents as stipulated in this protocol and any contract documents.

The IRB / EC / REB and regulatory authorities, as applicable, will be notified. Study subjects will be contacted, as applicable, and be informed of changes to study assessment schedule.

21 Study Registration and Results

21.1 Study Registration

This research-study will be registered on http://www.ClinicalTrials.gov, as required by U.S. Law and other jurisdictions, prior to the first enrollment.

21.2 Clinical Investigation Report

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the BSC Policy. A Clinical Investigation Report will be made available to all Investigators, IRB / EC / REB, and regulatory authorities, as applicable in accordance with the BSC Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

21.3 Publication Policy

BSC requires disclosure of its involvement as a Sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. BSC adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and Investigators in publication preparation provided the following guidelines are followed:

- All authorship and contributorship requirements as described above must be followed.
- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and / or Executive / Steering Committee at the onset of the project.

- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical trial may be made available to other researchers in accordance with the BSC Data Sharing Policy (https://www.bostonscientific.com/).

21.4 Study Applicability to Medicare Beneficiaries

The study results are directly applicable to Medicare beneficiaries as enrollment is anticipated to comprise a significant portion of Medicare-eligible patients that are age 65 or older. The primary target patient population for this clinical trial includes patients indicated for a cardiac ablation. Utilizing the HCUP National Inpatient Sample[11], approximately 62% of patients receiving heart conduction procedures (including cardiac ablation) in 2018 were Medicare beneficiaries. In addition, other published clinical studies indicate that the average age of cardiac ablation patients is above 65, making most of these patients Medicare eligible.[12]

Based on the Subject Selection for this clinical trial (**Section 5**), it is anticipated that the percentage of patients enrolled in the trial that are Medicare-eligible (i.e. age 65 or older) will be consistent with real-world experience, and as such, the trial results will be generalizable to the Medicare patient population.

22 Reimbursement and Compensation for Subjects

22.1 Subject Reimbursement

Reasonable travel and other expenses incurred by subjects as a result of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

22.2 Subject Incentives

Modest incentive payments to study subjects to encourage compliance with key study procedures such as transmitting electrocardiographic information may be offered in accordance with pertinent country laws and regulations and per the study site's regulations.

22.3 Compensation for Subject's Health Injury

BSC will purchase an insurance policy to cover the cost of potential health injury for study subjects, if required by applicable law.

23 Abbreviations and Definitions

23.1 Abbreviations and Acronyms

Table 23.1-1: Abbreviations and Acronyms

3D	Three dimensional
AAD	Antiarrhythmic drug
ACL	Arrhythmia Core Laboratory

[11] https://hcupnet.ahrq.gov/#setup, accessed October 8, 2020; Analysis 2017 hospital inpatient procedures utilizing ICD-10-PCS code for Destruction of conduction mechanism, percutaneous approach (02583ZZ)
[12] Bunch TJ, et al; Cardiovasc Electrophysiol. 2016 Feb;27(2):141-6. doi:10.1111/jce.12849. Epub 2015 Nov 20

ACT	Activated clotting time
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
BDB	Bidirectional block
BMI	Body Mass Index
BSC	Boston Scientific Corporation (Sponsor)
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)
CT	Computed tomography
CTI	Cavo-tricuspid isthmus
CXR	Chest X-ray
DOAC	Direct oral anticoagulant
DW, DWI	Diffusion weighted, Diffusion weighted image
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EM	Event monitor (any of several hardware modalities)
EQ-5D-3L	The 3-level EuroQol standardized questionnaire of health states
FDA	Food and Drug Administration
HCP	Health care personnel
HCT	Hematocrit
HGB	Hemoglobin
Holter	Holter monitor
ICE	Intracardiac echocardiography
ICF	Informed consent form
INR	International normalized ratio
IRB / EC / REB	Institutional Review Board / Ethics Committee / Research Ethics Board
IRE	Irreversible electroporation
ITT	Intent(ion)-to-Treat
IVC	Inferior vena cava
LA	Left atrium or left atrial
LAPW	Left atrial posterior wall
LBBB	Left bundle branch block
LTFU	Lost-to-follow-up
MITT	Modified Intent(ion)-to-Treat

MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
PAF	Paroxysmal atrial fibrillation
PersAF	Persistent atrial fibrillation
PFA	Pulsed field ablation
PP	Per Protocol
PV	Pulmonary vein
PVI	Pulmonary vein isolation
PW	Posterior wall
PWI	Posterior wall isolation
RFA	Radiofrequency ablation
SADE	Serious Adverse Device Effect
SAE	Serious adverse event
SOC	Standard of care
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TSF	Technical Source Form (see **Section 10.3**)
TTE	Transthoracic echocardiography
UADE	Unanticipated Adverse Device Effect

23.2 Definitions

Protocol terms not otherwise defined in the protocol are defined in **Table 23.2-1**:

Table 23.2-1: Definitions

Term	Definition
Acute Procedural Success	• Persistent AF Acute Procedural Success is defined in **Section 3.3.1**. • CTI-Mediated Flutter Acute Procedural Success is defined in **Section 3.4.2**
Antiarrhythmic Drugs, Class I and III	Class I / III AADs are those pharmaceutical agents approved or used in the relevant jurisdiction for the treatment of cardiac arrhythmia. For the ADVANTAGE AF Study, Class I and III AADs 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 relevant jurisdiction for the treatment of cardiac arrhythmia during the ADVANTAGE AF Study, they will be considered as Class I / III AADs for this protocol.
Attempt Subjects	Attempt Subjects are defined in **Section 6.6.4**.
Blanking Period	An interval in which recurrent AF, AFL or AT, cardioversion or a first re-ablation do not constitute 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 (Day 0) plus 90 days inclusive • For subjects treated with a Non-Failed AAD during the Blanking Period, a Treatment Failure due to the use of that drug only occurs if there is continued use of that drug following the earlier of either the Day 90 visit or Day 104.
Chronic Success	• Persistent AF Chronic Success is defined in **Section 3.3.2**. • CTI-Mediated Flutter Chronic Success is defined in **Section 3.4.2**
Composite Serious Adverse Events	Composite Serious Adverse Events are defined in **Section 3.2**.

Term	Definition
COVID-19 Related Disruptions	A disruption to any study procedure resulting directly or indirectly from the COVID 19 pandemic, including but not limited to subject illness, study site restrictions and limitations, shipping / manufacturing interruptions, significant changes in regulatory guidance and / or governmental restrictions on travel, association, and the prioritization of healthcare resources.
Dates	• Consent Date: The date a subject signs the ICF. • Exit Date: The date on which a subject's study participation ends. • Onset Date: The date on which a condition or AE begins. • Start Date: Day 0, the date of the Index Procedure or Rescheduled Index Procedure
Day (or Study Day)	A Day is an enumerated day of follow-up that begins on an Enrolled Subject's Start Date (Day 0).

Detectable AF, AFL, or AT	Detectable AF, AFL or AT is an episode of AF, AFL or AT which:
	• Is permanently recorded for review on a study-specific ECG, EM or Holter monitor
	  o Excludes arrhythmias recorded on other devices including implantable monitors and consumer wearables not specified in the ADVANTAGE AF Study procedures.
	• Contains at least 30 seconds of continuous interpretable signal
	  o 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

Failed AAD	Failed AADs include any and all Class I / III AAD determined at the time of enrollment to have been failed for effectiveness or intolerance. Failed AADs do not include Class I / III AADs determined at the time of enrollment solely to be contraindicated. Failed AADs must be established as part of the Baseline Assessment for agent, type of failure (arrhythmia recurrence or AAD intolerance) and the maximum failed dose (the total daily dose at which such failure occurred).
Intent Subjects	Intent Subjects are defined in **Section 6.6.3**.
Non-Failed AAD	A Non-Failed AAD is: • Any Class I / III AAD not established at the Baseline Assessment as a Failed AAD • Any Failed AAD used after Day 90 at a daily dose exceeding the maximum failed dose established at the Baseline Assessment

Term	Definition
Persistent atrial fibrillation	PersAF is defined as continuous AF that is sustained beyond 7 days, but not greater than 12 months duration.
Pulmonary vein dimensions	For the purpose of assessing potential PV stenosis: • 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.
Roll-In Subjects	Roll-In Subjects are defined in **Section 4.2.1**, **Section 4.3** and **Section 6.6.2**.
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.
Source data **Ref: ISO 14155**	All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation This includes source data initially recorded in an electronic format.
Source document **Ref: ISO 14155**	Original or certified copy of printed, optical, or electronic document containing source data, including TSFs.
Treatment Failure	Treatment Failure is the absence of Treatment Success due to one or more protocol-stipulated reasons.
Treatment Subjects	Treatment Subjects are defined in **Section 6.6.5**.
Treatment Success	Treatment Success is defined in **Section 3.3**.

Term	Definition
Vulnerable Subject **Ref: ISO 14155**	Individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response

24 Bibliography

1. Page RL. Clinical practice. Newly diagnosed atrial fibrillation. *N Engl J Med.* 2004;351(23):2408-2416.
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, Ryden 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. *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(1):121-126.
8. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm.* 2017;14(10):e275-e444.
9. Jais P, Cauchemez B, Macle L, et al. Catheter ablation versus antiarrhythmic drugs for atrial fibrillation: the A4 study. *Circulation.* 2008;118(24):2498-2505.

10. Mont L, Bisbal F, Hernandez-Madrid A, et al. Catheter ablation vs. antiarrhythmic drug treatment of persistent atrial fibrillation: a multicentre, randomized, controlled trial (SARA study). *Eur Heart J.* 2014;35(8):501-507.
11. Morillo CA, Verma A, Connolly SJ, et al. Radiofrequency ablation vs antiarrhythmic drugs as first-line treatment of paroxysmal atrial fibrillation (RAAFT-2): a randomized trial. *JAMA.* 2014;311(7):692-700.
12. Wilber DJ, Pappone C, Neuzil P, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. *JAMA.* 2010;303(4):333-340.
13. Blomstrom-Lundqvist C, Gizurarson S, Schwieler J, et al. Effect of Catheter Ablation vs Antiarrhythmic Medication on Quality of Life in Patients With Atrial Fibrillation: The CAPTAF Randomized Clinical Trial. *JAMA.* 2019;321(11):1059-1068.
14. Mark DB, Anstrom KJ, Sheng S, et al. Effect of Catheter Ablation vs Medical Therapy on Quality of Life Among Patients With Atrial Fibrillation: The CABANA Randomized Clinical Trial. *JAMA.* 2019;321(13):1275-1285.
15. Packer DL, Kowal RC, Wheelan KR, et al. Cryoballoon ablation of pulmonary veins for paroxysmal atrial fibrillation: first results of the North American Arctic Front (STOP AF) pivotal trial. *J Am Coll Cardiol.* 2013;61(16):1713-1723.
16. Kuck KH, Brugada J, Furnkranz A, et al. Cryoballoon or Radiofrequency Ablation for Paroxysmal Atrial Fibrillation. *N Engl J Med.* 2016;374(23):2235-2245.
17. Hindricks G, Potpara T, Dagres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS): The Task Force for the diagnosis and management of atrial fibrillation of the European Society of Cardiology (ESC) Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC. *Eur Heart J.* 2021;42(5):373-498.
18. Saglietto A, Gaita F, De Ponti R, De Ferrari GM, Anselmino M. Catheter Ablation vs. Anti-Arrhythmic Drugs as First-Line Treatment in Symptomatic Paroxysmal Atrial Fibrillation: A Systematic Review and Meta-Analysis of Randomized Clinical Trials. *Front Cardiovasc Med.* 2021;8:664647.
19. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol.* 2014;6:213-220.
20. Ghanbari H, Baser K, Jongnarangsin K, et al. Mortality and cerebrovascular events after radiofrequency catheter ablation of atrial fibrillation. *Heart Rhythm.* 2014;11(9):1503-1511.
21. Arbelo E, Brugada J, Hindricks G, et al. The atrial fibrillation ablation pilot study: a European Survey on Methodology and results of catheter ablation for atrial fibrillation conducted by the European Heart Rhythm Association. *Eur Heart J.* 2014;35(22):1466-1478.
22. Mansour M, Calkins H, Osorio J, et al. Persistent Atrial Fibrillation Ablation With Contact Force-Sensing Catheter: The Prospective Multicenter PRECEPT Trial. *JACC Clin Electrophysiol.* 2020;6(8):958-969.
23. Su WW, Reddy VY, Bhasin K, et al. Cryoballoon ablation of pulmonary veins for persistent atrial fibrillation: Results from the multicenter STOP Persistent AF trial. *Heart Rhythm.* 2020;17(11):1841-1847.

24. Brooks AG, Stiles MK, Laborderie J, et al. Outcomes of long-standing persistent atrial fibrillation ablation: a systematic review. *Heart Rhythm.* 2010;7(6):835-846.
25. Verma A, Jiang CY, Betts TR, et al. Approaches to catheter ablation for persistent atrial fibrillation. *N Engl J Med.* 2015;372(19):1812-1822.
26. Dixit S, Marchlinski FE, Lin D, et al. Randomized ablation strategies for the treatment of persistent atrial fibrillation: RASTA study. *Circ Arrhythm Electrophysiol.* 2012;5(2):287-294.
27. Verma A, Sanders P, Champagne J, et al. Selective complex fractionated atrial electrograms targeting for atrial fibrillation study (SELECT AF): a multicenter, randomized trial. *Circ Arrhythm Electrophysiol.* 2014;7(1):55-62.
28. Wong KC, Paisey JR, Sopher M, et al. No Benefit of Complex Fractionated Atrial Electrogram Ablation in Addition to Circumferential Pulmonary Vein Ablation and Linear Ablation: Benefit of Complex Ablation Study. *Circ Arrhythm Electrophysiol.* 2015;8(6):1316-1324.
29. Thiyagarajah A, Kadhim K, Lau DH, et al. Feasibility, Safety, and Efficacy of Posterior Wall Isolation During Atrial Fibrillation Ablation: A Systematic Review and Meta-Analysis. *Circ Arrhythm Electrophysiol.* 2019;12(8):e007005.
30. Elbatran AI, Anderson RH, Mori S, Saba MM. The rationale for isolation of the left atrial pulmonary venous component to control atrial fibrillation: A review article. *Heart Rhythm.* 2019;16(9):1392-1398.
31. Tahir KS, Mounsey JP, Hummel JP. Posterior Wall Isolation in Atrial Fibrillation Ablation. *J Innov Card Rhythm Manag.* 2018;9(6):3186-3194.
32. Suenari K, Chen YC, Kao YH, et al. Discrepant electrophysiological characteristics and calcium homeostasis of left atrial anterior and posterior myocytes. *Basic Res Cardiol.* 2011;106(1):65-74.
33. Markides V, Schilling RJ, Ho SY, Chow AW, Davies DW, Peters NS. Characterization of left atrial activation in the intact human heart. *Circulation.* 2003;107(5):733-739.
34. Miyazaki S, Kuwahara T, Kobori A, et al. Long-term clinical outcome of extensive pulmonary vein isolation-based catheter ablation therapy in patients with paroxysmal and persistent atrial fibrillation. *Heart.* 2011;97(8):668-673.
35. Jalife J. Rotors and spiral waves in atrial fibrillation. *J Cardiovasc Electrophysiol.* 2003;14(7):776-780.
36. Aryana A, Baker JH, Espinosa Ginic MA, et al. Posterior wall isolation using the cryoballoon in conjunction with pulmonary vein ablation is superior to pulmonary vein isolation alone in patients with persistent atrial fibrillation: A multicenter experience. *Heart Rhythm.* 2018;15(8):1121-1129.
37. Muneretto C, Bisleri G, Rosati F, et al. European prospective multicentre study of hybrid thoracoscopic and transcatheter ablation of persistent atrial fibrillation: the HISTORIC-AF trial. *Eur J Cardiothorac Surg.* 2017;52(4):740-745.
38. Bai R, Di Biase L, Mohanty P, et al. Proven isolation of the pulmonary vein antrum with or without left atrial posterior wall isolation in patients with persistent atrial fibrillation. *Heart Rhythm.* 2016;13(1):132-140.
39. Lee JM, Shim J, Park J, et al. The Electrical Isolation of the Left Atrial Posterior Wall in Catheter Ablation of Persistent Atrial Fibrillation. *JACC Clin Electrophysiol.* 2019;5(11):1253-1261.

40. Pak HN, Park J, Park JW, et al. Electrical Posterior Box Isolation in Persistent Atrial Fibrillation Changed to Paroxysmal Atrial Fibrillation: A Multicenter, Prospective, Randomized Study. *Circ Arrhythm Electrophysiol.* 2020;13(9):e008531.
41. Aryana A, Di Biase L, Pujara DK, et al. Long-term durability of posterior wall isolation using the cryoballoon in patients with persistent atrial fibrillation: a multicenter analysis of repeat catheter ablations. *J Interv Card Electrophysiol.* 2021;62(1):161-169.
42. Al-Sakere B, Andre F, Bernat C, et al. Tumor ablation with irreversible electroporation. *PLoS One.* 2007;2(11):e1135.
43. Neumcke B, Walz D, Lauger P. Nonlinear electrical effects in lipid bilayer membranes. 3. The dissociation field effect. *Biophys J.* 1970;10(2):172-182.
44. 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.
45. 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.
46. Chang DC. Cell poration and cell fusion using an oscillating electric field. *Biophys J.* 1989;56(4):641-652.
47. 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.
48. 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.
49. 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.
50. Olweny EO, Kapur P, Tan YK, Park SK, Adibi M, Cadeddu JA. Irreversible electroporation: evaluation of nonthermal and thermal ablative capabilities in the porcine kidney. *Urology.* 2013;81(3):679-684.
51. Maor E, Ivorra A, Leor J, Rubinsky B. Irreversible electroporation attenuates neointimal formation after angioplasty. *IEEE Trans Biomed Eng.* 2008;55(9):2268-2274.
52. Wittkampf FH, 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.
53. 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.
54. Neven K, van Driel V, van Wessel H, van Es R, Doevendans PA, Wittkampf F. Epicardial linear electroporation ablation and lesion size. *Heart Rhythm.* 2014;11(8):1465-1470.
55. van Driel VJ, Neven K, van Wessel H, Vink A, Doevendans PA, Wittkampf FH. Low vulnerability of the right phrenic nerve to electroporation ablation. *Heart Rhythm.* 2015;12(8):1838-1844.
56. BSC. PCR1225 Rev B FARAPULSE PFA System Effectiveness and Safety of an Efficient Waveform in a non-GLP 30-day Porcine Model

57. BSC. PCR0901 Rev A FARAWAVE 31mm and 35mm GLP Safety and Effectiveness Study in a 30-Day Chronic Porcine Model. 2020.
58. BSC. PCR1222 Rev B FARAWAVE Plus Safety and Effectiveness in 7 Day Porcine Report. 2021.
59. Koruth JS, Kuroki K, Kawamura I, et al. Pulsed Field Ablation Versus Radiofrequency Ablation: Esophageal Injury in a Novel Porcine Model. *Circ Arrhythm Electrophysiol.* 2020;13(3):e008303.
60. BSC. 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. 2020.
61. BSC. 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. 2020.
62. BSC. 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. 2020.
63. Reddy VY, Anic A, Koruth J, et al. Pulsed Field Ablation in Patients With Persistent Atrial Fibrillation. *J Am Coll Cardiol.* 2020;76(9):1068-1080.
64. Martinek M, Meyer C, Hassanein S, et al. Identification of a high-risk population for esophageal injury during radiofrequency catheter ablation of atrial fibrillation: procedural and anatomical considerations. *Heart Rhythm.* 2010;7(9):1224-1230.

66.
67. Waldo AL, Feld GK. Inter-relationships of atrial fibrillation and atrial flutter mechanisms and clinical implications. *J Am Coll Cardiol.* 2008;51(8):779-786.
68. Celikyurt U, Knecht S, Kuehne M, et al. Incidence of new-onset atrial fibrillation after cavotricuspid isthmus ablation for atrial flutter. *Europace.* 2017;19(11):1776-1780.
69. Brembilla-Perrot B, Girerd N, Sellal JM, et al. Risk of atrial fibrillation after atrial flutter ablation: impact of AF history, gender, and antiarrhythmic drug medication. *J Cardiovasc Electrophysiol.* 2014;25(8):813-820.
70. Candeias R, Adragcao P, Cavaco D, et al. Atrial fibrillation ablation: importance of cavotricuspid isthmus block. *Rev Port Cardiol.* 2009;28(10):1031-1040.
71. Moreira W, Timmermans C, Wellens HJ, et al. Can common-type atrial flutter be a sign of an arrhythmogenic substrate in paroxysmal atrial fibrillation? Clinical and ablative consequences in patients with coexistent paroxysmal atrial fibrillation/atrial flutter. *Circulation.* 2007;116(24):2786-2792.

.
72. 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 in Collaboration With the Society of Thoracic Surgeons. *Circulation.* 2019;140(2):e125-e151.

Appendix A: ADVANTAGE AF Study Phase 2

ADVANTAGE AF Study Phase 2 protocol will be provided to sites within the United States who are eligible for participation in ADVANTAGE AF Study Phase 2.

Appendix A: ADVANTAGE AF - Phase 2

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation

The ADVANTAGE AF Study: Phase 2

92836802
PF106

CLINICAL INVESTIGATION PLAN

G220079

NCT 05443594

Sponsored By

Boston Scientific Corporation

Sponsored By
Boston Scientific Corporation
4100 Hamline Ave N.
St. Paul, MN 55112

and

Boston Scientific International S.A.
Le Val Saint-Quentin
2 rue René Caudron
78960 Voisins le Bretonneux, France

Protocol Synopsis

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation **The ADVANTAGE AF Study – Phase 2**	
STUDY OBJECTIVE(S)	The objective of the ADVANTAGE AF Study is to establish the safety and effectiveness of the FARAPULSE Pulsed Field Ablation System for treatment of drug resistant, symptomatic persistent atrial fibrillation (PersAF). ADVANTAGE AF Phase 2 incorporates the use of the FARAPOINT PFA Catheter as an adjunctive device to the FARAPULSE PFA System.
INDICATION(S) FOR USE	The FARAPULSE™ Pulsed Field Ablation System is indicated for the treatment of drug resistant, symptomatic persistent atrial fibrillation. The FARAWAVE™ Pulsed Field Ablation Catheter is indicated for the isolation of pulmonary veins and posterior wall in the ablation of drug resistant, symptomatic persistent atrial fibrillation. The FARAPOINT™ Pulsed Field Ablation Catheter is indicated for use as an adjunctive device in the endocardial treatment of drug resistant, symptomatic persistent atrial fibrillation in conjunction with the FARAWAVE Catheter for the creation of an ablation line between the inferior vena cava and the tricuspid valve.
DEVICES UNDER STUDY (TEST DEVICE)	The investigational devices comprise the FARAPULSE™ Pulsed Field Ablation (PFA) System • FARAWAVE™ Pulsed Field Ablation (PFA) Catheter • FARAPOINT™ Pulsed Field Ablation (PFA) Catheter • FARASTAR™ Catheter Connection Cable • FARASTAR™ Pulsed Field Ablation (PFA) Generator and associated cables • FARASTAR™ Recording System Module and associated cables • FARASTAR™ Mapping System Module and associated cables (optional) • FARADRIVE™ Steerable Sheath

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation **The ADVANTAGE AF Study – Phase 2**	
STUDY DESIGN	Phase 2 of the ADVANTAGE AF Study is a prospective, single arm, open label, multi-center IDE pivotal study utilizing the FARAPULSE PFA System for treatment of drug resistant, symptomatic PersAF, including the adjunctive use of the PFA Catheter as an adjunctive device to the FARAPULSE PFA System. Subjects requiring ablative intervention for PersAF meeting study entry criteria will undergo percutaneous ablative pulmonary vein isolation (PVI) and left atrial posterior wall isolation (PWI) using the FARAWAVE PFA Catheter. Subjects meeting protocol criteria will undergo ablative intervention of a line between the inferior vena cava and the tricuspid valve with the FARAPOINT PFA Catheter. All subjects will have a commercially available LUX-Dx insertable cardiac monitor (ICM) inserted within seven (7) days after the Index Procedure (if not previously inserted) to detect the recurrence of cardiac arrhythmias. Subjects will be followed at Pre-Discharge, Day 7, Day 30, Day 90, Day 180, and Day 360. The Blanking Period will include Days 0 through 90.

INTERVENTIONS DURING INDEX PROCEDURE	**Pulmonary Vein Isolation (PVI):** PVI will be achieved in target veins using the FARAWAVE PFA Catheter.
	
	Posterior Wall Isolation (PWI): PWI will be achieved in the left atrial posterior wall between the PVs using the FARAWAVE PFA Catheter.
	
	CTI: Ablation of the CTI will be performed using the FARAPOINT PFA Catheter in the following situations:
	• Required: For subjects with a history of CTI-mediated (typical) AFL and
	  o Who have not had a CTI ablation procedure, or
	  o Who have had a CTI ablation procedure but have recurrent CTI conduction.
	• Required: subjects who manifest CTI-mediated AFL (spontaneous or induced) during the Index Procedure, or
	• At Investigator discretion: subject welfare indicates that CTI ablation should be performed.
	
	Other Ablation: When the Investigator determines that subject welfare requires intervention for either an accessory pathway, AVNRT or spontaneously occurring treatment-emergent AFL or AT, ablation for these arrhythmias may be performed using any commercially available RF ablation catheter. These permitted ablations and the associated data will be documented in the CRF and do not constitute Persistent AF Acute Procedural Failure.
	
	Ablation for an arrhythmia that is provoked only by catheter manipulation or is only inducible by pacing or pharmacologic stimulation is not permitted.

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation **The ADVANTAGE AF Study – Phase 2**	
PLANNED NUMBER OF SUBJECTS	Approximately 338 subjects will be enrolled in Phase 2 of the ADVANTAGE AF study (up to 80 Roll-In Subjects and approximately 258 Treatment Subjects) after enrollments in Phase 1 are complete. Roll-In Subjects (up to 80): The first subject enrolled and treated by each ablating Investigator at each site will be treated with the investigational devices as part of Investigator preparation, up to a maximum of 80 subjects across 40 investigational sites. Roll-In Subjects will be pre-screened prior to enrollment to ensure the criteria for CTI ablation will be met and the FARAPOINT PFA Catheter is utilized. Roll-In procedures may be adapted based on prior experience, used jointly by investigators, or additional subjects may be required as described in **Section 4.2**. Treatment Subjects (258): A planned 258 Treatment Subjects will be enrolled to support the proposed primary safety endpoint. No site may enroll more than ~13% of these planned subjects (n= 33 Treatment Subjects maximum). Subject enrollment will stop once approximately 258 Treatment Subjects are accrued and may be controlled to ensure an estimated 80 subjects are treated with the FARAPOINT PFA Catheter.
INVESTIGATIONAL SITES / COUNTRIES	Up to 40 clinical sites in the United States that participated in Phase 1 will contribute enrollments in Phase 2 of the ADVANTAGE AF Study. The number of active ablating Investigators at any site is limited to a maximum of three (3).

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation
The ADVANTAGE AF Study – Phase 2

PRIMARY SAFETY ENDPOINT

The primary safety endpoint (PSE) is the proportion of Treatment Subjects and Attempt Subjects with one or more of the following device or procedure-related Composite Serious Adverse Events (CSAEs) following the Index Procedure / Rescheduled Index Procedure or the Re-Ablation Procedure on or prior to the Day 90 Assessment, with an Onset Date following the procedure as specified in the Table below:

Composite Serious Adverse Events	Onset Date
• Myocardial infarction • Stroke • TIA • Peripheral or organ thromboembolism • Pulmonary edema • Unresolved phrenic nerve palsy / paresis • Vascular access complications • Heart block • Gastric motility / pyloric spasm disorders	Day 0 – Day 7
• Death • Cardiac tamponade / perforation • Pericarditis • Any PFA system related or PFA procedure-related cardiovascular or pulmonary adverse event	Day 0 – Day 30
• PV stenosis • Atrio-esophageal fistula	Day 0 –Day 90 Assessment

The CSAE components of the PSE are defined in **Table 3.3-2**.

ADDITIONAL SAFETY ENDPOINTS

- Primary Safety Endpoint Through Day 360 Assessment
- Composite Non-Serious Adverse Event
- Related AEs
- Any SAE
- Post-Blanking Arrhythmia Hospitalizations
- Post-Blanking Cardioversions
- Coronary Spasm Events
- Adverse Effects of Intraprocedural Administration of Nitroglycerin

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation **The ADVANTAGE AF Study – Phase 2**	
PRIMARY EFFECTIVENESS ENDPOINT	The primary effectiveness endpoint (PEE) is the proportion of LUX-Dx monitored Treatment Subjects with Treatment Success through the Day 360 Assessment. Treatment Success is defined as: 1. Persistent AF Acute Procedural Success AND 2. Persistent AF Chronic Success, defined as freedom from the following after the Blanking Period (excluding documented CTI-dependent flutter if subject was not treated with the FARAPOINT PFA Catheter): i. **Arrhythmia:** Occurrence of any Detectable AF, AFL or AT ii. **Re-ablation:** Any re-ablation for AF, AFL or AT iii. **Cardioversion:** Any electrical cardioversion for AF, AFL or AT iv. **AAD Use:** Use of a Non-Failed Class I / III AAD or amiodarone.
ADDITIONAL EFFECTIVENESS ENDPOINTS	• CTI-Mediated AFL Treatment Success • Re-Ablation Rate for CTI-Mediated AFL • Persistent AF Acute Procedural Success • Persistent AF Chronic Success • Freedom from Detectable AF, AFL, AT • Freedom from Symptomatic Recurrence and Intervention to Treat AF, AFL, or AT • Single Procedure Treatment Success • Off Drug Treatment Success • Re-Ablation Rate • AF, AFL, and AT Burden • Healthcare Utilization by AF, AFL, and AT Burden • Healthcare Utilization by AF, AFL, or AT Recurrence Duration
PROCEDURAL ASSESSMENTS	Assessments of procedure durations • Procedure Time • LA Dwell Time • PVI and PWI Ablation Time • CTI Ablation Time • Fluoroscopy Time Characterization of lesion sets • PVI Ablations • PWI Ablations • CTI Ablations • Other Ablations

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation **The ADVANTAGE AF Study – Phase 2**	
QUALITY OF LIFE ASSESSMENTS	Between Baseline and Day 180, and between Baseline and Day 360 • The 3-level EuroQol standardized questionnaire of health states (EQ-5D-3L) • The Atrial Fibrillation Effect on Quality of Life (AFEQT) instrument for the measurement of health related quality of life
METHOD OF ASSIGNING PATIENTS TO TREATMENT	Phase 2 of the ADVANTAGE AF Study is a single arm study, and any subject that signs the Informed Consent Form and meets all study inclusion criteria, and no exclusion criteria, will be eligible for treatment either as a Roll-In Subject or a Treatment Subject.
FOLLOW-UP SCHEDULE	• **Baseline Assessments** • **LUX-Dx Insertion** (from enrollment up to 7 days after Index Procedure) • **Index Procedure / Rescheduled Index Procedure (Day 0):** Cardiac ablation • **Pre-Discharge Assessment** • **Day 7 Assessment (remote):** safety assessment (Window Day 7 to 11) • **Day 30 Assessment (remote):** safety assessment (Window Day 30 – 37) • **Day 90 Assessment (in person):** clinical assessment (Window Day 90 ± 14) • **Day 180 Assessment (remote):** clinical assessment, QoL (Window Day 180 ± 30) • **Day 360 Assessment (in person):** clinical assessment, QoL (Window Day 360 ± 30) • **Re-Ablation Procedure** • **Unscheduled Assessments**
STUDY DURATION	Enrollment is expected to be completed in approximately 6 months, and subjects will be followed for 12 months. There will be an approximate 2-month period of site close-out visits, for an estimated first patient in until last patient last assessment duration of 20 months.
SUBJECT DURATION	The study duration for each subject will be approximately 13 ± 1 months to allow for screening, pre-procedural diagnostic procedures, treatment, and 12 ± 1 months of study follow-up.

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation
The ADVANTAGE AF Study – Phase 2

INCLUSION CRITERIA

Study subjects are required to meet all the following inclusion criteria:

Inclusion Category	Inclusion Definition
1. Age	≥ 18 years of age, or older if required by local law
2. Symptomatic, documented, drug-resistant, Persistent AF	
a. Documented	At a minimum a physician's note confirming the arrhythmia symptoms and durations AND within 180 days of the Enrollment Date, either: i. A 24-hour continuous ECG recording confirming continuous AF, OR ii. Two ECGs from any regulatory cleared rhythm monitoring device showing continuous AF taken at least 7 days apart
b. Drug-resistant	Effectiveness failure of, intolerance to, or specific contraindication to at least one (1) AAD (Class I or III) [1]
c. Persistent	Continuous AF for > 7 days and ≤ 365 days
3. Informed consent	Willing and capable of providing informed consent
4. Full participation	Willing and capable of participating in all follow-up assessments and testing associated with this clinical investigation at an approved clinical investigational center

[1] AADs previously failed for ineffectiveness or intolerance ("Failed AADs"), as well as those deemed contraindicated, must be recorded. For Failed AADs, the maximum daily dose associated with effectiveness or intolerance failure must also be recorded. See Sections 7.4 Antiarrhythmic Drugs, and 23.2 Definitions.

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation
The ADVANTAGE AF Study – Phase 2

EXCLUSION CRITERIA

Subjects who meet any one of the following criteria (Table 5 2) cannot be included in this study or will be excluded from this clinical study.

Exclusion Category	Exclusion Definition
1. Atrial exclusions – Any of the following atrial conditions:	
a. Atrial size	Left atrial anteroposterior diameter ≥ 5.5 cm. If LA diameter not available, non-indexed volume >100 ml (by MRI, CT or TTE report or physician note)
b. Prior atrial ablation	Any prior atrial endocardial, epicardial or surgical ablation procedure for arrhythmia other than ablation for right sided SVT
c. Atrial myxoma	Current atrial myxoma
d. Pulmonary veins	Any PV abnormality, stenosis, or stenting (common and middle PVs are admissible)
e. Atrial thrombus	Current left atrial thrombus
2. Cardiovascular exclusions – Any of the following CV conditions:	
a. Ventricular arrhythmia	History of sustained ventricular tachycardia or any ventricular fibrillation
b. Secondary AF	AF that is secondary to electrolyte imbalance, thyroid disease, alcohol, or other reversible / non-cardiac causes
c. Cardiac devices and implants	Current or anticipated pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices, interatrial baffle, closure device, patch, or patent foramen ovale occluder, LA appendage closure, device or occlusion, any insertable cardiac monitor other than LUX-Dx
d. Clinically significant valvular disease	Valvular disease that is any of the following: i. Symptomatic ii. Causing or exacerbating congestive heart failure iii. Associated with abnormal LV function or hemodynamic measurements
e. Cardiomyopathy	Hypertrophic cardiomyopathy
f. Valve prostheses	Any prosthetic heart valve, ring or repair including balloon aortic valvuloplasty
g. Access issues	Any IVC filter, known inability to obtain vascular access or other contraindication to femoral access
h. Rheumatic disease	Rheumatic heart disease
i. Anticipated cardiac surgery	Awaiting cardiac transplantation or other cardiac surgery within the next 12 months
j. Nitroglycerin intolerance	Known allergic drug reaction to nitroglycerin[1]
k. Coronary disease	Known severe non-revascularizable coronary disease

(CONTINUED NEXT PAGE)

EXCLUSION CRITERIA

l. Stents	Pre-existing right coronary artery stent
3. Any of the following conditions at baseline (**Section 7.5**):	
a. Heart failure NYHA	Heart failure associated with NYHA Class III or IV
b. Ejection fraction	LVEF < 40%
c. Uncontrolled hypertension	Uncontrolled hypertension (SBP > 160 mmHg or DBP > 95 mmHg on two (2) BP measurements at baseline assessment
d. Ventricular dysfunction	Right ventricular dysfunction
4. Any of the following events within 90 Days of the Consent Date:	
a. Coronary disease	Myocardial infarction (MI), unstable or Prinzmetal angina or coronary intervention
b. Cardiac surgery	Any cardiac surgery
c. Heart failure hospitalization	Heart failure hospitalization
d. Pericardium	Pericarditis or symptomatic pericardial effusion
e. GI bleeding	Gastrointestinal bleeding
f. Neurovascular event	Stroke, TIA, or intracranial bleeding
g. Thromboembolism	Any non-neurologic thromboembolic event
h. Carotid intervention	Carotid stenting or endarterectomy
5. Bleeding diathesis	Thrombocytosis, thrombocytopenia, disorder of blood clotting or bleeding diathesis
6. Contraindication to anticoagulation	Contraindication to, or unwillingness to use, systemic anticoagulation
7. Pre-ablation anticoagulation	Patients who have not been on anticoagulation therapy for at least 4 weeks prior to the ablation procedure
8. Pregnancy	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
9. Health conditions that in the investigator's medical opinion 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. Obesity	Body Mass Index (BMI) > 42.0
b. Transplantation	Solid organ or hematologic transplant, or currently being evaluated for a transplant
c. Diaphragmatic abnormality	Any prior history or current evidence of hemi-diaphragmatic paralysis or paresis
d. Pulmonary	• Severe pulmonary hypertension (at Baseline Assessment) • Severe lung disease

(CONTINUED NEXT PAGE)

EXCLUSION CRITERIA

	• Any lung disease involving abnormal blood gases or requiring supplemental oxygen
e. Renal	Renal insufficiency if an estimated glomerular filtration rate (eGFR) is < 30 mL / min / 1.73 m^2, or with any history of renal dialysis or renal transplant
f. Malignancy	Active malignancy or history of treated malignancy within 24 months of enrollment (other than cutaneous basal cell or squamous cell carcinoma)
g. Gastrointestinal	Clinically significant gastrointestinal problems involving the esophagus or stomach including severe or erosive esophagitis, uncontrolled gastric reflux, gastroparesis, esophageal candidiasis or active gastroduodenal ulceration
h. Infections	Active systemic infection
i. 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[2]
j. Diabetes	Uncontrolled diabetes mellitus or a recorded HgbA1c > 8.0% in the 90 days prior to the Consent Date
k. Sleep apnea	Untreated diagnosed obstructive sleep apnea with apnea hypopnea index classification of severe (>30 pauses per hour)
l. Medication Use	Required use of phosphodiesterase inhibitors within 24 hours of the ablation procedure
10. Life expectancy	Predicted life expectancy less than one (1) year
11. Participation in another trial	Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments; each instance must be brought to the attention of the Sponsor to determine eligibility
12. Any of the following congenital conditions:	
a. Congenital heart disease	Congenital heart disease with any clinically significant residual anatomic or conduction abnormality
b. Methemoglobinemia	History of known congenital methemoglobinemia
c. G6PD deficiency	History of known G6PD deficiency
13. Contraindication to ICM insertion	Patients who cannot tolerate a subcutaneous, chronically-inserted LUX-Dx device
14. LUX-Dx longevity	Patients with a LUX-Dx device inserted > 6 months prior to enrollment or an estimated longevity of less than 1 year

[1]Excluding hypotension which is a known physiological response

[2]Clinical resolution of COVID-19 disease is to be determined by the investigator, based on signs and symptoms of current active viral infection, not long-term sequelae of the disease such as anosmia or chronic fatigue.

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation **The ADVANTAGE AF Study – Phase 2**	
STATISTICAL METHODS	
PRIMARY SAFETY ENDPOINT: HYPOTHESIS AND METHOD	The analysis of the primary safety endpoint (PSE) is a test comparing the proportion of Treatment Subjects and Attempt Subjects with one or more CSAEs through the Day 90 Assessment to a performance goal (PG). The null and alternative hypotheses are: H_0: P ≥ PG versus H_A: P < PG where P is the proportion of Treatment Subjects and Attempt Subjects with one or more CSAEs through the Day 90 Assessment and the PG is 12%. The proportion of Treatment Subjects and Attempt Subjects with one or more CSAEs will be estimated using the Kaplan-Meier method. The 97.5% one-sided upper confidence limit of the observed event rate will be compared to the performance goal of 12%. If the upper confidence limit is less than the performance goal, the null hypothesis will be rejected. The upper confidence limit will be calculated as the pointwise confidence limit using the log-log methodology. **Both the PSE and PEE must be met for study success.**
PRIMARY EFFECTIVENESS ENDPOINT: HYPOTHESIS AND METHOD	The analysis of the primary effectiveness endpoint (PEE) is a test comparing the proportion of LUX-Dx monitored Treatment Subjects with Treatment Success through the Day 360 Assessment to a PG. The null and alternative hypotheses are: H_0: P ≤ PG versus HA: P > PG where P is the proportion of LUX-Dx monitored Treatment Subjects with Treatment Success through the Day 360 Assessment and the PG is 40%. The proportion of subjects with Treatment Success through the Day 360 Assessment will be estimated using the Kaplan-Meier method. The 97.5% one-sided lower confidence limit of the observed Treatments Success rate will be compared to the performance goal of 40%. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected. The confidence limit will be calculated as the pointwise confidence limit using the log-log methodology. **Both the PSE and PEE must be met for study success.**

A Prospective Single Arm Open Label Study of the FARAPULSE Pulsed Field Ablation System in Subjects with Persistent Atrial Fibrillation **The ADVANTAGE AF Study – Phase 2**	
SAMPLE SIZE	The sample size estimates for the primary safety endpoint (PSE) and primary effectiveness endpoint (PEE) were obtained through Binomial exact methods, using the following assumptions. **Assumption** / **PSE** / **PEE** Expected rate / 6% / 55% Performance goal / 12% / 40% Attrition / 5% / 10% Significance level (one-sided) / 0.025 / 0.025 Power / 88% / 90% Evaluable subjects / 245 / 122 Subjects accounting for attrition / 258 / 136 The overall sample size of 258 Treatment Subjects is driven by the analysis of the Primary Safety Endpoint through the Day 90 Assessment.

Table of Contents

List of Figures

List of Tables

1 Introduction

The primary study introduction content remains unchanged and is included within Phase 1 of the ADVANTAGE AF clinical investigational plan. New background specific to Phase 2 of the ADVANTAGE AF study is provided below.

1.1 Cavo-Tricuspid Isthmus (CTI) Mediated Atrial Flutter

Atrial flutter (AFL) is a supraventricular arrhythmia caused by a macro-reentrant loop in either the right or left atrium. The macro-reentrant circuits of AFL are well defined with the critical zone of slowing the reentrant rhythm, defined as the isthmus between the tricuspid valve and the inferior vena cava (IVC). Other names for right atrial flutter have included "common", "type 1", "typical" and "cavotricuspid isthmus (CTI)-dependent atrial flutter.[1] Cosio et al[2] describes the two more common circuits of AFL that are best denoted as typical counter-clockwise (CCW) cavotricuspid isthmus CTI-dependent AFL and reverse typical clockwise (CW) cavotricuspid isthmus CTI-dependent AFL. While the CCW and CW forms of CTI-dependent AFL are easily diagnosed and distinguished from other atypical types of AFL or atrial tachycardia during invasive electrophysiology study, these types, in general, can also be diagnosed using routine surface 12-lead electrocardiograms (ECG).

Historically, treatment options for patients that suffer from this arrhythmia have been life-long drug therapy, ablation of the atrio-ventricular junction (AVJ) or His bundle area creating permanent complete heart block (CHB) and leaving the patient dependent on pacemaker therapy. However, RF cardiac ablation using conventional small and large tip electrode catheters has evolved into a mature technology also using open-irrigation catheters and cryoablation.[3] Nonetheless, cardiac ablation is the first line therapy for AFL with highly predictable results. For successful ablation of any reentrant circuit involving a protected isthmus of slow conduction, a lesion (or lesions) must be placed such that the isthmus is severed completely. Current literature on RF ablation for CTI AFL with bi-directional block (BDB) report procedural long-term success rates are between 80-100%, depending on the definition of success and the catheter used.[4,5]

Although AF and CTI-dependent atrial flutter (AFL) are different arrhythmias with their own mechanisms and electrophysiologic presentation, their interrelationship has long been recognized and they coexist in a significant percentage of patients.[6] The relationship is reciprocal since patients diagnosed with AFL may develop AF after CTI ablation and patients with AF often go on to develop AFL.[7-9] In particular, the presentation of AFL in the context of AF may be the sign of additional atria remodeling or the presence of non-PV triggers.[10]

Accordingly, a strategy that includes both Pulmonary Vein Isolation (PVI) and CTI ablation has become an established practice in the percutaneous ablative treatment of patients with AF. The current guidelines for the management of AF indicate that CTI ablation may be beneficial during procedures of AF ablation, in particular for those patients with history of typical AFL and where AFL is induced at the time of AF ablation.[11] Adjunctive prophylactic CTI isolation is emerging as a potential strategy during AF ablation as a means to reduce rates of AFL. Previous studies reported that prophylactic CTI ablation may lead to recurrence rates of AFL lower than or equal to those for AF ablation only.[12-15] Additionally, adjunctive CTI ablation may mitigate the effect of adjunctive non-PV triggers on AF recurrences in patients with Persistent AF (PersAF).[16]

1.2 FARAPOINT Pulsed Field Ablation Catheter

An additional catheter included in the ADVANTAGE AF Phase 2 Study is the FARAPOINT PFA Catheter, which is designed for ablation of the cavotricuspid isthmus (CTI).

Initial data on the safety and feasibility of the FARAPOINT Catheter has been collected in twenty subjects in the PersAFOne II Study. In this study subjects undergoing ablation for PersAF using the FARAWAVE Catheter for PVI and Left Atrium Posterior Wall (LAPW) ablation also received ablation of the CTI using the FARAPOINT Catheter delivering two applications per site at 2000V. Study follow-up included an invasive electrophysiological remapping procedure to assess index treatment durability at 60 days post-index procedure.

No primary safety events were reported in any subjects. Two SAEs (pericardial effusion) have been reported in two subjects during study follow-up during required remapping procedures. Neither was deemed related to the FARAPULSE PFA devices or ablation procedure. All subjects had successful acute CTI ablation as determined by electrophysiological assessment of bidirectional block across the cavotricuspid isthmus. As reported in the interim progress report, dated 02-Feb-2022, 17 subjects had undergone the protocol-specified re-mapping procedures. Among these, bidirectional isthmus block remained in 14 of the 17 subjects (82.4%).[17]

It has been reported that CTI ablation may cause subclinical spasm of the coronary arteries[18]. Less often, patients may develop spasm that manifests in a clinically relevant manner such as ECG changes, hemodynamic changes or an arrhythmia requiring additional intervention. In the PersAFOne II feasibility study there were no events related to clinical signs of coronary spasm such as ECG changes or wall motion abnormalities on echocardiogram at the time of the procedure or post-procedure. PersAFOne III is an additional European prospective, multi-center safety and feasibility study in subjects with PersAF. Subjects undergo percutaneous PFA for PVI as well as CTI interruption and other left atrial ablations at the Investigator's discretion. The most recent revision of the PersAFOne III Clinical Investigation Plan (CIP) allows coronary assessments, including angiography and fractional flow reserve (FFR), to assess potential response to PFA application at the discretion of the Investigator in addition to prophylactic administration of nitroglycerin at the Investigator's discretion to mitigate the likelihood of coronary spasm. Accordingly, the ADVANTAGE AF Phase 2 Study incorporates a workflow during CTI ablation including administration of nitroglycerin to prevent the occurrence of coronary spasm.

1.3 Arrhythmia Detection via Implantable Cardiac Monitor (ICM)

Post-ablation assessment of arrhythmia recurrence over time is an important aspect to determine the chronic success of ablation therapy and has been extensively introduced in the definition of the effectiveness endpoints into ablation trials. Traditionally, recurrence has been assessed by means of short-duration monitoring strategies such as Holter and trans-thoracic monitors (TTM), which have been extensively used in clinical trials. The standard assessment recommended for arrhythmia monitoring from the 2017 expert consensus statement[20] requires both a 24 hours Holter monitoring at standard follow up timeframes (3, 6, and 12 months post procedure) and the use of a TTM to transmit periodically (at least twice a month) recordings of the heart rhythm. However, these methods have limited sensitivity in detecting AF and tend to underestimate the true AF recurrence rates, achieving a sensitivity of arrhythmia detection far inferior to the rates that could be captured by a continuous source of rhythm monitoring.[19]

The capability to use a source of continuous monitoring for heart rhythm has been recently introduced with the use of implantable loop recorders or implantable cardiac monitors (ICM). A ICM is a device

able to monitor the heart rhythm over an extended period and it is implanted subcutaneously with a minor surgery. This kind of device, available since the 1990s, has been improved and miniaturized over the past few years and has become an important tool to detect and diagnose heart arrhythmias. The implantation of an ICM in the subcutaneous tissue is currently a safe procedure with very rare complications, generally limited to mild pain or small hematoma at the implant site.

Compared to a TTM, the ICM has the advantage of allowing the continuous recording of patient rhythm and to transmit automatically arrhythmia episodes whenever they occur. This also implies the capability to capture all arrhythmias independently from patient symptoms and the possibility to simplify the device management compared to TTMs, that requires adequate patient compliance to ensure periodic transmission. An ICM also allows the calculation of the *AF burden*, which is the proportion of time an individual spends in AF over a certain period,expressed as a percentage. This metric is gaining importance in the management of AF and is increasingly considered a crucial factor.[11]

Thus, the utilization of ICM in this setting could potentially identify a new and more efficient approach for detecting arrhythmia and quantifying AF burden. As such, it has the potential to become the gold standard for arrhythmia detection in clinical trials in the near future. Since this is a novel method of assessment in the context of AF ablation trials (in particular persistent AF), the standards for the determination of a successful treatment in terms of arrhythmia rates and distribution (time to first recurrence, minimal duration, and AF burden) still need to be established in clinical trials.

1.4 Summary

The present IDE study incorporates the treatment strategy for PersAF ablation utilized in the PersAFOne studies using the FARAWAVE PFA Catheter for electrical isolation of the PV and isolation of the LAPW region between the PVs, coupled with selective CTI isolation using the FARAPOINT PFA Catheter. In addition to further characterizing PVI, PWI, and CTI ablation, this study will also give the opportunity to explore the effectiveness of ablation therapy assessed through a continuous source of recording (ICM) and evaluate recurrence rates and AF burden which may help to define a standard in the PersAF population useful for the design of future studies.

2 Device Description

2.1 Intended Use

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

The FARAWAVE Catheter is indicated for the isolation of pulmonary veins and posterior wall in the ablation of drug resistant, symptomatic persistent atrial fibrillation.

The FARAPOINT Catheter is indicated for use as an adjunctive device in the endocardial treatment of drug resistant, symptomatic persistent atrial fibrillation in conjunction with the FARAWAVE Catheter for the creation of an ablation line between the inferior vena cava and the tricuspid valve.

2.2 Investigational Devices

2.2.1 FARAPULSE Pulsed Field Ablation System

The FARAPULSE Pulsed Field Ablation (PFA) System is comprised of the following. Device description information of the FARAWAVE PFA Catheter, FARASTAR Cather Connection Cable, FARASTAR PFA Generator, and FARADRIVE Steerable Sheath remain unchanged from Phase 1 of the ADVANTAGE AF study, and full details can be found within their respective sections of the main protocol. The full list of components is provided in **Table 2.2-1**.

- FARAWAVE Pulsed Field Ablation Catheter (FARAWAVE PFA Catheter)
- FARAPOINT Pulsed Field Ablation Catheter (FARAPOINT PFA Catheter)
- FARASTAR Catheter Connection Cable
- FARASTAR Pulsed Field Ablation Generator and associated cables
- FARASTAR Mapping System Module (optional)
- Recording System Module and associated cables
- FARADRIVE Steerable Sheath

Table 2.2-1: Components of the FARAPULSE Pulsed Field Ablation System

Component	Subcomponents
FARAWAVE PFA Catheter	1. FARAWAVE Pulsed Field Ablation Catheters (31mm and 35mm) 2. FARASTAR Catheter Connection Cable
FARAPOINT PFA Catheter	1. FARAPOINT Pulsed Field Ablation Catheter
FARASTAR PFA Generator and Related Equipment	1. FARASTAR Pulsed Field Ablation Generator 2. FARASTAR Recording System Module 3. FARASTAR Mapping System Module (optional) <u>Sub-components of the FARASTAR Generator, MSM and RSM:*</u> 4. FARASTAR Stimulation Module Cable 5. FARASTAR Recording System Module Catheter Pin Cable 6. FARASTAR EGM Cable for FARAWAVE 7. FARASTAR Recording System Module ECG Trunk Cable 8. FARASTAR Recording System Module ECG Output Module 9. FARASTAR Recording System Module EGM Input Module 10. FARASTAR Recording System Module Auxiliary Cable 11. FARASTAR Mapping System Module Connection Cable 12. FARASTAR Mapping System Module Back Patch Cable 13. FARASTAR Mapping System Module Back Patch Cable, Male 14. FARASTAR Mapping System Module BNC/Phono Cable 15. FARASTAR Mapping System Module RHYTHMIA HDx ABL Cable 16. FARASTAR Cable Set 17. FARASTAR Stimulation Module Male Cable 18. FARASTAR Stimulation Module Female Cable 19. FARASTAR Stimulation Module Y-Cable – Long 20. FARASTAR Stimulation Module Y-Cable – Short
FARADRIVE Steerable Sheath	FARADRIVE Steerable Sheath

*Sub-components are not tracked for clinical device accountability

Diagrams of the FARAPULSE Pulsed Field Ablation System set-up with and without the optional FARASTAR Mapping System Module (MSM) are provided in
Figure 2-1 and **Figure Figure** 2-2, respectively.

Figure 2-1: Diagram of FARAPULSE Pulsed Field Ablation System Connections with FARAPOINT and Mapping System Module

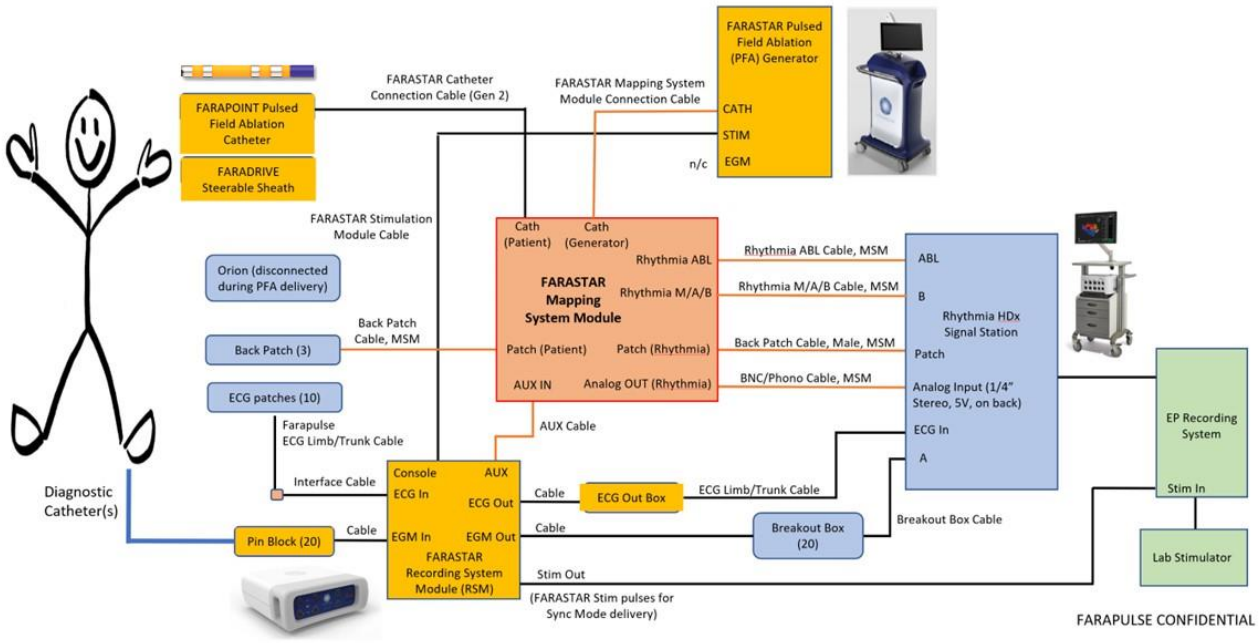
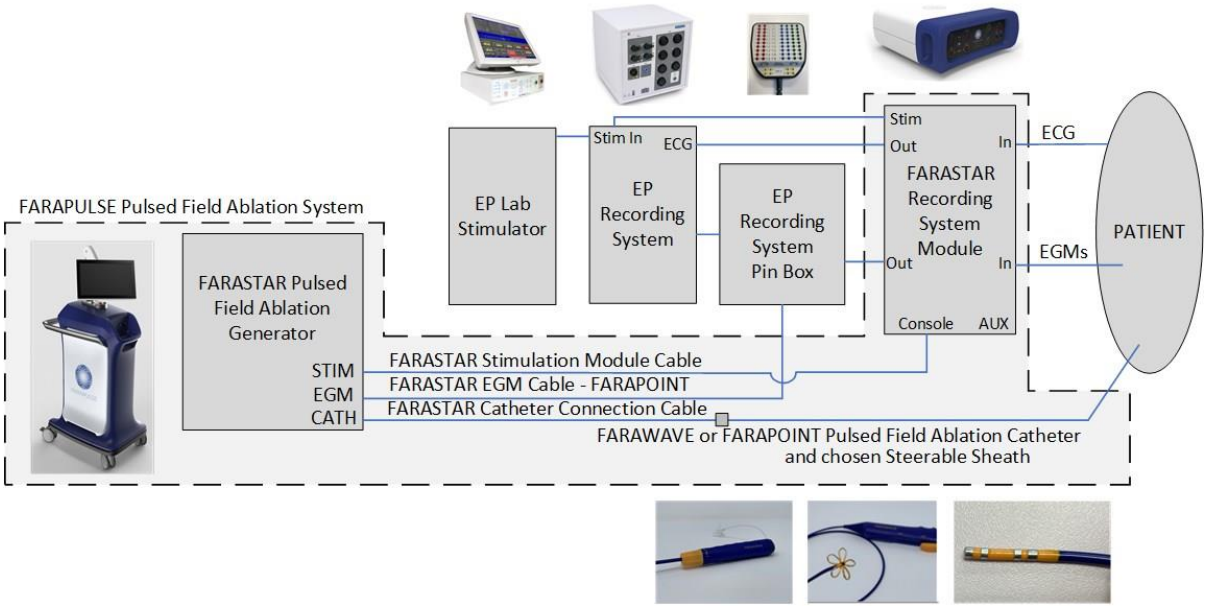


Figure 2-2: Diagram of FARAPULSE Pulsed Field Ablation System Connections



2.2.2 FARAPOINT Pulsed Field Ablation Catheter

The FARAPOINT PFA Catheter is a multi-electrode bidirectional, deflectable percutaneous catheter that connects to the FARASTAR PFA Generator via the FARASTAR Connection Cable (GEN2) and is designed to deliver Pulsed Electric Field (PEF) energy for cardiac tissue ablation. The FARAPOINT PFA Catheter is an adjunctive catheter designed to create focal-type lesions for the creation of an ablation line between the inferior vena cava and the tricuspid valve.

The catheter consists of the following major sections: 1) a deflectable distal section with electrodes, 2) an 8F catheter shaft, and 3) a proximal handle with a manually operated deflection control and a connector for attachment to the FARASTAR Pulsed Field Ablation Generator.

Figure 2-3: FARAPOINT Pulsed Field Ablation Catheter

The FARAPOINT Catheter is an 8F device with a bi-directional deflectable section length of 9.5cm and a usable length of 110cm measured from the catheter strain relief to the catheter tip when in the undeflected state. Two pairs of 2mm and 1.5mm length electrodes enable bipolar delivery of PFA energy. These electrodes attach to the FARASTAR PFA Generator through one FARASTAR Connection Cable. The FARAPOINT Catheter can be used with the FARADRIVE Steerable Sheath or any commercially available sheath at least 8.5Fr. The FARAPOINT PFA Catheter also includes a magnetic sensor to facilitate navigation with the Rhythmia mapping system.

Figure 2-4: FARAPOINT Pulsed Field Ablation Catheter – Distal Section

Table 2.2-2: FARAPOINT Feature List

Feature	Description
Shaft Outside Diameter	8 F
Steerable Introducer Compatibility	Minimum 8.5Fr sheath
Usable Length	110 cm
Number of Electrodes	4
Electrode Length	2 mm, 1.5 mm, 1.5 mm, 2 mm (distal to proximal)
Electrode Spacing	E1 (distal) to E2: 1.5 mm E2 to E3: 6 mm E3 to E4 (proximal): 1.5 mm
Deflection	F curve (bidirectional)

Additional important information is provided in the FARAPOINT PFA Catheter IFU regarding precautions, warnings, specific use instructions and procedural steps of the FARAPOINT PFA Catheter.

2.2.3 FARASTAR Mapping System Module (optional)

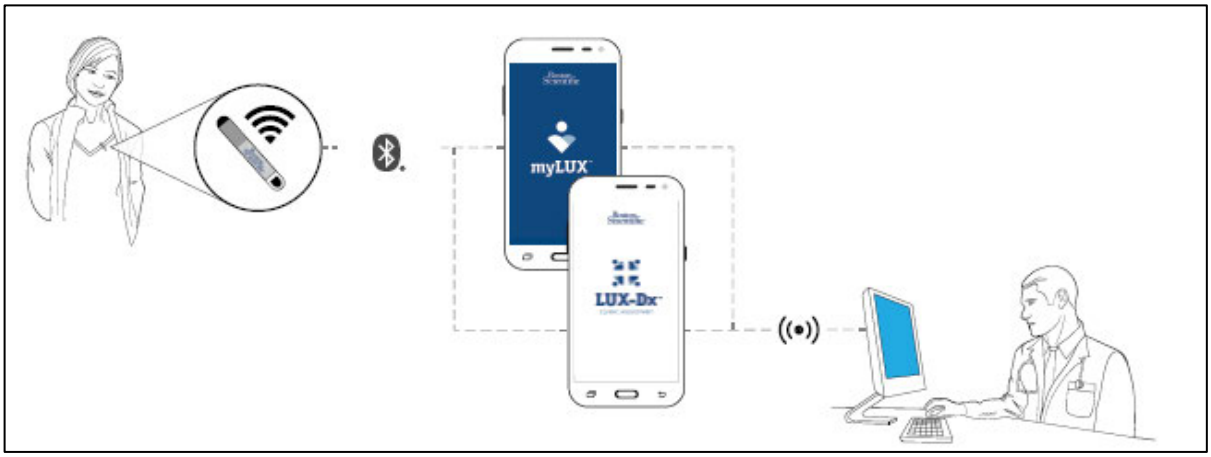
The FARASTAR Mapping System Module (MSM) is an optional filtering and protection accessory component to the FARASTAR PFA Generator which is placed between the patient and the Rhythmia HDx™ Mapping System. The primary function of the FARASTAR MSM is to disconnect the inputs of the Boston Scientific Rhythmia HDx™ Mapping System from their connections to the patient during Pulse Field Ablation delivery. These inputs include ablation catheter EGMs, back patch signals, and magnetic tracking sensor signals. The secondary function of the MSM is to provide a notification signal to the Rhythmia HDx™ Mapping System during the intervals of the active PFA delivery.

2.3 Non-Investigational Devices

2.3.1 LUX-Dx Insertable Cardiac Monitor

The LUX-Dx ICM is a small, leadless electronic device implanted under the skin in the left anterior chest wall. Its primary functions are to monitor, record, and store data related to cardiac arrhythmias. Two electrodes on the body of the device are used to monitor and record the patient's subcutaneous ECG (S-ECG) data when specific arrhythmias (according to the device-programmed settings) are detected, which include pause, bradycardia, tachycardia, AF, and atrial tachyarrhythmias (AT). In addition, the device will record S-ECG data when the patient triggers the device to record via the myLUX patient app. The ICM's memory can store up to 60 minutes of S-ECG recordings. Initial default arrhythmia detection parameters are provided by LATITUDE Clarity according to the Reason for Monitoring.

Figure 2-5: LUX-Dx ICM Device and Mobile App



2.3.2 Mobile Applications

There are two mobile applications used to interrogate the LUX-Dx ICM and transmit data from the device to the LATITUDE Clarity™: a patient-specific app called myLUX, and a clinic specific- app called LUX-Dx Clinic Assistant. The patient app also allows patients to record and send S-ECGs of symptomatic events to the LATITUDE server. Both apps communicate with the device using Bluetooth Low Energy (BLE) technology, and with the LATITUDE server using a Wi-Fi or cellular connection. Refer to **Figure 2-5** for a diagram of the LUX-Dx ICM System.

3 Study Objectives and Endpoints

3.1 Study Rationale

Phase 2 of the ADVANTAGE AF study is an appendix to Phase 1 of the ADVANTAGE AF protocol and contains relevant sections detailing requirements that differ from the original protocol. If protocol requirements remain unchanged from Phase 1 of the ADVANTAGE AF study, it will be noted as such within the Phase 2 appendix, and full details will be contained with and followed within the Phase 1 protocol.

ADVANTAGE AF Phase 2 is a prospective, non-randomized, multi-center, investigation being conducted to establish the safety and effectiveness of Boston Scientific's FARAPULSE PFA System, including the FARAPOINT PFA Catheter, for treatment of drug resistant, symptomatic persistent atrial fibrillation (PersAF). The aim of the trial is to collect data with the FARAPULSE PFA System and ensure a sufficient number of subjects are treated with the FARAPOINT PFA Catheter. This study seeks to obtain approval for the FARAPULSE PFA System with the FARAPOINT PFA Catheter for adjunctive use in the endocardial treatment of drug resistant, symptomatic persistent atrial fibrillation in conjunction with the FARAWAVE Catheter for the creation of ablation line between the inferior vena cava and the tricuspid valve.. Data from up to 338 additional subjects who will undergo treatment with the FARAPULSE PFA System will be evaluated in this second phase of the ADVANTAGE AF study.

3.2 Study Objective

The objective of the ADVANTAGE AF Study is to establish the safety and effectiveness of the FARAPULSE Pulsed Field Ablation System for treatment of drug resistant, symptomatic persistent atrial fibrillation (PersAF). ADVANTAGE AF Phase 2 incorporates the use of the FARAPOINT PFA Catheter as an adjunctive device to the FARAPULSE PFA System.

3.3 Primary Safety Endpoint

The primary safety endpoint (PSE) is the proportion of Treatment Subjects and Attempt Subjects with one or more of the following device or procedure-related Composite Serious Adverse Events (CSAEs) assessed through Day 90 following the Index Procedure / Rescheduled Index Procedure or the Re-Ablation Procedure on or prior to the Day 90 Assessment, with an Onset Date following the procedure as specified in **Table 3.3-1**.

Table 3.3-1: Primary Safety Endpoint Composite Serious Adverse Events

Composite Serious Adverse Events	Onset Date
• Myocardial infarction • Stroke • Transient Ischemic Attack (TIA) • Peripheral or organ thromboembolism • Pulmonary edema • Unresolved phrenic nerve palsy / paresis • Vascular access complications • Heart block • Gastric motility / pyloric spasm disorders	Day 0 – Day 7
• Death • Cardiac tamponade / perforation • Pericarditis • Any PFA system related PFA procedure-related cardiovascular or pulmonary adverse event	Day 0 – Day 30
• PV stenosis • Atrio-esophageal fistula	Day 0 – Day 90

For the analysis of the PSE, CSAEs are only defined for the following procedures that include the use of investigational devices:

- The Index Procedure / Rescheduled Index Procedure (**Section 7.7**)
- A Re-Ablation Procedure for AF, AFL or AT on or prior to the Day 90 Assessment (FARAWAVE only) (**Section 7.14**)

Device or procedure-related SAEs related to any other ablation procedure that does not include an investigational device will not be included in the analysis of the PSE, including those from Other Re-ablation Procedures (**Section 7.14.2**).

3.3.1 Composite Serious Adverse Event Definitions

Each of the adverse events (AEs) comprising a PSE CSAE is specifically defined in **Table 3.3-2**:

Table 3.3-2: Composite Serious Adverse Event Definitions

Related SAE	Description / Criteria
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
Unresolved phrenic nerve palsy / paresis	A phrenic nerve palsy / paresis is defined as absent or reduced phrenic nerve function assessed as a change in the elevation of a hemi-diaphragm from baseline, that is: • Not resolved by the end of the procedure • Demonstrated radiographically by pacing, an inspiration / expiration chest X-ray or fluoroscopic sniff test • Not due to a demonstrable pulmonary process such as atelectasis or pleural disease. An unresolved phrenic nerve palsy or paresis is defined for this endpoint as not resolved at the time of the last in-person follow-up assessment.
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.

Related SAE	Description / Criteria
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.
Death	AE resulting in subject death; any subject death that occurs within 30 days of an ablation procedure with the FARAPULSE PFA System will be considered as device or procedure related unless proven otherwise and adjudicated as not related to the FARAPULSE PFA System or ablation procedure by the Clinical Events Committee.
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.
PFA system or procedure related cardiovascular or pulmonary event	Any PFA system-related or procedure-related cardiovascular or pulmonary adverse event that occurs within 30 days of an ablation procedure with the investigational device and prolongs or requires hospitalization > 48 hours (excluding AF, AFL, and AT).
Pulmonary vein stenosis	>70% reduction of an ablated measured PV diameter compared to the baseline CT / MRI scan, as determined by the Cardiac Imaging Core Laboratory (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.

For the purposes of Clinical Event Committee (CEC) adjudication of trial outcomes and the associated analyses of safety endpoints:

- Procedures (such as cardioversion and endocardial ablation) are not adverse events.
- Pre-existing diseases or conditions (including AF, AFL, AT) will not be reported as adverse events unless there has been a substantial increase in severity or frequency of the problem as compared to the subject's baseline which cannot be attributed to the expected progression of the disease or condition.

- AEs will be deemed serious according to the criteria and notes in **Section 17** of the Phase 1 ADVANTAGE AF protocol.

3.4 Primary Effectiveness Endpoint

The primary effectiveness endpoint (PEE) is the proportion of LUX-Dx monitored Treatment Subjects with Treatment Success through the Day 360 Assessment. Treatment Success is defined as Persistent AF Acute Procedural Success AND Persistent AF Chronic Success.

3.4.1 Persistent AF Acute Procedural Success

Persistent AF Acute Procedural Success is defined as:

- The isolation of all attempted PVs as clinically assessed at the end of the procedure by entrance block performed with or without adenosine testing, AND
- The isolation of the left atrial PW as clinically assessed at the end of the procedure, performed with or without adenosine testing, via interrogation by multipolar diagnostic catheter or 3D electroanatomical mapping.

Both PWI and PVI must be achieved using only the FARAWAVE Catheter to be classified as a Persistent AF Acute Procedural Success. If the Investigator determined that subject welfare required intervention for an accessory pathway, AVNRT or spontaneously occurring treatment-emergent AFL or AT, ablation for these arrhythmias may be performed using any commercially available RF ablation catheter, and these permitted ablations do not constitute Persistent AF Acute Procedural Failure.

3.4.2 Persistent AF Chronic Success

Persistent AF Chronic Success is defined as freedom from any of the following through the Day 360 Assessment after the Blanking Period, excluding documented CTI-dependent AFL[1]:

a. **Arrhythmia:** Occurrence of any Detectable AF, AFL or AT
b. **Re-ablation:** Any re-ablation for AF, AFL or AT
c. **Cardioversion:** Any electrical cardioversion for AF, AFL or AT
d. **AAD Use:** Use of a Non-Failed Class I / III AAD or amiodarone

Within the Blanking Period, recurrent arrhythmias can be managed with AADs, cardioversion or one re-ablation procedure with the FARAPULSE PFA System without constituting Persistent AF Chronic Failure. Titration of Class I/III antiarrhythmic medications are allowed during the Blanking Period. Subjects are allowed to remain on Class I/III antiarrhythmic medications at the historic maximum ineffective dose (prior to the ablation procedure) after the 90-day Blanking Period, except amiodarone. Subjects that undergo more than one re-ablation procedure within the Blanking Period will be classified as a Persistent AF Chronic Failure. Complete definitions of the endpoint terms (including Blanking Period, Detectable AF, AFL, or AT, Failed AAD and Non-Failed AAD), can be found in **Section 23.2**.

[1] Post-blanking CTI-dependent AFL or re-ablation or cardioversion for CTI-dependent AFL does not constitute Treatment Failure if the subject did not have a CTI ablation with the FARAPOINT PFA Catheter but will be a Treatment Failure if the subject did receive ablation with the FARAPOINT PFA Catheter.

3.5 Additional Endpoints and Assessments

The following additional endpoints and assessments will be analyzed and reported for Phase 2 of the ADVANTAGE AF Study.

3.5.1 Additional Safety Endpoints

The following endpoints will be descriptively analyzed:

- **Primary Safety Endpoint Through Day 360 Assessment:**
  Defined as the proportion of subjects with one or more device or procedure-related CSAEs assessed through Day 360 (Treatment) or Day 30 (Attempt)
- **Composite Non-Serious Adverse Events:**
  Defined as the proportion of subjects with one or more composite non-serious AEs otherwise as defined in **Table 3.3-2: Composite Serious Adverse Event Definitions**.
- **Related Adverse Events**
  Defined as the proportion of subjects with one or more device or procedure-related AEs
- **Any Serious Adverse Event**
  Defined as the proportion of subjects with one or more SAEs whether or not device or procedure-related
- **Post-Blanking Arrhythmia Hospitalizations**
  Defined as the proportion of Treatment subjects with one or more physician-directed admission to an inpatient hospital facility for at least two consecutive calendar days for the primary purpose of diagnosing or treating AF, AFL or AT beginning after Day 90
- **Post-Blanking Cardioversions**
  Defined as the proportion of Treatment subjects with one or more electrical cardioversions for AF, AFL or AT after Day 90
- **Coronary Spasm Events**
  Defined as the proportion of subjects with CTI-mediated AFL ablation using FARAPOINT PFA catheter with any of the following events 0-48 hours following procedure:
  - Angiography performed with visualization of severe (≥70%) spasm
  - ST elevation, defined by ST elevation of 2mm in two contiguous leads and adjudicated to be a result of coronary spasm
  - Cardiac arrest adjudicated to be a result of coronary spasm.
- **Adverse Effects of Intraprocedural Administration of Nitroglycerin**
  Defined as the proportion of subjects with CTI-mediated AFL ablation using FARAPOINT PFA catheter with any of the following events 0-48 hours following procedure:
  - Persistent hypotension unresponsive to medical intervention
  - Respiratory distress due to acquired methemoglobinemia assessed by an arterial blood gas with co-oximetry with MetHb >10%.

3.5.2 Additional Effectiveness Endpoints

The following endpoints will be descriptively analyzed in LUX-Dx monitored Treatment Subjects with CTI Ablation using the FARAPOINT PFA Catheter at the indicated time points:

- **CTI-Mediated AFL Treatment Success**
  Defined as both of the following outcomes:
  CTI-Mediated AFL Acute Procedural Success: defined as the absence of conduction through the cavo-tricuspid isthmus in both directions achieved with the FARAPOINT PFA Catheter, confirmed at the end of the Index Procedure/ Rescheduled Index Procedure. Use of a catheter modality for treatment of CTI-

Mediated AFL other than FARAPOINT PFA Catheter will be considered a CTI-Mediated AFL Acute Procedural Failure.

CTI-Mediated AFL Chronic Success: defined as freedom from documented recurrence of CTI-mediated AFL as of the Day 90, Day 180, and Day 360 Assessment(s), without repeat CTI ablation. If recurrence of AFL is indicated on the LUX-Dx recording, recurrence of CTI-mediated AFL must be confirmed with a 12-lead ECG.

- **Re-ablation Rate for CTI-Mediated AFL**
  Defined as the proportion of subjects who receive one or more re-ablations during study follow-up for CTI-Mediated AFL, at any time during follow-up, and subdivided by Day 90 and Day 180 Assessment.

The following endpoints will be descriptively analyzed in all LUX-Dx monitored Treatment Subjects at the indicated time points:

- **Persistent AF Acute Procedural Success**
  Defined in **Section 3.4.1** at the conclusion of the Index Procedure / Rescheduled Index Procedure
- **Persistent AF Chronic Success**
  Defined in **Section 3.4.2** through the Day 360 assessment
- **Freedom from Detectable AF, AFL, AT**
  Defined as freedom from recurrence of any Detectable AF, AFL, or AT as defined in **Section 23.2** and additionally assessed using different minimum thresholds for the duration of asymptomatic episodes which count as recurrence of AF, AFL, or AT based on continuous monitoring after the blanking period. Thresholds will include 30 seconds, 4 minutes, 6 minutes, 1 hour, 6 hours, and 24 hours.
- **Freedom from Symptomatic Recurrence and Intervention to Treat AF, AFL, or AT**
  Defined as freedom from recurrence of any symptomatic Detectable AF, AFL, or AT as defined in **Section 23.2** and freedom from intervention to treat AF, AFL, or AT, including re-ablation, cardioversion, or use of a Non-Failed Class I/III AAD or amiodarone.
- **Single Procedure Treatment Success**
  Treatment Success as defined in **Section 3.4** but counting subjects with any re-ablation for AF, AFL, or AT as Treatment Failures
- **Off Drug Treatment Success**
  Treatment Success as defined in **Section 3.4** but counting subjects treated with any Class I / III AAD after Day 90 as Treatment Failures
- **Re-Ablation Rate**
  Defined as the proportion of subjects who receive one or more re-ablations during study follow-up for AF, AFL, or AT, at any time during follow-up, and subdivided by re-ablation during Days 0 – 90 and by Days 91 and thereafter. CTI only re-ablation is excluded for subjects who did not receive CTI ablation with the FARAPOINT catheter.
- **AF, AFL, and AT Burden**
  Descriptive statistics on AF, AFL, and AT burden, as defined in Section 23.2 and assessed during the observation period from Day 91 to Day 360 Assessment. AF, AFL, and AT burden will also be calculated for the days from LUX-Dx activation to the Index/ Rescheduled Index Procedure (up to 30 days pre-procedure) and compared to the burden calculated from Day 91 to Day 360 Assessment. Additionally, AF, AFL, and AT burden statistics from Day 91 to Day 360

will be stratified by recurrence based on LUX-Dx detected AF, AFL, or AT using various episode duration thresholds.

- **Healthcare Utilization by AF, AFL, and AT Burden**
  Healthcare utilization, defined by outcomes of all-cause hospitalization, cardioversion for AF, AFL, or AT recurrence outside of an ablation procedure, re-ablation for AF, AFL, or AT and unscheduled cardiovascular follow-up assessments, will be compared between subjects grouped by AF, AFL, and AT burden from Day 91 to Day 360 Assessment. Burden groups will include rates of 0%, 0-0.1%, 0.1-1%, 1-5%, 5-10%, and >10% AF, AFL, and AT burden.
- **Healthcare Utilization by AF, AFL, or AT Recurrence Duration**
  Healthcare utilization, defined by outcomes of all-cause hospitalization, cardioversion for AF, AFL, or AT recurrence outside of an ablation procedure, re-ablation for AF, AFL, or AT and unscheduled cardiovascular follow-up assessments will be compared between subjects grouped by longest duration of AF, AFL, or AT captured by LUX-Dx (based on continuous monitoring) between Day 91 and Day 360 Assessment. Groups will include no recurrence and longest duration of 0-6 minutes, 6 minutes – 1 hour, 1-6 hours, 6-24 hours, and ≥24 hours.

3.5.3 Procedural Assessments

The following assessments will be descriptively analyzed at the completion of the Index Procedure / Rescheduled Index Procedure:

Assessments of procedure durations (recorded and rounded to the nearest minute)

- **Procedure Time**
  Defined as the recorded time of initiation of venous access to the recorded time of venous access closure completion
- **LA Dwell Time**
  Defined as the recorded time between the insertion of the first device into the LA and the removal of the last device from the LA
- **PVI and PWI Ablation Time**
  Defined as the recorded time from the first FARAWAVE PFA Catheter application to the last FARAWAVE PFA Catheter application.
- **CTI Ablation Time**
  Defined as the recorded time from the first application at the isthmus to the last application at the isthmus
- **Fluoroscopy Time**
  Defined as the recorded total duration of exposure to fluoroscopic imaging.

Characterization of lesion sets

- **PVI Ablations**
  Defined as the number of applications in each attempted vein
- **PWI Ablations**
  Defined as the number of applications during ablation of the LA posterior wall
- **CTI Ablations**
  Defined as the number of applications during CTI ablation
- **Other Ablations**
  For subjects undergoing welfare-required ablations for an accessory pathway, AVNRT, left-sided AFL or incessant AT a listing and descriptive summary of ablation lesions delivered.

3.5.4 Quality of Life Assessments

The following assessments will be descriptively analyzed between Baseline and Day 180, and between Baseline and Day 360.

- The 3-level EuroQol standardized questionnaire of health states (EQ-5D-3L)
- The Atrial Fibrillation Effect on Quality of Life (AFEQT) instrument for the measurement of health-related quality of life

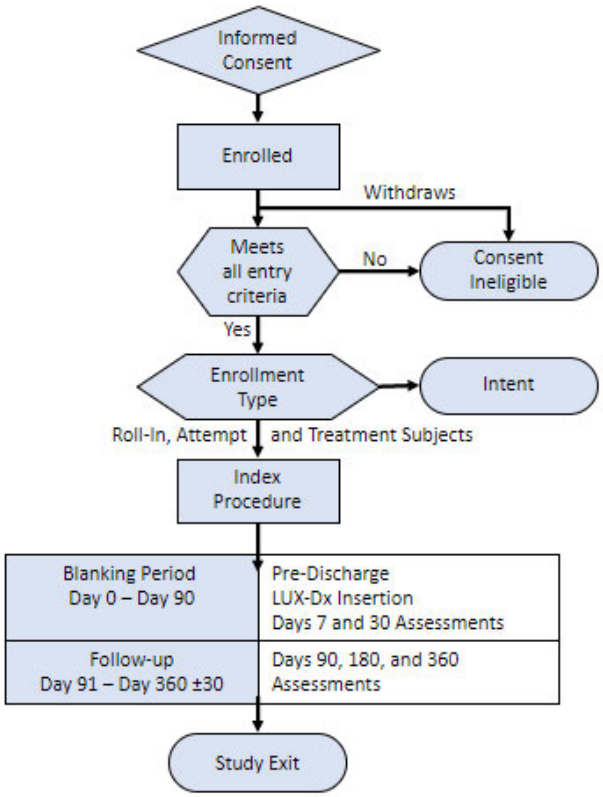
4 ADVANTAGE AF Phase 2 Study Design

Phase 2 of the ADVANTAGE AF Study is a prospective, single arm, open label, multi-center IDE pivotal study enrolling additional subjects and utilizing the FARAPULSE PFA System for treatment of drug resistant, symptomatic PersAF, including the adjunctive use of the FARAPOINT ablation catheter for the concomitant treatment of CTI-mediated atrial flutter (AFL).

Subjects requiring ablative intervention for PersAF meeting study entry criteria will undergo percutaneous ablative pulmonary vein isolation (PVI) and left atrial posterior wall isolation (PWI) using the FARAWAVE PFA Catheter. Subjects meeting protocol criteria will undergo ablative interruption of the CTI using the FARAPOINT PFA Catheter.

All subjects will receive a commercially available LUX-Dx insertable cardiac monitor (ICM) within seven (7) days following the Index Procedure to detect recurrence of cardiac arrhythmias; it is highly recommended for LUX-Dx insertion to occur 30 days prior to the Index Procedure. Subjects will be followed at Pre-Discharge, Day 7, Day 30, Day 90, Day 180, and Day 360. The Blanking Period will include Days 0 through 90.

Figure 4-1: ADVANTAGE AF Phase 2 Study Design



4.1 Scale and Duration

4.1.1 Phase 1 of ADVANTAGE AF

All subjects enrolled under Phase 1 of the ADVANTAGE AF protocol will be treated, followed, and analyzed as defined within the protocol version in which they were enrolled.

4.1.2 Number of ADVANTAGE Phase 2 Subjects

Approximately 338 treated subjects will be enrolled in Phase 2 of the ADVANTAGE AF study (up to 80 Roll-In Subjects and approximately 258 Treatment Subjects) after enrollments in Phase 1 of the study are complete. Subjects participating in Phase 1 cannot be approached for participation in Phase 2 for treatment with the FARAPOINT Catheter.

Roll-In Subjects (up to 80): The first subject enrolled by each ablating Investigator at each site will be treated with the investigational devices as part of Investigator preparation, up to a maximum of 80 subjects across 40 investigational sites. Subjects will be pre-screened prior to enrollment to ensure the criteria for CTI ablation will be met and the FARAPOINT PFA Catheter is utilized. Roll-In procedures may be adapted based on prior experience, or additional subjects may be required as described further in **Section 4.2**.

Treatment Subjects (258): A planned 258 Treatment Subjects will be enrolled to support the Primary Safety Endpoint. No site may enroll more than 33 Treatment Subjects (13% of those planned). Subject enrollment will stop once approximately 258 Treatment Subjects are accrued. It is expected

that approximately 30% of the Treatment subjects will be treated with the FARAPOINT PFA Catheter for CTI-mediated AFL. Enrollments may be controlled to ensure an estimated 80 subjects are treated with the FARAPOINT PFA Catheter. There is no predetermined upper limit for the number of Treatment subjects receiving CTI ablation with the FARAPOINT PFA Catheter, therefore the FARAPOINT- treated subjects may exceed 80 when the total number of 258 Treatment subjects are accrued.

4.1.3 Investigational Sites / Countries

Up to 40 clinical sites in the United States that participated in Phase 1 will contribute enrollments in Phase 2 of the ADVANTAGE AF Study.

The number of active ablating Investigators at any site is limited to a maximum of three (3).

4.1.4 Study Duration

Enrollment in Phase 2 is expected to be completed in approximately 6 months, and subjects will be followed for 12 months. There will be an approximate 2-month period of site close-out visits, for an estimated first patient in until last patient last assessment duration of 20 months.

Subjects who retain the LUX-Dx beyond the Day 360 Assessment for the study may be requested to consent to provide long-term follow-up data from the LUX-Dx device, if needed, to potentially fulfill post-approval requirements.

4.1.5 Participant Duration

The study duration for each subject will be approximately 13 ± 1 months to allow for screening, pre-procedural diagnostic procedures, treatment, and 12 ± 1 months of study follow-up.

4.2 Treatment Assignment (Roll-In vs Treatment)

The first subject enrolled by each Investigator at each site will be classified as a Roll-In Subject and will be treated with the FARAPULSE PFA System, including the FARAPOINT PFA Catheter as part of Investigator preparation. Investigators will pre-screen the first subject(s) prior to enrollment to ensure the first subject(s) will meet the protocol criteria for the FARAPOINT PFA Catheter to be utilized.

The number of Roll-In Subjects for each investigator will be determined by BSC depending on prior experience. Sites with more than one (1) active investigator may utilize available Roll-In Subjects jointly as required since each site will be allocated a maximum of 2 Roll-In Subjects total and will be allowed to have a maximum of three (3) ablating investigators. Investigators that enrolled and ablated subjects within Phase 1 will be required to utilize a Phase 2 Roll-In subject in order to obtain the appropriate experience with the FARAPOINT PFA Catheter.

After each ablating investigator has completed the Roll-In Subject requirements, BSC will provide the investigator with authorization to proceed with the enrollment of Treatment Subjects.

4.3 Justification for the Study Design

The currently ongoing ADVANTAGE AF (Phase 1) clinical trial (NCT05443594) is a prospective, single arm, open label IDE trial Study designed to establish the safety and effectiveness of the FARAPULSE PFA System, for treatment of drug resistant, symptomatic persistent atrial fibrillation.

The rationale of using the same design of the ADVANTAGE AF trial stands in that Phase 2 will enroll a similar patient population and deliver of the same intended therapy, with the primary difference being the addition of the FARAPOINT PFA Catheter as an adjunctive tool for the creation of ablation line between the inferior vena cava and the tricuspid valve. Accordingly, safety will be supported by the same assumptions used in Phase 1 of the ADVANTAGE AF study. As described in Section 8, as the recurrence monitoring method for Phase 2 is using continuous monitoring, effectiveness is supported by slightly modified assumptions as compared to Phase 1. Subjects will continue to be followed for the full 12-months and additional endpoints analyzed and submitted once available.

5 Subject Selection

5.1 Study Population and Eligibility

Study eligibility criteria are described in **Section 5.2** and **Section 5.3** below. No vulnerable populations will be enrolled in this study. See **Section 23.2** for the definition of a vulnerable subject.

Study eligibility criteria are determined at the time of study entry based on currently available information. If testing is required, it must take place within the various intervals specified for the Baseline Assessment in **Section 7.5**

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, a protocol deviation exists, but this does not change the enrolled status of the subject or the inclusion of their data in study analyses.

5.2 Inclusion Criteria

Subjects who meet all the following inclusion criteria (**Table 5.2-1**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see **Section 5.3**) is met.

Table 5.2-1: Inclusion Criteria

Inclusion Category	Inclusion Definition
1. Age	≥ 18 years of age, or older if required by local law
2. Symptomatic, documented, drug-resistant, Persistent AF	
a. Documented	At a minimum a physician's note confirming the arrhythmia symptoms and durations AND within 180 days of the Enrollment Date, either: i. A 24-hour continuous ECG recording confirming continuous AF, OR ii. Two ECGs from any regulatory cleared rhythm monitoring device showing continuous AF taken at least 7 days apart

Inclusion Category	Inclusion Definition
b. Drug-resistant	Effectiveness failure of, intolerance to, or specific contraindication to at least one (1) AAD (Class I or III) [2]
c. Persistent	Continuous AF for > 7 days and ≤ 365 days
3. Informed consent	Willing and capable of providing informed consent
4. Full participation	Willing and capable of participating in all follow-up assessments and testing associated with this clinical investigation at an approved clinical investigational center

5.3 Exclusion Criteria

Subjects who meet any one of the following criteria (**Table 5.3-1**: Exclusion Criteria) cannot be included in this study or will be excluded from this clinical study. Exclusion criteria that are remediated and are no longer present prior to the Index Procedure / Rescheduled Index Procedure do not preclude enrollment once resolved, including but not limited to the presence of left atrial thrombus, noncompliant pre-procedural systemic anticoagulation, COVID-19, risk of unplanned pregnancy or the presence of an active implantable loop recorder other than LUX-Dx.

Table 5.3-1: Exclusion Criteria

Exclusion Category	Exclusion Definition
1. Atrial exclusions – Any of the following atrial conditions:	
a. Atrial size	Left atrial anteroposterior diameter ≥ 5.5 cm. If LA diameter is <u>not</u> available, non-indexed volume >100 ml (by MRI, CT or TTE report or physician note).
b. Prior atrial ablation	Any prior atrial endocardial, epicardial or surgical ablation procedure for arrhythmia, other than ablation for right sided SVT
c. Atrial myxoma	Current atrial myxoma
d. Pulmonary veins	Any PV abnormality, stenosis, or stenting (common and middle PVs are admissible)
e. Atrial thrombus	Current left atrial thrombus
2. Cardiovascular exclusions – Any of the following CV conditions:	
a. Ventricular arrhythmia	History of sustained ventricular tachycardia or any ventricular fibrillation
b. Secondary AF	AF that is secondary to electrolyte imbalance, thyroid disease, alcohol, or other reversible / non-cardiac causes

[2] All AADs previously failed for ineffectiveness or intolerance ("Failed AADs"), as well as those deemed contraindicated, must be recorded. For Failed AADs, the maximum daily dose associated with effectiveness or intolerance failure must also be recorded. See **Sections 7.4 Antiarrhythmic Drugs,** and **23.2 Definitions**.

Exclusion Category	Exclusion Definition
c. Cardiac devices and implants	Current or anticipated pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices, interatrial baffle, closure device, patch, or patent foramen ovale occluder, LA appendage closure, device or occlusion, any insertable cardiac monitor other than LUX-Dx
d. Clinically significant valvular disease	Valvular disease that is any of the following: . Symptomatic i. Causing or exacerbating congestive heart failure ii. Associated with abnormal LV function or hemodynamic measurements
e. Cardiomyopathy	Hypertrophic cardiomyopathy
f. Valve prostheses	Any prosthetic heart valve, ring or repair including balloon aortic valvuloplasty
g. Access issues	Any IVC filter, known inability to obtain vascular access or other contraindication to femoral access
h. Rheumatic disease	Rheumatic heart disease
i. Anticipated cardiac surgery	Awaiting cardiac transplantation or other cardiac surgery within the next 12 months
j. Nitroglycerin intolerance	Known adverse drug reaction to nitroglycerin[3]
k. Coronary disease	Known severe non-revascularizable coronary disease
l. Stents	Pre-existing right coronary artery stent
3. Any of the following conditions <u>at baseline</u> (**Section 7.5**):	
a. Heart failure NYHA	Heart failure associated with NYHA Class III or IV
b. Ejection fraction	LVEF < 40%
c. Uncontrolled hypertension	Uncontrolled hypertension (SBP > 160 mmHg or DBP > 95 mmHg on two (2) BP measurements at baseline assessment
d. Ventricular dysfunction	Right ventricular dysfunction
4. Any of the following events <u>within 90 Days of the Consent Date</u>:	
a. Coronary disease	Myocardial infarction (MI), unstable or Prinzmetal angina or coronary intervention
b. Cardiac surgery	Any cardiac surgery
c. Heart failure hospitalization	Heart failure hospitalization
d. Pericardium	Pericarditis or symptomatic pericardial effusion
e. GI bleeding	Gastrointestinal bleeding
f. Neurovascular event	Stroke, TIA, or intracranial bleeding
g. Thromboembolism	Any non-neurologic thromboembolic event

[3] Excluding hypotension which is a known physiological response

Exclusion Category	Exclusion Definition
h. Carotid intervention	Carotid stenting or endarterectomy
5. Bleeding diathesis	Thrombocytosis, thrombocytopenia, disorder of blood clotting or bleeding diathesis
6. Contraindication to anticoagulation	Contraindication to, or unwillingness to use, systemic anticoagulation
7. Pre-ablation anticoagulation	Patients who have not been on anticoagulation therapy for at least 4 weeks prior to the ablation procedure
8. Pregnancy	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
9. Health conditions that in the investigator's medical opinion 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. Obesity	Body Mass Index (BMI) > 42.0
b. Transplantation	Solid organ or hematologic transplant, or currently being evaluated for a transplant
c. Diaphragmatic abnormality	Any prior history or current evidence of hemi-diaphragmatic paralysis or paresis
d. Pulmonary	• Severe pulmonary hypertension (at Baseline Assessment) • Severe lung disease • Any lung disease involving abnormal blood gases or requiring supplemental oxygen
e. Renal	Renal insufficiency if an estimated glomerular filtration rate (eGFR) is < 30 mL / min / 1.73 m^2, or with any history of renal dialysis or renal transplant
f. Malignancy	Active malignancy or history of treated malignancy within 24 months of enrollment (other than cutaneous basal cell or squamous cell carcinoma)
g. Gastrointestinal	Clinically significant gastrointestinal problems involving the esophagus or stomach including severe or erosive esophagitis, uncontrolled gastric reflux, gastroparesis, esophageal candidiasis or active gastroduodenal ulceration

Exclusion Category	Exclusion Definition
h. Infections	Active systemic infection
i. COVID-19 disease	iv. Current confirmed, active COVID-19 disease v. Current positive test for SARS-CoV-2 vi. Confirmed COVID-19 disease not clinically resolved at least 3 months prior to the Consent Date[4]
j. Diabetes	Uncontrolled diabetes mellitus or a recorded HgbA1c > 8.0% in the 90 days prior to the Consent Date
k. Sleep apnea	Untreated diagnosed obstructive sleep apnea with apnea hypopnea index classification of severe (>30 pauses per hour)
l. Medication Use	Required use of phosphodiesterase inhibitors within 24 hours of the ablation procedure
10. Life expectancy	Predicted life expectancy less than one (1) year
11. Participation in another trial	Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments; each instance must be brought to the attention of the Sponsor to determine eligibility
12. Any of the following congenital conditions:	
a. Congenital heart disease	Congenital heart disease with any clinically significant residual anatomic or conduction abnormality
b. Methemoglobinemia	History of known congenital methemoglobinemia
c. G6PD deficiency	History of known G6PD deficiency
13. Contraindication to ICM insertion	Patients who cannot tolerate a subcutaneous, chronically-inserted LUX-Dx device
14. LUX-Dx longevity	Patients with a LUX-Dx device inserted > 6 months prior to enrollment or an estimated longevity of less than 1 year

6 Subject Enrollment and Accountability

The subject enrollment and accountability sections of Phase 2 of the ADVANTAGE AF study remain the same as Phase 1 and can be referenced in **Section 6** of the Phase 1 clinical investigational plan.

As the LUX-Dx device is not considered an investigational device, if a subject enrolled in the study receives a LUX-Dx device and then withdraws from the study prior to having the FARAPULSE investigational devices inserted into the body, the subject will be classified as an Intent or Consent Ineligible subject (Refer to Phase 1 protocol **Section 6.6.3**).

[4] Clinical resolution of COVID-19 disease is to be determined by the investigator, based on signs and symptoms of current active viral infection, not long-term sequelae of the disease such as anosmia or chronic fatigue.

7 Study Methods

7.1 Overview of Study Interactions

Each Treatment subject will undergo the following formal study interactions:

- Baseline Assessment
- LUX-Dx Insertion (Enrollment to Day 7 post Index Procedure, highly recommended to occur 30 days prior to Index Procedure)
- Index Procedure / Rescheduled Index Procedure (Day 0)
- Pre-Discharge Assessment (immediately prior to discharge after the Index Procedure)
- Day 7 Safety Assessment (window Day 7 – 11, remote)
- Day 30 Safety Assessment (window Day 30-37, remote)
- Day 90 Assessment (window 90 ± 14 days, in-person)
- Day 180 Assessment (window 180 ± 30 days, remote)
- Day 360 Assessment (window 360 ± 30 days, in-person)

In addition, the following events may also occur for some study subjects:

- Re-ablation Procedure: Re-ablations for AF, AFL and AT will be captured in the EDC database using the Re-Ablation Procedure CRF
- Unscheduled Assessments: Any unscheduled cardiovascular assessments will be captured in the EDC database using the Unscheduled Assessment CRF.

The data collection schedule for these various interactions is shown in **Table 7.2-1**.

7.2 Data Collection Schedule

Table 7.2-1: Data Collection Schedule

Assessment	Screen / Baseline[1] (In-person)	Index Procedure Day 0 (In-person)	Pre-Discharge (In-person)	Day 7 (7-11 days) (Remote[2])	Day 30 (30-37 days) (Remote[2])	Re-Ablation within Blanking[10] (In-person)	Day 90 (90 ± 14 days) (In-person)	Day 180 (180 ± 30 days) (Remote[2])	Day 360 (360 ± 30 days) (In-person)	Unscheduled CV (In-person / Remote[2])
Informed consent, eligibility, baseline assessments (incl. NYHA Class)	X[3]	--	--	--	--	--	--	--	--	--
Laboratory testing[4]	X	--	X	--	--		--	--	--	--
AAD and anticoagulant medications	X	--	X	X	X	X	X	X	X	X
Recurrent arrhythmia, cardioversions, ablations, hospital admissions	--	--	X	X	X	X	X	X	X	X
12-lead ECG	X	X[12] (x2)	X[12]	--	--	X	X	--	X	X
Transthoracic echo (TTE)	X[5]	--	X[11]	--	--	--	--	--	--	--
Cardiac CT / MRI	X[6]	--	--	--	--	X[6]	X[6]	--	X[6]	X[6]
Ablation procedure data	--	X	--	--	--	X	--	--	--	--
LUX-Dx Insertion	X[13]				--	--	--	--	--	--
Radiologic examination of diaphragm	--	X	--	--	--	X	X[8]	--	X[8]	--
EQ-5D-3L & AFEQT assessments	X	--	--	--	--	--	--	X	X	--
Pre- / post-NIHSS	X	--	X	--	--	X	--	--	--	--
Neuro assessment	--	--	X[9]	--	--	X[9]	--	--	--	--
Adverse events	--	X	X	X	X	X	X	X	X	X

[1] Baseline Assessments must be generated in the window beginning 30 days (within 180 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 7.5**.
[4] Laboratory tests include hematocrit, hemoglobin, electrolytes, blood urea nitrogen, creatinine and if applicable a pregnancy test at baseline, or for the Index or Re-ablation procedure (if baseline pregnancy test done more than 30 days prior to Index Procedure/re-scheduled procedure)
[5] Within 180 days of Consent Date. Must include baseline ventricular wall motion.
[6] MRI / CT cardiac imaging at baseline within 180 days of Consent Date; subsequently only if required if there is a clinical suspicion of PV stenosis
[7] Performed within 48 hours prior to (TEE or CT) or at the procedure prior to transeptal puncture (TEE or ICE).
[8] Only if resolution of phrenic nerve palsy has not yet been demonstrated.
[9] 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 DW-MRI scan.
[10] Re-ablation post-Blanking Period procedure data collection will only include adverse events, gaps identified and ablated and number of applications required
[11] Required post-ablation for FARAPOINT subjects with ischemic changes on their post-ablation 12-lead ECG only
[12] Including one pre- and one post-ablation. If the post-ablation 12-lead ECG indicates any changes, an additional 12-lead ECG is required prior to hospital discharge.
[13] Required insertion between enrollment and up to 7 days after the Index/Rescheduled Index Procedure; highly recommended to occur 30 days prior to Index Procedure

7.3 Anticoagulation

Anticoagulation regimen is consistent with Phase 1 of the ADVANTAGE AF Study. Anticoagulation will be guided by the 2017 Heart Rhythm Society Expert Consensus Statement[20] and the 2019 American Heart Association / American College of Cardiology / Heart Rhythm Society Focused Update[21] relating to this issue.

With the exception of substantial compliance with 4 weeks of anticoagulation prior to the Index / Rescheduled Index Procedure (**Section 7.7.3**), adjustments in anticoagulation therapy 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.
- DOACs 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 4 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 DOAC should have either uninterrupted treatment (if receiving rivaroxaban) or a single dose interruption in DOAC with a restart shortly after the procedure, at Investigator discretion.
- A heparin bolus will be delivered prior to or immediately following transseptal puncture according to institutional standard of care. Procedural activated clotting times (ACTs) will be sampled regularly throughout the procedure according to institutional standard of care and maintained at a minimum of 300 seconds at least until all devices are withdrawn from the left atrium.

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 guidelines referenced in this section.

7.4 Antiarrhythmic Drugs

Use of Class I / III AADs during the ADVANTAGE AF Study must be managed carefully.

The terms "Antiarrhythmic Drugs, Class I and III", "Blanking Period", "Failed AAD" and "Non-Failed AAD" are defined specifically in **Section 23.2**.

Failed AADs

At the Baseline Assessment, **Section 7.5**, all Class I and III AADs previously used by the subject must be defined as Failed AADs or Non-Failed AADs in the CRF, including for any Failed AADs the maximum failed dose (see **Section 23.2**).

Amiodarone

- May not be used after the Blanking Period or the subject becomes a Treatment Failure.
- If subjects are prescribed Amiodarone, treatment must be stopped by the Day 30 Assessment.

Managing AADs During the Blanking Period

During the Blanking Period the subject should be assessed for AAD continuation. Titration of Class I / III AADs is allowed during the Blanking Period.

To account for the hard cutoff of the Blanking Period at 90 days and given the permitted visit window for the Day 90 Assessment (90 ± 14 days), AADs that are taken during the Blanking Period but are stopped at the time of a within-window Day 90 visit (up to and including Day 104) will not be counted as potential Treatment Failures to allow the necessary physician evaluation.

Managing AADs After the Blanking Period

If indicated, subjects may remain on Class I / III AADs following the Blanking Period, preferably those established as Failed AADs (see **Section 23.2**) at or below the maximum failed dose so as not to create a post-Blanking Period Treatment Failure.

Use of a Non-Failed AAD after the Day 90 Assessment constitutes a Treatment Failure for the primary effectiveness endpoint.

AAD Monitoring

At all subsequent follow-up assessments, subject compliance with, and changes in drugs and daily doses for any Class I / III AAD, will be elicited and recorded.

7.5 Baseline Assessment

Type of Assessment: In-person at investigational site
The completion of the Baseline Assessment requires an in-person assessment. 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 but is not limited to:

- Demographics including gender, height, and weight, race and ethnicity, in accordance with local requirements[5]
- Pertinent medical and cardiovascular history
- AAD history to establish Failed AAD and Non-Failed AAD status
- 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 according to investigation site requirements. The following information is not required if it is not a site requirement, but if available the data should be recorded:
    - A negative PCR for SARS-CoV-2 virus or equivalent testing, or
    - Confirmation of vaccination with a commercially available vaccine

[5] With a goal of achieving an unbiased estimate of treatment effect in the general population, Boston Scientific seeks to enroll a diverse population including representative proportions of relevant age, racial, and ethnic subgroups, which are consistent with the intended use population of the device. Case Report Forms will collect data on age, race and ethnicity in order to achieve this goal, in accordance with local regulations.

- 12-lead ECG
- Imaging (within the window beginning 180 days prior to the Consent Date and ending on the date of the Index Procedure)
  - TTE or Cardiac CT/ MRI for LA dimensions
  - TTE for LVEF and ventricular wall motion
  - Cardiac CT or MRI establishing cardiac anatomy for mapping and PV dimensions
- NYHA Classification
- National Institutes of Health Stroke Scale (NIHSS) score by NIHSS-certified site personnel
- CHA_2DS_2-VASc score
- Quality of Life Measures:
  - The 3-level EuroQol standardized questionnaire of health states (EQ-5D-3L)
  - The Atrial Fibrillation Effect on QualiTy-of-Life Questionnaire (AFEQT) quality of life assessments
- Only if available, coronary anatomy characterization based on data obtained from previous heart catheterization or CT angiography: left-dominant, right dominant or co-dominant.

7.6 LUX-Dx Insertion

A LUX-Dx is required for post ablation rhythm monitoring for all Roll-In and Treatment Subjects. As described in the **Section 5**, subjects with an active LUX-Dx inserted within 6 months of enrollment or an estimated one year or greater of battery life may be considered for participation in ADVANTAGE AF Phase 2. For those subjects enrolled without a pre-existing LUX-Dx ICM, the LUX-Dx insertion must occur after enrollment and within seven (7) days post Index Procedure/Rescheduled Index Procedure. It is highly recommended for the LUX-Dx to be inserted 30 days prior to the Index Procedure to allow collection of baseline arrhythmia assessment. The LUX-Dx insertion shall be performed according to the recommended insertion technique described in the LUX-Dx ICM User's Manual. The study site will collect data associated with the procedure, including printing the LATITUDE Clarity programming report. Subjects enrolled with an active LUX-Dx implanted prior to enrollment in the study must have LUX-Dx programming settings updated, if necessary, in accordance with the initial programming described directly below, and a LATITUDE Clarity programming report printed to document the ICM settings. Enrollment in LATITUDE Clarity can be performed prior to, during, or immediately after the insertion procedure. Subjects should be shown how to use their myLUX patient application to complete manual transmissions when experiencing symptoms, and reminded of the importance to remain connected to the LATITUDE Clarity system throughout the duration of the trial. Subjects who become disconnected from the LATITUDE Clarity system for greater than 7 days should be contacted and notified to reconnect and remain connected through their MyLUX Mobile Patient Device/App.

Initial programming of the LUX-Dx device aligns with all detection algorithm nominal parameters as defined in Table 7.6-1 for Post AF Ablation as the reason for monitoring[6], in addition to those parameters listed in **Table 7.6-1** below.

[6]The LATITUDE Clarity Alert Settings are associated with the Post AF Ablation reason for management settings with exception of turning on the Alert for AT Events – which is not a nominal setting for "Post AF Ablation" reason for monitoring).

Table 7.6-1: LUX-Dx Initial Parameter Settings

Parameter	Post AF Ablation Setting	Latitude Clarity Alert Setting
AF Detection	On	Alert for AF Event – On Yellow Alert
AF Response	More	
AF Duration	4 min	
Pause Response	Less	Alert for AF Event – On Yellow Alert
Tachy Response	Less	Alert for Tachy Events – On Red Alert
AT Detection	On	Alert for AT Events – On Yellow Alert
AT Duration	4 hours at 110 bpm	

Any programming outside of these nominal parameters prior to a confirmed recurrence of Detectable AF, AT or AFL must be entered into the EDC and justification provided.

7.7 Index Procedure / Rescheduled Index Procedure

7.7.1 Index Procedure / Rescheduled Index Procedure Data Collection

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 assessment. The Index Procedure / Rescheduled Index Procedure must be deferred if this is not possible.

Procedural data will be collected including but not limited to:

- The results of transesophageal echocardiography (TEE) or volumetric CT within 48 hours prior to procedure, or intracardiac echocardiography (ICE) prior to transseptal puncture, utilized for exclusion of LA thrombus.
- Pregnancy test (all women of childbearing potential if the baseline pregnancy test was obtained more than 30 days prior to the Index Procedure / Rescheduled Index Procedure)
- Documentation of PVI for each attempted vein, of PWI, and if performed, of CTI BDB
- Post-ablation electroanatomical maps, if performed with Rhythmia
- The functional status of both phrenic nerves will be assessed radiographically pre and post ablation.
- Method of sedation or anesthesia
- Whether adenosine was used to confirm PVI and / or PWI
- Whether a post-procedure cardioversion was performed
- Adverse events
- For the 3D mapping system: Manufacturer and model, when applicable
- 12-lead ECGs pre- and post-ablation
- Procedural times
- Ablation data

- Procedural anticoagulation data:
  - For subjects on a DOAC whether DOAC therapy was interrupted for procedure
  - For subjects on warfarin, a pre-ablation international normalized ratio (INR) value
  - Procedural heparin administration and timing
- Device deficiencies and malfunctions

7.7.2 Index Procedure Workflow

This section contains important information regarding the procedures for cardiac ablation specified in Phase 2 of the ADVANTAGE AF Study. Investigators and staff should refer to training materials and the IFU documents as applicable per device.

Ablation under this protocol will generally follow the order below. If performed, CTI ablation should be performed after PVI and PWI. However, the Investigator may alter the ablation sequence if necessary for subject welfare.

Unless otherwise directed by Sponsor, at the conclusion of the procedure, all single-use components of the FARAPULSE PFA System should be returned to the Sponsor.

7.7.2.1 Preparation

Subjects must be screened for substantial compliance with 4 weeks of systemic anticoagulation prior to the Index Procedure and, if in the opinion of the Investigator, this condition has not been met, the subject will be rescheduled as defined in **Section7.7.3**.

TEE or volumetric CT 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 before accessing the left atrium, no ablation will be performed, and the subject will be rescheduled as defined in **Section7.7.3**.

Phrenic nerve function will be assessed prior to ablation per Investigator standard of care, preferably by a pre-sedation fluoroscopic sniff test. 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 aseptically under ultrasound guidance.

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

A heparin bolus will be delivered prior to or immediately after transseptal puncture. Procedural ACTs will be monitored according to the investigational site's standard of care and maintained at a minimum of 300 seconds at least until all devices are withdrawn from the left atrium.

Topical anesthetic agents, particularly benzocaine, **must not be used** for the TEE on the same day as the procedure in order to minimize the likelihood of the development of methemoglobinemia due to polypharmacy, in those subjects that will undergo the nitro administration protocol (**Section 7.7.2.5**) during CTI ablation with the FARAPOINT PFA Catheter. Methemoglobinemia is a rare but potentially serious side effect of nitroglycerin, a blood disorder in which there is an abnormal increase in the level of methemoglobin, a form of hemoglobin that cannot carry oxygen effectively.

7.7.2.2 Pulmonary Vein Isolation

Ablation of the PVs will be performed according to the IFU documents and institutional practice.

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

The use of ICE is recommended but not required for Pulsed Field Ablation procedures.

All catheter exchanges should be carefully performed to avoid introducing air bubbles into the FARADRIVE Steerable Sheath.

Esophageal temperature monitoring, esophageal cooling and esophageal deviation are unnecessary during PVI and PWI ablation with the FARAWAVE PFA Catheter and should not be utilized.

7.7.2.3 Posterior Wall Isolation

Following PVI ablation, LAPW ablation will be performed according to the IFU documents and institutional practice.

LAPW ablation will be performed in the area below the superior aspect of the superior PVs, above the inferior aspect of the inferior veins, and between the insertions of the left sided and right sided PVs. In the event the PW is found to be electrically isolated following PVI, LAPW ablation will still be performed using the same anatomically guided approach until there is sufficient overlap between PFA application sites. No ablation in other locations, including the left atrial appendage, is permitted.

LAPW ablation should be guided by electroanatomical mapping, ICE and / or fluoroscopy to ensure the entire area of LAPW is ablated with the appropriate amount of overlap between PFA application sites.

All catheter exchanges should be carefully performed to avoid introducing air bubbles into the FARADRIVE Steerable Sheath.

Esophageal temperature monitoring, esophageal cooling and esophageal deviation are unnecessary during PVI and LAPW ablation with the FARAWAVE PFA Catheter and should not be utilized.

7.7.2.4 Assessment of Isolation and Phrenic Nerve Function

Assessment of Isolation

After the completion of the planned PV and LAPW ablations, isolation will be assessed as:

- The isolation of all attempted PVs at least 20 minutes following the last PFA application in each respective vein by entrance block performed with or without adenosine testing, AND
- The isolation of the LAPW at the end of the LAPW ablation, performed with or without adenosine testing, via interrogation by multipolar diagnostic catheter or 3D electroanatomical

mapping. If electroanatomical mapping is used, electrograms demonstrating PWI are required per **Section 7.18**. At the Investigator's discretion, exit block pacing of the PW may be performed to detect any epicardial exit pathways.

Additional PV and LAPW ablation as described above may be performed as needed at any time to achieve complete PVI and PWI. Alternative dosing or fewer applications may be performed as needed for subject welfare, technical difficulties, or anatomical challenges and will not constitute a Treatment Failure if electrical isolation is still confirmed as required. In the event that touch-ups are performed after the initial isolation assessment, further waiting periods are not required.

Assessment of Phrenic Nerve Function

Once all PV and LAPW ablation is completed and isolation is confirmed, the functional status of both phrenic nerves will be assessed per Investigator standard of care (e.g., radiographically either by pacing, fluoroscopy, or a sniff test.[7])

7.7.2.5 CTI Ablation

The following subjects will undergo CTI ablation with the FARAPOINT PFA Catheter:

- Required: For subjects with a history of CTI-mediated (typical) AFL and
  - Who have not had a CTI ablation procedure, or
  - Who have had a CTI ablation procedure but have recurrent CTI conduction.
- Required: Subjects who manifest CTI-mediated AFL (spontaneous or induced) during the Index Procedure
- At Investigator discretion: Subject welfare indicates that CTI ablation should be performed.

CTI Ablation with the FARAPOINT PFA Catheter will be performed according to the IFU documents and institutional practice. Per the FARAPOINT Catheter IFU, no more than two energy applications should be delivered at any given catheter placement. Repeat placement of the FARAPOINT Catheter at nearly identical locations should be avoided unless there is a clear clinical need for such placements.

The FARAWAVE Catheter is **not** allowed to complete any CTI lesion.

CTI ablation with the FARAPOINT PFA Catheter **must** adhere to the following protocol requirements in order to mitigate the risk of coronary spasm during ablation application. No ablations outside CTI with the FARAPOINT PFA Catheter are allowed.

The following prophylactic workflow is required to be followed when CTI ablation is performed with the FARAPOINT PFA Catheter:

- **Pre-Treatment (Required)**: Administer a three milligrams (3mg) nitroglycerin IV bolus via the FARADRIVE sheath (or other sheath with central access) approximately one minute prior to the first PFA application at the anterior position of the CTI line.
- **During Ablation (Required):**

[7] If anesthesia necessitates, a pre-discharge fluoroscopic sniff test or inspiration / expiration CXR may be acceptable. See **Section 7.8**.

- Depending upon procedure duration and patient condition, administer an additional 2mg IV bolus via the FARADRIVE sheath (or other sheath with central access) approximately two (2) minutes apart until the ablation is complete or a maximum total of 9mg IV of nitroglycerin has been administered.
- If bidirectional block (BDB) is assessed and not present and additional ablation lesions are required in the anterior aspect of the cavo-tricuspid isthmus line, Investigator discretion will determine whether to administer an additional 2-3 mg of nitroglycerin IV via the FARADRIVE sheath (or other sheath with central access) prior to re-ablation.

Adjustments to the nitroglycerin dosing protocol defined above are allowed per Investigator discretion based on patient condition, but the rationale for any changes to the defined workflow will be collected. Failure to administer any pre-treatment nitroglycerin will be a protocol deviation.

Vasopressors may be administered per physician discretion given that comorbidities, drug regimens, mode of anesthesia, and baseline blood pressure will vary among subjects.

200 micrograms (µg) of phenylephrine should be administered prior to the first dose of nitroglycerin. If not administered, the rationale will be collected.

Additional vasopressor doses may be administered at the discretion of the physician depending upon the blood pressure response to nitroglycerin. Investigators may choose to administer a different vasopressor depending upon the clinical profile of the subject. All medications administered during the procedure, dose, route and timing of administration in relation to the PFA applications will be recorded.

For those subjects with a known left dominant coronary artery system, as defined by a left heart catheterization or coronary CT angiography, the above prophylactic nitroglycerin workflow is **not required**. The proximity of the catheter to the artery may be directly visualized in real-time via intracardiac echocardiography. Routine hemodynamic monitoring for patients undergoing sedation and cardiac ablation is recommended.

A post-procedure 12-lead ECG will be recorded following CTI ablation to assess absence of ischemia. If the post-procedure ECG shows any ischemic changes, a transthoracic echocardiographic assessment is **required** the same day as the procedure to assess if intraventricular wall motion abnormalities are observed compared to the pre-procedure echocardiographic assessment (Section 7.8).

After CTI ablation is completed, BDB will be assessed, and if necessary, additional applications may be performed until BDB is confirmed. The CTI ablation data will be documented in the CRF.

7.7.2.6 Other Ablations for Atrial-Dependent Arrhythmias

When the Investigator determines that subject welfare requires intervention for either an accessory pathway, AVNRT or spontaneously occurring treatment-emergent AFL or AT, ablation for these arrhythmias may be performed using any commercially available RF ablation catheter. These ablations must not be performed with the FARAPULSE PFA System and should be performed after all ablation with the FARAPULSE PFA System is complete. These permitted ablations and the associated data will be documented in the CRF and do not constitute Persistent AF Acute Procedural Failure. FARAWAVE usage is not allowed to complete any lesion outside of the PVs and LAPW, as described in the IFU.

Ablation for an arrhythmia that is provoked only by catheter manipulation or is only inducible by pacing or pharmacologic stimulation is not permitted.

IMPORTANT: FARAWAVE cannot be used to complete any lesion in the Left Atrium except for the PVs and LAPW, under any circumstances.

FARAWAVE cannot be used in any other location, including the right atrium or either ventricle!

7.7.3 Rescheduled Index Procedure

If, at the Index Procedure, the subject is found to have inadequate pre-procedural anticoagulation, a current atrial thrombus, COVID-19, or other temporarily disqualifying condition, the subject may have their Index Procedure rescheduled not later than 45 days later. The Rescheduled Index Procedure will otherwise follow the data and procedural requirements of **Section 7.7.2**.

The Rescheduled Index Procedure must be scheduled within 45 days of the Index Procedure, and only one Rescheduled Index Procedure may be allowed; otherwise, the subject will be exited from the study as an Intent Subject.

This rescheduling is permissible and does not create an Acute Procedural Failure. The subject remains a potential Treatment Subject.

References to "Index Procedure" in this protocol should be assumed when appropriate to include "Rescheduled Index Procedure" as well if not otherwise specified.

7.8 Pre-Discharge Assessment

Subjects should be prescribed a form of systemic anticoagulation treatment for at least two months following the ablation procedure. See **Section 7.3** regarding post-ablation anticoagulation requirements.

Type of Assessment: In-person at investigational site

Prior to hospital discharge, study data will be collected including but not limited to:

- Adverse events
- Hematocrit, hemoglobin, electrolytes, BUN, creatinine
- 12-lead ECG to document the subject's rhythm and if any new conduction disturbances are observed.
    - A 12-lead ECG collected at the end of the Index Procedure / Rescheduled Index Procedure after all ablation was complete also fulfills this data collection requirement.
- If the post-ablation ECG collected at the end of the Index Procedure/ Rescheduled Index Procedure showed any new ischemic changes the following are required:
    - An <u>additional</u> 12-lead ECG at Pre-Discharge
    - <u>A transthoracic echocardiographic assessment (TTE)</u>
        - <u>The TTE is required the same day as the procedure to assess if ventricular wall motion abnormalities are observed compared to the pre-procedure echocardiographic assessment.</u>
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs.
- Occurrence, date, indication and outcome of any post-procedure cardioversion(s)
- Phrenic nerve assessment, as only applicable:

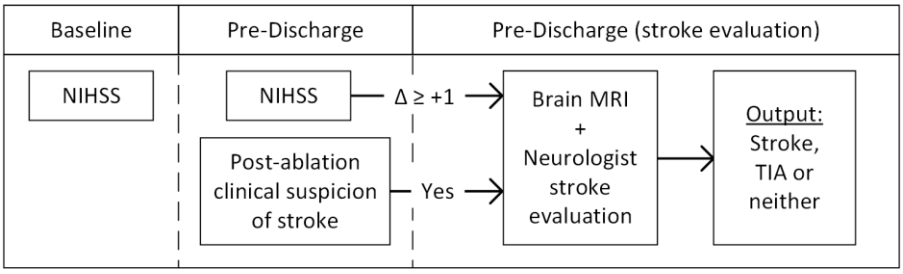
- If the function of both phrenic nerves could not be confirmed at the end of the Index Procedure / Rescheduled Index Procedure, a radiologic examination of the diaphragm (fluoroscopic sniff test or inspiration / expiration CXR)
- If the post-Index Procedure / Rescheduled Index Procedure fluoroscopy indicated diminished phrenic nerve response and resolution has not been previously demonstrated, complete a radiologic examination of the diaphragm

Pre-Discharge Stroke Evaluation:

- NIHSS score by NIHSS-certified site personnel after the effects of anesthesia have fully resolved.
- 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 DW-MRI scan. This assessment will be sufficient to determine with reasonable certainty whether a stroke, TIA or neither have occurred, using the definitions in **Table 3.3-2**. Please refer to **Figure 7-1**.

Figure 7-1: Pre-Discharge Stroke Evaluation



7.9 Day 7 Safety 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. Any subject who continues to be hospitalized at the time of the assessment will have their Day 7 assessment performed in-hospital.

Study data will be collected by interview, including but not limited to:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs.

- Recurrent arrhythmia, cardioversions, ablations, or hospital admissions since discharge
- Site staff will confirm successful LUX-Dx insertion and LATITUDE Clarity transmissions (if available)
- The date and communication method(s) used to collect the data remotely.

7.10 Day 30 Safety Assessment

Type of Assessment: Remote; In-person allowed
Window: Days 30 – Day 37
The Day 30 Assessment is essential to establish the primary safety endpoint and every effort must be made to complete this assessment between Day 30 and Day 37.
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 30, or thereafter.
AAD Treatment: Between the Day 30 Assessment and the Day 90 Assessment – the subject should be assessed for AAD continuation. See Section 7.11.

Discharged subjects will be assessed remotely between Day 30 and Day 37 post-Index Procedure / Rescheduled Index Procedure. Any subject who is hospitalized at the time of the assessment will have their Day 30 assessment performed in-hospital.

Study data will be collected by interview including but not limited to:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs
- Recurrent arrhythmia, cardioversions, ablations, or hospital admissions since 7-day telephonic assessment
- Site staff will confirm ICM programming and successful LATITUDE Clarity transmissions since last assessment
    - Assess for any recurrence of AF/AFL/AT
        - Any reported AFL recurrence will require a 12-lead ECG for ACL adjudication
    - Confirm ICM programming parameters
        - Any programming outside of the defined nominal parameters (Section 7.6) prior to a confirmed recurrence of Detectable AF, AT or AFL must be entered into the EDC and justification provided.
        - ICM may be reprogrammed, as needed, to facilitate appropriate arrhythmia identification and investigator notification after the subject experiences a confirmed recurrence of Detectable AF, AT or AFL.
- The date and communication method(s) used to collect the data remotely
- If the post-Index Procedure / Rescheduled Index Procedure fluoroscopy indicated diminished phrenic nerve response and resolution has not been previously demonstrated, the patient must return for a radiologic examination of the diaphragm between Day 30 and Day 37.

7.11 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 assessment within window: • As much data as possible may be collected remotely. • The absence of a 12-lead ECG during a remote assessment is not a protocol deviation. • If a radiologic 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.

AAD Treatment: During the Blanking Period the subject should be assessed for AAD continuation. At Investigator discretion, Class I / III AADs may be stopped to allow assessment of the subject's potential for off-drug freedom from recurrent AF, AFL, or AT. Subjects who require continued AAD treatment may be continued; preferably with a Failed AAD. Using a Non-Failed AAD or amiodarone would create an unnecessary Treatment Failure.

Subjects will be assessed at Day 90 ± 14 days following the Index Procedure / Rescheduled Index Procedure. Study data will be collected at the Day 90 Assessment including but not limited to:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs
- Recurrent arrhythmia, cardioversions, ablations, or hospital admissions since last assessment
  - Site staff will confirm ICM programming and successful LATITUDE Clarity transmissions since last assessment
    - Assess for any recurrence of AF/AFL/AT
      - Any reported AFL recurrence will require a 12-lead ECG for ACL adjudication
    - Confirm ICM programming parameters
      - Any programming outside of the defined nominal parameters (Section 7.6) prior to a confirmed recurrence of Detectable AF, AT or AFL must be entered into the EDC and justification provided.
      - ICM may be reprogrammed, as needed, to facilitate appropriate arrhythmia identification and investigator notification after the subject experiences a confirmed recurrence of Detectable AF, AT or AFL.
- Cardiac rhythm as determined by a 12-lead ECG at the time of the assessment (in-person assessment only). All 12-lead ECGs for Treatment Subjects will be provided to the Arrhythmia Core Laboratory (ACL).
- If the post-Index Procedure / Rescheduled Index Procedure fluoroscopy indicated diminished phrenic nerve response and resolution has not been previously demonstrated, complete a radiologic examination of the diaphragm
- If there is a clinical suspicion of PV stenosis, a cardiac CT or MRI scan of the same type as the baseline scan to assess the dimensions of the PVs.
- If data is collected remotely, the date, time and communication method(s) used to collect the data remotely.

7.12 Day 180 Assessment

Type of Assessment: Remote; In-person allowed
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 Day 180 ± 30 days following the Index Procedure / Rescheduled Index Procedure. Any subject who is hospitalized or seen in the office as standard of care at the time of the assessment may have their Day 180 assessment performed in-person.

Study data will be collected at the Day 180 Assessment including but not limited to:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs
- Recurrent arrhythmia, cardioversions, ablations, or hospital admissions since last assessment
- Site staff will confirm ICM programming and successful LATITUDE Clarity transmissions since last assessment
    - Assess for any recurrence of AF/AFL/AT
        - Any reported AFL recurrence will require a 12-lead ECG for ACL adjudication
        - If the investigator determines that the subject has experienced the first recurrence after the blanking period of Detectable AF, AFL or AT, upload documentation to EDC
    - Confirm ICM programming parameters
        - Any programming outside of the defined nominal parameters (Section 7.6) prior to a confirmed recurrence of Detectable AF, AT or AFL must be entered into the EDC and justification provided.
        - ICM may be reprogrammed, as needed, to facilitate appropriate arrhythmia identification and investigator notification after the subject experiences a confirmed recurrence of Detectable AF, AT or AFL.
- Quality of Life Measures:
    - The 3-level EuroQol standardized questionnaire of health states (EQ-5D-3L) The Atrial Fibrillation Effect on QualiTy-of-Life Questionnaire (AFEQT) quality of life assessments
- The date, time and communication method(s) used to collect the data remotely.

7.13 Day 360 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.

- If a radiologic 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.

Study data will be collected at the Day 360 Assessment including but not limited to:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs
- Recurrent arrhythmia, cardioversions, ablations, or hospital admissions since last assessment
- Site staff will confirm ICM programming and successful LATITUDE Clarity transmissions since last assessment
    - Assess for any recurrence of AF/AFL/AT
        - Any reported AFL recurrence will require a 12-lead ECG for ACL adjudication
        - If the investigator determines that the subject has experienced the first recurrence after the blanking period of Detectable AF, AFL or AT, upload documentation to EDC
    - Confirm ICM programming parameters
        - Any programming outside of the defined nominal parameters (Section 7.6) prior to a confirmed recurrence of Detectable AF, AT or AFL must be entered into the EDC and justification provided.
        - ICM may be reprogrammed, as needed, to facilitate appropriate arrhythmia identification and investigator notification after the subject experiences a confirmed recurrence of Detectable AF, AT or AFL.
- If the post-Index Procedure / Rescheduled Index Procedure fluoroscopy indicated diminished phrenic nerve response and resolution has not been previously demonstrated, complete a radiologic examination of the diaphragm
- If there is a new clinical suspicion of PV stenosis, a cardiac CT or MRI scan of the same type as the baseline scan to assess the dimensions of the PVs.
- Cardiac rhythm as determined by a 12-lead ECG at the time of the assessment (in-person assessment only). All 12-lead ECGs for Treatment subjects will be provided to the ACL.
- Quality of Life Measures:
    - The 3-level EuroQol standardized questionnaire of health states (EQ-5D-3L)
    - The Atrial Fibrillation Effect on QualiTy-of-Life Questionnaire (AFEQT) quality of life assessments
- 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 Day 360 Assessment a Study Exit CRF will be completed.

7.14 Re-Ablation Procedures

7.14.1 Re-Ablation Procedure within the Blanking Period

For subjects undergoing a first re-ablation procedure within the Blanking Period for Detectable AF, AFL or AT, the procedure will be performed by the investigator under the procedures and data

requirements of **Section 7.7.1**, modified to assess and treat only those locations required, and including the pre- and post-procedure NIHSS.

The FARAPOINT PFA Catheter will not be utilized for any re-ablation procedure. If repeat ablation is required for CTI-mediated flutter, any commercially available BSC RF catheter will be used. Such re-ablation using the methods and devices described in **Section 7.7.1** does not constitute a Treatment Failure.

7.14.2 Other Re-Ablation Procedures

For a second re-ablation during the Blanking Period and for any re-ablation after the Blanking Period, any commercially available ablation catheter will be used for re-ablation.

The FARAPULSE Pulsed Field Ablation System is not permitted to be used for these procedures.

Such re-ablations constitute Treatment Failures, and therefore during such procedures other sites may be ablated at Investigator discretion.

The following data will be collected for these procedures:

- Adverse events
- During re-ablation procedures, a mapping procedure will be performed to characterize the reconnection status for each originally treated PV and the PW (if a left-sided re-ablation), and the CTI, to characterize lesion durability.
- Limited ablation data.

7.15 Unscheduled Assessments

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

Any unscheduled follow-up assessments for cardiovascular events that occur throughout study follow-up will be documented. Study data will be collected including but not limited to:

- Adverse events
- Data regarding the use, changes in or discontinuation of anticoagulation, rate control and / or AADs
- Recurrent arrhythmia, cardioversions, ablations, or hospital admissions since last assessment
- Site staff will confirm ICM programming and successful LATITUDE Clarity transmissions since last assessment
    - Assess for any recurrence of AF/AFL/AT
        - Any reported AFL recurrence will require a 12-lead ECG for ACL adjudication
        - If the investigator determines that the subject has experienced the first recurrence after the blanking period of Detectable AF, AFL or AT, upload documentation to EDC
    - Confirm ICM programming parameters
        - Any programming outside of the defined nominal parameters (Section 7.6) prior to a confirmed recurrence of Detectable AF, AT or AFL must be entered into the EDC and justification provided.

- ICM may be reprogrammed, as needed, to facilitate appropriate arrhythmia identification and investigator notification after the subject experiences a confirmed recurrence of Detectable AF, AT or AFL.

- Cardiac rhythm documentation:
  - At the investigational site: 12-lead ECGs will be collected and provided to the ACL.
  - At another health care site: a record of any ECG should be obtained if available.
  - Remote, not at a health care site: An LUX-Dx manual transmission should be requested.
- If there is a new clinical suspicion of PV stenosis, a cardiac CT or MRI scan of the same type as the baseline scan to assess the dimensions of the PVs.
- If data is collected remotely, the date, time and communication method(s) used to collect the data remotely.

7.16 Unforeseen Circumstances

There may be unforeseen circumstances that occur during the course of the study, such as a natural disaster or a global pandemic (e.g., COVID-19) that prevents a subject from participating in study assessments during the required follow-up window. While every attempt should be made to avoid disruptions in collecting study data, it is important to collect as much data as possible, by any available means and from any available resources. This may include obtaining records from an outside clinic, hospital or other healthcare facility that is not IRB / EC / REB approved.

In the event that study data must be collected remotely, every effort should be made to collect the data within the study assessment window. Critical data collected during the study includes any device or procedure-related adverse events, recurrence of any AF / AT / AFL, and a Cardiac CT or MRI (if PV stenosis is suspected). The LUX-Dx will continue to be used to assess the subjects' heart rhythm. If a Cardiac CT or MRI is required because PV stenosis is suspected, the Cardiac CT or MRI – preferably using the baseline modality – may be performed at another healthcare facility and the window to conduct this test may be extended by up to one month (30 days) following the normal study assessment window.

When such unforeseen circumstances result in a deviation from the requirements of the protocol, the deviations will be distinguished from routine protocol deviations and reported separately.

7.17 Study Completion

Each Roll-In Subject and Treatment Subject will be followed until the Day 360 Assessment. Participation in the study is considered complete upon completion of the Day 360 Assessment. Each Attempt Subject will be followed through the Day 30 Assessment following the Index Procedure / Rescheduled Index Procedure and then exited from the study. In case of premature termination of the study, please refer to **Section 20.1** of the Phase 1 ADVANTAGE AF clinical investigational plan.

Following termination or completion of the study, subjects will be managed according to local institution practice. Sites will need to document and complete the "End of Study" CRF to signify study completion.

7.18 Source Documents

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the

context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in **Table 7.18-1** below.

Table 7.18-1: Source Documentation Requirements

Requirement	Disposition
Screening and enrollment log	Retain at Center
Informed consent documentation process	Retain at Center
Medical history documents pertaining to eligibility criteria	Retain at Center
Documentation of demographics data	Retain at Center
Pregnancy testing, if applicable	Retain at Center
Required laboratory testing	Retain at Center
Cardiovascular / pulmonary examination	Retain at Center
Procedural Medications Administered, AADs, and Anticoagulation Medication Regimen and Changes	Retain at Center
Medical history	Retain at Center
Quality of Life Instruments (AFEQT and EQ-5D-3L)	Retain at Center
NIH Stroke Scale Assessments	Retain original at center and submit copies and copies of all associated source documents if an increase in scale is observed from baseline
If determined necessary, neurological consultation and brain MRI (DW-MRI)	Retain originals at center and submit copies of all source documents and copy of complete scan to BSC
Baseline cardiac imaging and any required follow-up imaging	Retain at Center
LUX-Dx insertion details and arrhythmia recurrence recordings	Retain insertion data at Center and Upload recurrence data to BSC EDC
12-Lead ECGs data including ongoing rhythm	Retain at Center Submit copies of the ECGs collected at Day 90 and Day 360 Follow up, from LUX-Dx detected AFL recurrence, and Unscheduled visits when applicable to the ACL.
Post-ablation electrograms showing entrance block for each treated PV	Retain at Center (Submit to BSC if Rhythmia)
Post-ablation electrogram documentation demonstrating PWI	Retain at Center (Submit to BSC if Rhythmia)
Post-ablation electrograms showing bidirectional isthmus block (CTI ablations only)	Retain at Center (Submit to BSC if Rhythmia)
Recording lab logs, showing PV entrance block, PW isolation and CTI BDB (if applicable)	Retain at Center
Signed Technical Source Form	Retain at Center
Printed EP Lab Procedure Report	Retain at Center

Requirement	Disposition
Adverse Events	Retain at Center, copy may be requested by BSC
In the event of a patient death: • Death narrative • Relevant medical records • Death Certificate • Autopsy report	Submit one copy to BSC, Retain one copy at center
For events adjudicated by CEC: • Relevant medical records	Submit one copy to BSC, Retain one copy at center

7.19 Local Laboratory Documentation

Normal values for the required blood tests for each participating laboratory will be collected for each study site. Appropriate certifications and documentation records are required to be maintained at the site for participating laboratories.

8 Statistical Considerations

8.1 Endpoints

The ADVANTAGE AF Phase 2 Study has endpoints designed to assess the safety and effectiveness of the FARAPULSE PFA System for treatment of drug resistant, symptomatic persistent atrial fibrillation using the FARAWAVE Catheter, and when applicable using the FARAPOINT Catheter for the CTI-mediated atrial flutter as an adjunctive use.

8.1.1 Primary Safety Endpoint

The primary safety endpoint (PSE) is defined in **Section 3.3**.

The expected safety event rate for the PSE has been estimated by performing a meta-analysis on recently completed studies (see **Table 8.1-1**).

The selection of the studies eligible for the meta-analysis for safety was based on the following criteria:

- Prospective studies either single cohort or randomized trials with only large sample size (N>100), high quality, multi-center.
- Patients with PersAF: Studies with PAF or long-standing PersAF were excluded from the analysis. Also, studies with mixed population (i.e., including both PersAF and other forms of AF) were excluded if the safety results were not presented for PersAF subset only.
- Patients undergoing transcatheter ablation of AF, with approved energy source (e.g., radiofrequency, cryoballoon, laser). Studies that included any other concomitant treatment, surgical or trans-catheter (e.g., LAA closure, surgical ablation) were excluded.
- Collection of procedure-related serious adverse events had to be identified as an endpoint in the study (indicated as primary, secondary, or additional in the methods section of the paper, into SSED or supplementary material) and adequately reporting all the components of the safety endpoint were included in the ADVANTAGE AF protocol Phase 2 (i.e.: Death, Myocardial infarction, Stroke, TIA, Peripheral or organ thromboembolism, Pulmonary

edema, Unresolved phrenic nerve palsy / paresis, Vascular access complications , Heart block, Gastric motility / pyloric spasm disorders, Cardiac tamponade / perforation, pericarditis, PV stenosis and Atrio-esophageal fistula). The timeframe of reporting had to be at least 7 days post-procedure (i.e., peri-procedural events).

The analysis included 6 studies: event rates and their 95% confidence intervals were estimated from SSED, primary publications or results disclosed on clinicaltrials.gov and calculated based on the occurrence of the events that constitute the PSE defined in this protocol.

Table 8.1-1: Meta-Analysis to Determine Primary Safety Endpoint Parameters

Study	Design Info.	Technology	Event / Total	Rate (%)	95% CI
PRECEPT Trial	IDE, Prospective, multicenter, PersAF	RF with THERMOCOOL SMARTTOUCH SF catheter (PVI)	18/344	5.23	(3.13, 8.14)
CRYO4PERSISTENT AF	Prospective, multicenter, single arm, PersAF	Arctic Front Advance Cryo (PVI)	4/101	3.96	(1.09, 9.83)
Schmidt et al., 2017	Randomized, multicenter, PersAF	Laser Balloon vs. RF (PVI WACA)	7/134	5.22	(2.13, 10.47)
Wynn et al., 2016, SWAN-PAF	Prospective, multicenter, randomized, PersAF + sustained PAF	PVI vs. PVI + lines	8/124	6.45	(2.83, 12.32)
REAFFIRM Trial	Randomized, PersAF	RF (PVI vs. PVI+ FIRM)	25/350	7.14	(4.68, 10.36)
STOP Persistent AF Trial	IDE Prospective, PersAF	Cryo (PVI)	5/165	3.03	(0.99, 6.93)
*PersAF - Persistent AF, CFS- Contact Force-Sensing, PVI -pulmonary vein isolation					
Overall				**5.41**	**(4.21, 6.75)**
* Overall Rate, 95% CI calculated using a binary random effects model					

All events reported in the meta-analysis had an onset date <30 days after the ablation procedure and will therefore be considered as supportive data for formulation of an endpoint assessment of Day 90.

The overall safety event rate from this meta-analysis is 5.41%. We conservatively chose the expected rate of 6% based on potential unknown factors:

(1) ablation includes both the posterior ablation wall and PVI ablation, a technique not commonly utilized in the studies listed above.

(2) the FARAPULSE PFA System is different from those of listed studies in which either Cryoballoon ablation or RF ablation or other ablation systems were utilized.

The PSE performance goal of 12% was chosen based on the approximate upper limit of each individual study from the above analysis and deemed reasonable with an absolute difference of 6% from the expected rate 6%. The absolute difference is comparable to meaningful clinical difference of 8% used in both IDE single arm trials ((STOP Persistent AF trial[23] with performance goal 13% and (PRECEPT Trial[22] with performance goal 16%).

8.1.1.1 Hypotheses

Let P be the proportion of Treatment Subjects and Attempt Subjects with one or more CSAEs through the Day 90 Assessment and PG be the performance goal, the following hypothesis will be tested in a one-sided test at 0.025 significance level.

- H_0: $P \geq PG$
- H_A: $P < PG$

Where PG = 12%.

8.1.1.2 Sample Size

The sample size estimate was obtained using the binomial exact method. The following assumptions were used in the sample size calculation:

Table 8.1-2: Assumptions for the Primary Safety Endpoint Sample Size Estimate

Assumptions	Primary Safety Endpoint
Expected rate	6%
Performance goal	12%
Attrition	5%
Significance level (one-sided)	0.025
Power	88%
Evaluable subjects	245
Subjects accounting for attrition	258

Under the method and assumption outlined above, the required sample size for this endpoint after attrition is 245, so a minimum of 258 Treatment Subjects are required for the analysis of primary safety endpoint. In addition, all Attempt Subjects will be included in the primary safety endpoint analysis.

8.1.1.3 Statistical Methods

The proportion of Treatment Subjects and Attempt Subjects with one or more CSAEs will be estimated using the Kaplan-Meier method. The 97.5% one-sided upper confidence limit of the observed event rate will be compared to the performance goal of 12%. If the upper confidence limit is less than the performance goal, the null hypothesis will be rejected. The upper confidence limit will be calculated as the pointwise confidence limit using the log-log methodology.

Subjects who withdraw from the study prior to the Day 90 Assessment without experiencing a primary endpoint event will be censored on the date of withdrawal. Subjects who undergo a re-ablation procedure using a commercially available ablation catheter before the Day 90 Assessment without experiencing a primary endpoint event will be censored as of the date of that re-ablation procedure. Subjects who are determined to be Severe COVID-19 Subjects during trial participation without experiencing a primary endpoint event will be censored as of the Onset Date of the condition.

8.1.2 Primary Effectiveness Endpoint

The Primary Effectiveness Endpoint (PEE) is defined in **Section 3.4**. The definition of the PEE remains consistent with the ADVANTAGE AF Phase 1 PEE, apart from the definition of Detectable AF, AFL, or AT (Section 23.2), which has been adjusted for recurrence monitoring using an ICM in place of standard recurrence monitoring methods.

The observed one-year treatment success based on standard non-continuous monitoring methods (12-lead ECG at each follow-up visit, 24-hour Holter every 6 months, regular or scheduled event monitor transmissions, and symptom-driven event monitoring) is expected to be higher than what could be observed from an ICM, given its capability of continuously monitoring the heart rhythm during the entire period of observation. Based on a comparison with data obtained from the CIRCA-DOSE trial which included subjects with paroxysmal AF, it has been estimated that an arrhythmia recurrence assessment based on ECG, Holter monitoring and symptomatic episodes captured from event monitors would lead only to 40.9% sensitivity and 65.3% negative predictive value when compared to an ICM[19].

While the value in implementing continuous arrhythmia monitoring post AF ablation is well accepted, to date no standards are defined for determining one-year treatment success when using ICMs for arrhythmia monitoring, leading to inconsistency in methodology including but not limited to, different episode duration cutoffs, variable ICM programming, and inconsistency in symptom-driven monitoring. The limited number of studies assessing post ablation outcomes with ICM to date report variable one-year arrhythmia recurrence rates ranging from 27% to 64%[22-32]. These studies use different arrhythmia duration criteria (from >30 seconds to 24 hours), different timelines for ICM insertion in respect to ablation procedure, and different endpoint definitions (recurrence vs burden). Accordingly, results obtained from different ablation studies using ICM are heterogeneous and not comparable, so they cannot be analyzed collectively to form a hypothesis for the ADVANTAGE Phase 2 PEE based on continuous monitoring.

Alternatively, non-continuous monitoring will be simulated using ICM data to allow for robust hypothesis generation. Time periods representing bi-monthly event monitor transmissions and 24-hour Holter monitor recordings will be selected and reviewed for LUX-Dx detected AF, AFL, and AT. The duration and frequency of the time periods will mimic the use of event monitors and Holter monitors in ADVANTAGE Phase 1, which is consistent with recommendations set by the 2017 HRS consensus statement on AF ablation for monitoring recurrence in persistent atrial fibrillation patients. 12-lead ECGs will also be used for recurrence monitoring with no change to their contribution to Detectable AF, AFL, or AT compared to Phase 1.

As such, PEE assumptions remain identical to ADVANTAGE Phase 1 (**Table 8.1-3**). Derivation of the expected rate is described in Phase 1 Section 8.1.2.

A PEE performance goal of 40% has been chosen as it preserves the standard provided by the 2017 HRS/EHRA/ECAS Expert Consensus document on the minimum chronic acceptable success rate for persistent AF at 12-month follow-up:[20]

> "*If minimum chronic success rate is selected as an objective effectiveness endpoint for a clinical trial, we recommend that the minimum chronic acceptable success rate for persistent AF at 12-month follow-up is 40%.*"

8.1.2.1 Hypothesis

Let P be the proportion of LUX-Dx monitored Treatment Subjects with Treatment Success through the Day 360 Assessment and PG be the performance goal, the following hypothesis will be tested in a one-sided test at 0.025 significance level.

H0: $P \leqslant PG$

HA: $P > PG$

Where PG = 40%.

8.1.2.2 Sample Size

The sample size estimate was obtained using the binomial exact method. The following assumptions were used:

Table 8.1-3: Assumptions for the Primary Effectiveness Endpoint Sample Size Estimate

Assumptions	Primary Effectiveness Endpoint
Expected rate	55%
Performance goal	40%
Attrition (per year)	10%
Significance level (one-sided)	0.025
Power	90%
Evaluable patients	122
Patients accounting for attrition	136

Under the methods and assumptions outlined above, the required sample size for this endpoint after attrition is 122; therefore, approximately 136 LUX-Dx monitored Treatment Subjects are required for the analysis of the primary effectiveness endpoint.

8.1.2.3 Statistical Methods

The proportion of LUX-Dx monitored Treatment Subjects with PersAF Treatment Success through the Day 360 Assessment will be estimated using the Kaplan Meier method. The 97.5% one-sided lower confidence limit of the observed Treatment Success rate will be compared to the performance goal of 40%. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected The confidence limit will be calculated as the pointwise confidence limit using log-log methodology.

Each LUX-Dx monitored Treatment subject will be classified as Treatment Success (event-free) or Treatment Failure (PEE event). Subjects must have an active LUX-Dx device with established LATITUDE Clarity connection by the end of the effectiveness evaluation period to be included in PEE analysis. Subjects who withdraw or die from the study prior to the Day 360 Assessment, without experiencing a PEE event, will be censored on the date of withdrawal or death. Subjects who are determined to be Severe COVID-19 Subjects during trial participation without experiencing a PEE event will be censored as of the Onset Date of the condition.

LUX-Dx data will be used to simulate intermittent arrhythmia monitoring methods consistent with the methods used in ADVANTAGE AF Phase 1. Bi-monthly (asymptomatic) event monitor transmissions will be simulated by randomly selecting LUX-Dx data from two, 2-minute time windows every 30 days starting on the date of the Day 90 assessment. Each 30-day interval contains 2,592,000 seconds from which 2 seconds will be selected via simple random sampling and used as the starting point for a 2-minute (120 second) window. The first 2-minute window will be removed prior to sampling the second 2-minute window to avoid overlapping windows. The sampling seed will equal the date of the first subject enrollment..

Only 2-minute windows occurring after the blanking period will be used for analysis. Thirty-day intervals will repeat until an interval contains an in-window Day 360 Assessment, Day 390, or subjects' End of Study date, whichever occurs first. In the final 30-day interval, only 2-minute windows occurring on or prior to the in-window Day 360 Assessment, Day 390, or subjects' End of Study date, will be used for analysis. If a 2-minute window occurs on the same day as a scheduled study visit (Day 180 or Day 360 Assessment) or on the same day as the simulated Holter patch, then a new 2-minute window will be randomly selected to avoid overlapping with the 12-lead ECG recording and simulated Holter patch recording.

Twenty-four (24) hour Holter patches will be simulated by selecting LUX-Dx data from the day before the Day 180 and Day 360 Assessments. The day before was selected to avoid overlapping with the 12-Lead ECG recordings from each visit. For subjects that had a missed visit for the Day 180 or Day 360 assessment, the last day of the subject's visit window will be used for the simulated Holter patch.

Recurrence will be defined as a stored LUX-Dx AT or AF episode that is adjudicated as containing at least 30 seconds of atrial arrhythmia and that overlaps a simulated window by any amount. Additionally, all LUX-Dx recorded symptomatic episodes and all 12-lead ECGs will be assessed for AF, AFL, or AT recurrence as defined in Protocol Section 23.2.

8.1.3 Other Endpoints and Assessments

The following analyses will also be performed as defined in the referenced sections using descriptive statistics:

- Additional Safety Endpoints (**Section 3.5.1**)
- Additional Effectiveness Endpoints (**Section 3.5.2**)
- Procedural Assessments (**Section 3.5.3**)
- Quality of Life Assessments (**Section 3.5.4**)

8.2 General Statistical Methods

8.2.1 Analysis Sets

All Attempt and Treatment Subjects will be used for the primary safety endpoint and additional safety endpoint analyses, unless otherwise specified. All LUX-Dx monitored Treatment Subjects will be used for the primary effectiveness endpoint and additional effectiveness endpoint analyses, unless otherwise specified. Subjects who do not receive a LUX-Dx device or do not establish a LATITUDE Clarity connection by the end of the effectiveness evaluation period will not be included in the main effectiveness endpoints. Effectiveness endpoints will be summarized separately for these subjects as binary rates or a listing.

Endpoint data will be summarized separately for Roll-In Subjects. Roll-In Subjects will not be used in the main endpoint analyses.

8.2.2 Control of Systematic Error / Bias

Control and reduction of potential bias associated with a single-arm study design have been addressed by a series of measures including but not limited to:

- Patients meeting the eligibility criteria and signing the ICF will be eligible for sequential enrollment in the study.
- ECG recurrence data for Non-Roll-In Treatment subjects reported by the site from 12-Lead ECGs will be evaluated by a third-party Arrhythmia Core Laboratory according to standardized protocols.
- LUX-Dx episodes will be adjudicated to verify recurrence meeting the definition of Detectable AF, AFL or AT.
- Cardiac MRI / CT images utilized for assessing potential PV stenosis will be evaluated by a third-party Cardiac Imaging Core Laboratory according to standardized protocols.
- The use of a comprehensive set of study procedures as defined in the protocol which ensure consistent patient management.
- Comprehensive site and data monitoring to ensure accurate and complete recording of study data.
- The use of an independent Clinical Events Committee (Phase 1 Protocol **Section 19.2**Error! Reference source not found.) will review and adjudicate all potential SAEs and primary safety outcomes.
- Creation of a complete Clinical Study Report and full dataset to allow scientific and clinical reviewers to independently assess potential error and bias.
- To avoid any center effect and bias, no center will be authorized to enroll more than 33 Treatment Subjects (13% of the total planned enrollment of 258 Treatment Subjects).

8.2.3 Study Success and Control of Type I Error

The Primary Safety Endpoint and Primary Effectiveness Endpoint must pass in order to achieve study success. Both primary endpoints will be tested at a significance level of 2.5% while still maintaining the overall Type I error level at no greater than 2.5%. This follows the methodology of the Intersection-Union Test (IUT).

8.3 Data Analyses

8.3.1 Roll-In Subject Analyses

The stipulated analyses for Roll-In Subjects will be summarized with descriptive statistics. Endpoint data for Roll-In Subjects will be summarized but no hypothesis testing, subgroups, tipping point, or multivariate analyses will be performed. Recurrence data from 12-Lead ECGs for Roll-in subjects will not be evaluated by a third-party. Site assessment of the rhythm found on the 12-Lead ECG will be captured in the EDC system and used to identify recurrence of AF, AFL, or AT for effectiveness endpoint evaluations.

8.3.2 Interim Analyses

No formal interim analyses are planned for the purpose of stopping the study early for declaring success or futility. Analysis of each endpoint will be performed for regulatory submission when all

applicable data for that endpoint has been collected or based on specific geographic requirements[Error! Bookmark not defined.]. The ADVANTAGE AF Study may be used to satisfy the requirements of multiple regulatory bodies. Details on these analyses will be included in the ADVANTAGE AF SAP when available.

8.3.3 Sensitivity Analyses

8.3.3.1 Sensitivity to Missing Data

Tipping point analyses will be performed for the PSE and PEE to evaluate the impact of missing data due to subjects exiting the study prior to the Day 90 Assessment for the PSE or prior to the Day 360 Assessment for the PEE.

8.3.3.2 Sensitivity of Effectivness to Other Ablations in the Left Atrium

The impact of allowing ablation in the left atrium for concomitant arrhythmias (when deemed clinically necessary) without constituting Acute Procedural Failure will be assessed for the PEE. The PEE will be calculated counting subjects who received said ablations (excluding ablation of an accessory pathway or atypical AVNRT) as Treatment Failures.

8.3.3.3 Sensitivity of Effectiveness to Amiodarone Use Post Ablation Procedure

The impact of allowing Amiodarone use to the end of the blanking period without constituting Chronic Treatment Failure will be assessed for the PEE. The PEE will be calculated counting subjects with Amiodarone use beyond 30 days after the Index Ablation Procedure as Treatment Failures.

8.3.3.4 Sensitivity of Effectiveness to the timing of AAD discontinuation

The impact of allowing the use of Non-failed Class I/III AADs and Amiodarone through the Day 90 Assessment (or Day 104 when Day 90 Assessment is completed late or missed) without constituting Chronic Treatment Failure will be assessed for the PEE. The PEE will be calculated counting subjects with any Non-Failed Class I/III AAD or Amiodarone use after the blanking period as Treatment Failures.

8.3.3.5 Sensitivity of Effectness to the timing of Day 360 Assessment

For the PEE, if the Day 360 Assessment is completed late (after Day 390) only events that occurred within window count as Treatment Failures, as described in Appendix A of the ADVANTAGE AF SAP. In this sensitivity analysis, the PEE will be calculated counting events that occur outside of the visit window (after Day 390) as Treatment Failures.

8.3.3.6 Sensitivity of Effectiveness to AT/AFL Detectection Method (Tipping Point Analysis)

A tipping point analysis will be performed for the PEE to assess the impact of using the LUX-Dx AT algorithm with a minimum duration setting of 4 hours to detect AT and AFL events. All Treatment subjects with PEE Success will be one by one considered to have had an undetected AT/AFL event counting as a PEE failure. The number of subjects that would need to have had an undetected AT/AFL event to fail the PEE will be considered the tipping point. The probability of the tipping point occurring will be calculated based on the rate of PEE Failures observed in ADVANTAGE AF Phase 1 that were due to AT or AFL recurrence recorded by Holter or Event Monitor with no other mode of failure. Additional details for this analysis will be included in the Statistical Analysis Plan.

8.3.3.7 Sensitivity of Effectiveness to LUX-Dx S-ECG Storage

The impact of the LUX-Dx S-ECG storage capacity on the determination of Detectable AF, AFL, and AT will be assessed for the PEE. LUX-Dx detected AT and AF episodes or patient-triggered symptomatic episodes without a stored S-ECG will be considered to have confirmed AF, AFL, or AT and included in the determination of Detectable AF, AFL, and AT.

8.3.4 Subgroup Analyses

Analyses will be performed to evaluate whether any significantly different effects exist in the Primary Safety Endpoint or Primary Effectiveness Endpoint within subgroups of subjects. The list of covariates (with applicable subgroups in parentheses) will include at least the following:

- Subject demographics (e.g., age-[e.g. age >=65 vs. <65, Medicare eligible], gender)
- Subject baseline characteristics (e.g., LVEF, cardioversion history, BMI, LA diameter, and years since AF diagnosis)
- Index Procedure lesion sets
  - PV + LAPW ablation alone versus PV + LAPW plus additional ablations
  - CTI ablation versus no CTI ablation
- Operator learning curve (e.g. number of prior procedures completed by operator at time of procedure, counting at a minimum, the procedures from ADVANTAGE AF Phase 1 and Phase 2)
- Mapping of the PW during Index Procedure

Additional covariates for the Primary Effectiveness Endpoint only include:

- Amiodarone use post Index Procedure versus no Amiodarone use post Index Procedure.
- LUX-Dx model (LUX-Dx II+ [M312] vs LUX-Dx [M301] or LUX-Dx II [M302])

Each subgroup covariate will be included as a single independent variable in a logistic regression model with the endpoint outcome as the dependent variable and a test for significance at the 15% level will be performed**.**

In addition to subgroup analyses, descriptive statistics of subject demographic and baseline characteristics will be presented for each subgroup listed in this section.

8.3.5 Center Pooling Analysis

Center-to-center heterogeneity will be assessed for the primary endpoints. Descriptive statistics for each primary endpoint will be presented by site and heterogeneity will be tested with a Chi-square test, treating site as a fixed effect. If sites are not deemed poolable in the initial Chi-square analysis, poolability analysis will be reperformed by treating site as a random effect. A significance level of 15% will be used for each test. Sites with less than five Non Roll-in Treatment and Attempt subjects will be excluded from statistical tests for heterogeneity on the Primary Safety Endpoint, and sites with less than five Non Roll-in, LUX-Dx monitored Treatment subjects will be excluded from tests for heterogeneity on the Primary Effectiveness Endpoint.

8.3.6 Treatment Success Rate by Arrhythmia Detection Method

PersAF Treatment Success rates through Day 360 Assessment will be compared between ADVANTAGE AF Phase 1 and Phase 2 Treatment Subjects to assess differences in chronic success when using the continuous monitoring from an ICM to simulate non-continuous monitoring for recurrence compared to standard assessment based on true Holter monitoring and periodic

transmissions from event monitors. A propensity score analysis utilizing inverse probability of treatment weights (IPTW) will be used to estimate the absolute difference in PersAF Treatment Success rates between detection groups (ICM vs. Standard) while minimizing the effects of confounding variables. Details of this analysis will be included in the Appendix A of the ADVANTAGE AF SAP.

8.3.7 Multivariable Analyses

For the Primary Safety Endpoint and Primary Effectiveness Endpoint, univariable analyses of the following covariates will be performed, and any found to be significantly associated with the outcome at the 0.15 alpha level will be included as covariates in a multivariable regression model. Backward selection with 0.15 alpha level stay criterion will be used to determine the final multivariable model.

The list of baseline covariates includes, but is not necessarily limited to:

- Subject demographics (e.g., age, gender)
- Subject baseline characteristics (e.g., LVEF, cardioversion history, BMI, LA diameter, and years since AF diagnosis)
- Index Procedure lesion sets
    - PVI + LAPW ablation alone versus PVI + LAPW plus additional ablations
    - CTI ablation versus no CTI ablation
- Operator learning curve (e.g., number of prior procedures completed by operator at time of procedure, counting at a minimum, the procedures from ADVANTAGE AF Phase 1 and Phase 2)
- Mapping of the PW during Index Procedure

Additional covariates for the Primary Effectiveness Endpoint only include:

- Amiodarone use post Index Procedure versus no Amiodarone use post Index Procedure
- LUX-Dx model (LUX-Dx II+ [M312] vs LUX-Dx [M301] or LUX-Dx II [M302])

8.3.8 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Phase 2 Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

9 Health Economics Outcomes

A formal health economics analysis may be completed as part of this trial study, given meaningful clinical results are obtained. This will take into consideration complication rates, quality of life, and resource utilization. The EQ-5D-3L, a generic quality of life measure, will be used to assess health utilities. Costs associated with the health care utilization measures may be estimated at all sites. These inputs may be used in health economics analysis performed.

10 Data Management

Data management processes and requirements remain the same as Phase 1 of the ADVANTAGE AF study and can be referenced in **Section 10** of the Phase 1 clinical investigational plan.

11 Core Laboratories and Independent Assessment

11.1 Arrhythmia Core Laboratory

Specified arrhythmic events will be analyzed by an ACL to determine if the episodes are associated with Detectable AF, AFL or AT.

During the ADVANTAGE AF Study, more than one ACL may be utilized to optimize equipment availability, vendor capacity or other factors as determined by BSC. Each vendor utilized will be described in the final study report.

11.1.1 Study ECGs

To ensure objective assessment of rhythm monitoring data, the following 12-lead ECG tracings for Non Roll-in Treatment subjects will be reviewed by the ACL and/or CEC and included as study data:

- ECGs obtained during the following assessments: Day 90 and Day 360
- ECGs submitted during monitoring and adjudication of adverse events
- ECGs submitted during the evaluation of potential arrhythmias during the effectiveness evaluation period.

11.2 LUX-Dx Recordings

Atrial arrhythmia episodes (asymptomatic and symptomatic) captured by the LUX-Dx ICM will be analyzed by BeatLogic Core Lab Adjudicator Tool for atrial arrhythmia rhythm determination, including episodes captured by LUX-Dx during the pre-defined time periods for the Primary Effectiveness Endpoint. Specified arrhythmic events recorded by LUX-Dx ICM may additionally be analyzed by independent experts for rhythm determination. The ADVANTAGE AF Phase 2 Statistical Analysis Plan will define the formal process for adjudication of recurrence episodes collected by LUX-Dx for the study for endpoint analyses.

11.3 Cardiac Imaging Core Laboratory

A qualified CICL will be established to receive, review, and assess any cardiac MRIs and CTs obtained for the evaluation of potential PV stenosis.

Baseline cardiac MRIs and CTs will only be read by the CICL if subsequent events result in follow-up imaging for the assessment of potential PV stenosis.

Pulmonary Vein Dimensions

Treated veins to be assessed will have the baseline and post-ablation assessments of standardized diameters (See definition of PV Diameter in **Section 23.2**).

Cardiac Imaging Data Review and Transmission

The CICL will analyze 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 Sponsor for inclusion in the study dataset.

12 Deviations

Deviation requirements remain the same as Phase 1 of the ADVANTAGE AF study and can be found in **Section 12** of the Phase 1 clinical investigational plan.

13 Device Accountability

13.1 Investigationally Labeled Test Devices

Table 13.1-1 below shows a list of FARAPULSE PFA System components for which device accountability is required by the investigational site.

Table 13.1-1 : Device Accountability for the FARAPULSE PFA System

Component	Subcomponents
FARAWAVE PFA Catheter	1. FARAWAVE Pulsed Field Ablation Catheters (31mm and 35mm) 2. FARASTAR Catheter Connection Cable
FARAPOINT PFA Catheter	1. FARAPOINT Pulsed Field Ablation Catheters
FARASTAR PFA Generator and Related Equipment	1. FARASTAR Pulsed Field Ablation Generator 2. FARASTAR Recording System Module 3. FARASTAR Mapping System Module
FARADRIVE Steerable Sheath	FARADRIVE Steerable Sheath

Accountability requirements for investigational, commercially-available devices, and non-medical devices/components remain the same as Phase 1 of the ADVANTAGE AF study and can be referenced in **Section 13** of the Phase 1.

14 Compliance

Compliance requirements remain the same as Phase 1 of the ADVANTAGE AF study and can be referenced in **Section 14** of the Phase 1 clinical investigational plan.

14.1 Institutional Review Board/ Ethics Committee

Consistent with the requirements outlined Section 14.3 of the Phase 1 protocol, the investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC/REB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written IRB/EC/REB and/or regulatory authority approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol which may impact the conduct of the study and patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, will require review and approval by the IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB approved; a determination

will be made regarding whether a new ICF needs to be obtained from subjects who provided consent, using a previously approved ICF.

Annual IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor. any amendment to the protocol which may impact the conduct of the study and patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, will require review and approval by the IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB approved; a determination will be made regarding whether a new ICF needs to be obtained from subjects who provided consent, using a previously approved ICF.

15 Monitoring

Monitoring requirements remain the same as Phase 1 of the ADVANTAGE AF study and can be referenced in **Section 15** of the Phase 1 clinical investigational plan.

16 Potential Risks and Benefits

16.1 Anticipated Adverse Events

Based upon the current literature, prior reports on adverse events with an ablation catheter, and available data on clinical use of the FARAPULSE PFA System, below is an alphabetical list of the possible anticipated adverse events and possible adverse device effects associated with ablation with the FARAPULSE PFA System for the treatment of PersAF and adjunctive ablation of the CTI for isthmus-mediated AFL. The occurrence of any of the listed events could lead to harm, the need for intervention, or prolonged hospitalization for the subject.

These anticipated events may 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. There may also be additional risks which are unknown at this time.

- Access site complications (e.g., hematoma, fistula, pseudo-aneurysm, laceration, bleeding) potentially requiring surgical intervention
- Allergic reaction or fever resulting from contact with catheters or drugs
- Anemia
- Arrhythmia, potentially requiring cardioversion, defibrillation, or rhythm management device
- Arteriovenous fistulah
- 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/impingement potentially requiring endovascular or surgical intervention
- Conduction system injury, either transient or permanent, potentially requiring pacemaker insertion
- Coronary artery or vein injury
- Damage to cardiac structure
- Death
- Esophageal injury, ulcer, or fistula
- Gastric motility / pyloric spasm disorders
- Harmful large muscular contraction
- Heart failure
- 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, and lung).
- Pericardial effusion
- Pericarditis
- Peritonitis
- Phrenic nerve injury with potential paralysis of the diaphragm and breathing impairment
- Pneumomediastinum
- Pneumopericardium
- Pneumoperitoneum
- Pneumothorax
- Procedural delay
- PV injury, perforation, or stenosis
- Respiratory Distress
- 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.
- Vessel obstruction due to thrombus, debris, introduction of gas, or vascular spasm

16.2 Anticipated Adverse Events – LUX-Dx ICM

As part of study participation, subjects must have a commercially available LUX-Dx inserted for arrhythmia monitoring. Potential adverse events related to the insertion of the device are provided in the User's Manual. These risks for subjects pariticpating in the ADVANTAGE AF study do not differ from those subjects with a LUX-Dx ICM insertion not participating in the trial.

16.3 Risks Associated with the Study Device(s)

Benchtop studies, pre-clinical research, feasibility studies, and CE Mark clinical studies have demonstrated that the FARAPULSE PFA System is safe for human use. Potential risks have been evaluated and mitigation strategies have been implemented to reduce potential risks to acceptable levels.

16.4 Risks associated with Participation in the Clinical Study

The investigational aspects related to the use of the FARAPOINT Catheter in the ADVANTAGE AF Phase 2 study may increase the risk of coronary artery spasm. There may also be additional risks which are unknown at this time.

16.5 Possible Interactions with Concomitant Medical Treatments

Anti-arrhythmic and anticoagulant medications included in ADVANTAGE AF procedures are all approved for their indicated uses in the relevant geography. Therefore, there is no foreseen increased risk to subjects for participating in the ADVANTAGE AF Study.

16.6 Risk Minimization Actions

Additional risks may exist. Risks can be minimized through compliance with this protocol, performing procedures in the appropriate hospital environment, ensuring that an interventional cardiologist and cardiac catheterization laboratory are available, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and / or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol. The use of nitroglycerin as described in Section 7.7.2.5 is intended to minimize the risk of harm from vascular spasm related to the investigational use of the FARAPOINT Catheter. Additionally, sites should ensure availability of co-oximetry to perform the diagnosis of methemoglobinemia and methylene blue to potentially treat the condition for subjects undergoing the nitroglycerin workflow when treated with the FARAPOINT PFA Catheter.

16.7 Anticipated Benefits

Subjects may or may not receive any benefit from participating in the ADVANTAGE AF Study as compared to the current standard of care received for treatment of PersAF. Potential benefits of the FARAPULSE PFA System for the subject may include the following:

- Complete or partial reduction in symptoms related to PersAF
- Complete or partial reduction in the number of cardioversions, medications a subject is taking, and in the number of hospitalizations related to PersAF
- Treatment using an investigational device which has demonstrated the ability to isolate PVs and the PW 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.

16.8 Risk to Benefit Rationale

Risk management activities, including Hazard Analyses (HA) and Failure Mode Effects Analyses (FMEA), have been performed on the FARAPULSE PFA System and its components to identify and analyze known and foreseeable hazards (in both normal and fault conditions) and reasonably foreseeable sequences or combinations of events that could result from using this product and the risks associated with each hazard. Mitigations have been implemented in the design, processes, and / or labeling and directions for use of the product to reduce the residual risk of each hazard as necessary and practicable. The HA has been reviewed and approved and the remaining risks are acceptable when weighed against the anticipated benefits to the subject.

17 Safety Reporting

Safety, device deficiency, and death reporting requirements and definitions remain the same as Phase 1 of the ADVANTAGE AF study and can be referenced in **Section 17** of the Phase 1 clinical investigational plan.

17.1 Reportable Events by Investigator to BSC

In addition to those events defined in Section 17.1 of the Phase 1 ADVANTAGE AF study, it is the responsibility of the Investigator to assess and report to BSC any event which occurs in any of following categories:

- The occurrence of ST elevation or clinical signs of ischemia or injury for those subjects receiving treatment for CTI-mediated AFL with the FARAPOINT Catheter as a component of the FARAPULSE PFA System.
- All study procedure related events, related to the LUX-Dx ICM insertion procedure.

The start of the FARAPULSE™ Index study procedure is defined as the point in which the investigational device is inserted into the subject's body.

17.2 Investigator Reporting Requirements

In addition to those events defined in Section 17.4 and Table 17.4-1 of Phase 1 of the ADVANTAGE AF study, the following must be reported as described in Table 17.2-1 of Phase 2 of the ADVANTAGE AF study.

Table 17.2-1: Investigator Reporting Requirements

Event Classification	Communication Method	Communication Timeline Pre-Market Studies*
For those subjects receiving treatment for CTI-mediated AFL with the FARAPOINT Catheter as a component of the FARAPULSE PFA System: • Angiography performed with visualization of severe (≥70%) spasm • ST elevation, defined by ST elevation of 2mm in two contiguous leads and adjudicated to be a result of coronary spasm • Cardiac arrest adjudicated to be a result of coronary spasm.	Complete AE eCRF page with all available new and updated information.	• Immediately, but not later than 3 calendar days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• When documentation is available. • Upon request of Sponsor.

17.3 Reporting to Regulatory Authorities / IRBs / ECs / REBs / Investigators

In addition to those events defined in Section 17.6 of Phase 1 of the ADVANTAGE AF study, BSC is responsible for reporting adverse event information to all participating Principal Investigators, IRBs / ECs / REBs and regulatory authorities, as applicable. Sponsor reporting to the FDA will adhere to applicable requirements, including 10 working days following Sponsor awareness for occurrence of ST elevation or clinical signs of ischemia or injury for those subjects receiving treatment for CTI-mediated AFL with the FARAPOINT Catheter as a component of the FARAPULSE PFA System.

18 Informed Consent

Informed consent requirements remain the same as Phase 1 of the ADVANTAGE AF study and can be referenced **Section 18** of the Phase 1 clinical investigational plan.

19 Committees

The safety monitoring operations team, clinical events committee, data monitoring committee and executive steering committee will operate in the same manner for Phase 2 of the ADVANTAGE AF study as defined in Phase 1. Refer to **Section 19** of the Phase 1 clinical investigational plan for additional information.

20 Suspension or Termination

Suspension and termination requirements remain the same as Phase 1 of the ADVANTAGE AF study and can be referenced in **Section 20** of the Phase 1 clinical investigational plan.

21 Study Registration and Results

Study registration and results requirements remain the same as Phase 1 of the ADVANTAGE AF study and can be referenced in **Section 21** of the Phase 1 clinical investigational plan.

22 Reimbursement and Compensation for Subjects

Reimbursement and subject compensation requirements remain the same as Phase 1 of the ADVANTAGE AF study and can be referenced in **Section 22** of the Phase 1 clinical investigational plan.

23 Abbreviations and Definitions

23.1 Abbreviations and Acronyms

Table 23.1-1: Abbreviations and Acronyms

3D	Three dimensional
AAD	Antiarrhythmic drug
ACL	Arrhythmia Core Laboratory
ACT	Activated clotting time
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
BDB	Bidirectional block
BMI	Body Mass Index
BSC	Boston Scientific Corporation (Sponsor)
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)
CT	Computed tomography
CTI	Cavo-tricuspid isthmus
CXR	Chest X-ray
DOAC	Direct oral anticoagulant
DW, DWI	Diffusion weighted, Diffusion weighted image

ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EM	Event monitor (any of several hardware modalities)
EQ-5D-3L	The 3-level EuroQol standardized questionnaire of health states
FDA	Food and Drug Administration
HCP	Health care personnel
HCT	Hematocrit
HGB	Hemoglobin
Holter	Holter monitor
ICE	Intracardiac echocardiography
ICF	Informed consent form
INR	International normalized ratio
IRB / EC / REB	Institutional Review Board / Ethics Committee / Research Ethics Board
IRE	Irreversible electroporation
ITT	Intent(ion)-to-Treat
IVC	Inferior vena cava
LA	Left atrium or left atrial
LAPW	Left atrial posterior wall
LBBB	Left bundle branch block
LTFU	Lost-to-follow-up
MITT	Modified Intent(ion)-to-Treat
MRI	Magnetic resonance imaging
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
PAF	Paroxysmal atrial fibrillation
PersAF	Persistent atrial fibrillation
PFA	Pulsed field ablation
PP	Per Protocol
PV	Pulmonary vein
PVI	Pulmonary vein isolation
PW	Posterior wall
PWI	Posterior wall isolation
RFA	Radiofrequency ablation
SADE	Serious Adverse Device Effect
SAE	Serious adverse event
SOC	Standard of care
TEE	Transesophageal echocardiography
TIA	Transient ischemic attack
TSF	Technical Source Form (see **Section 10.3** of ADVANTAGE AF – Phase 1 protocol)
TTE	Transthoracic echocardiography
UADE	Unanticipated Adverse Device Effect

23.2 Definitions

Protocol terms not otherwise defined in the protocol are defined in **Table 23.2-1**:

Table 23.2-1: Definitions

Term	Definition
AF, AFL, and AT Burden	The proportion of time spent in atrial arrhythmia determined by the ratio of the total duration of LUX-Dx detected AF and AT episodes adjudicated as true AF, AFL, or AT divided by the total follow-up duration less the duration of AF and AT episodes without a stored ECG to analyze. Adjudication of episodes will be described in the Statistical Analysis Plan.
Acute Procedural Success	Defined in **Section 3.4.1**.
Antiarrhythmic Drugs, Class I and III	Class I / III AADs are those pharmaceutical agents approved or used in the relevant jurisdiction for the treatment of cardiac arrhythmia. For the ADVANTAGE AF Study, Class I and III AADs 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 relevant jurisdiction for the treatment of cardiac arrhythmia during the ADVANTAGE AF Study, they will be considered as Class I / III AADs for this protocol.
Attempt Subjects	Attempt Subjects are defined in **Section 6.6.4** of ADVANTAGE Phase 1 protocol.
BeatLogic	The BeatLogic Core Lab Adjudicator Tool (Adjudicator Tool) is a software component (ECG Classification system) of the BodyGuardian Remote Monitoring System (BGRMS; K192732). The BeatLogic software component detects and identifies various rhythms. The Adjudicator Tool applies the BeatLogic software algorithm to ECGs recorded by the LUX-Dx Insertable Cardiac Monitor (ICM) and classifies each episode as atrial arrhythmia or non-atrial arrhythmia.

Term	Definition
Blanking Period	An interval in which recurrent AF, AFL or AT, cardioversion or a first re-ablation do not constitute 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 (Day 0) plus 90 days inclusive • For subjects treated with a Non-Failed AAD during the Blanking Period, a Treatment Failure due to the use of that drug only occurs if there is continued use of that drug following the earlier of either the Day 90 visit or Day 104.
(Persistent AF) Chronic Success	Defined in **Section 3.4.2**.
Composite Serious Adverse Events	Composite Serious Adverse Events are defined in **Section 3.3**.
COVID-19 Related Disruptions	A disruption to any study procedure resulting directly or indirectly from the COVID 19 pandemic, including but not limited to subject illness, study site restrictions and limitations, shipping / manufacturing interruptions, significant changes in regulatory guidance and / or governmental restrictions on travel, association, and the prioritization of healthcare resources.
Dates	• Consent Date: The date a subject signs the ICF. • Exit Date: The date on which a subject's study participation ends. • Onset Date: The date on which a condition or AE begins. • Start Date: Day 0, the date of the Index Procedure or Rescheduled Index Procedure
Day (or Study Day)	A Day is an enumerated day of follow-up that begins on an Enrolled Subject's Start Date (Day 0).

Term	Definition
Detectable AF, AFL, or AT	Detectable AF, AFL or AT is an episode of AF, AFL or AT which: • Is recorded for review on a LUX-Dx ICM and meets any of the following criteria: o Adjudicated symptomatic (patient initiated) recording that contains ⩾ 30 seconds of continuous atrial arrhythmia. o Adjudicated AF or AT episode captured by LUX-Dx that contains at least 30 seconds of atrial arrhythmia and overlaps a simulated bi-monthly, 2 minute event monitor transmission period. o Adjudicated AF or AT episode captured by LUX-Dx that contains at least 30 seconds of atrial arrhythmia and overlaps a simulated 24 hour holter period occurring the day before the Day 180 and Day 360 Assessments (or last day of respective visit window if visit(s) is missed) [8]. • Continuous AF, AFL or AT for the entirety of a 12 lead ECG if the continuous interpretable signal is 10 seconds or longer • Exclusions: o CTI isthmus-dependent AFL if the subject did not have a CTI ablation with the FARAPOINT PFA Catheter o Arrhythmias recorded on other devices, including implantable monitors and consumer wearables, not specified in the ADVANTAGE AF Study procedures
Failed AAD	Failed AADs include any and all Class I / III AAD determined at the time of enrollment to have been failed for effectiveness or intolerance. Failed AADs do not include Class I / III AADs determined at the time of enrollment solely to be contraindicated. Failed AADs must be established as part of the Baseline Assessment for agent, type of failure (arrhythmia recurrence or AAD intolerance) and the maximum failed dose (the total daily dose at which such failure occurred).
Intent Subjects	Intent Subjects are defined in **Section 6.6.3** of the ADVANTAGE Phase 1 Protocol.
Non-Failed AAD	A Non-Failed AAD is: • Any Class I / III AAD not established at the Baseline Assessment as a Failed AAD • Any Failed AAD used after Day 90 at a daily dose exceeding the maximum failed dose established at the Baseline Assessment

[8] Day prior to the Day 180 and Day 360 visits was selected to prevent overlap in the rhythm captured by the visit-required 12-lead ECG.

Term	Definition
Persistent atrial fibrillation	PersAF is defined as continuous AF that is sustained beyond 7 days, but not greater than 12 months duration.
Pulmonary vein dimensions	For the purpose of assessing potential PV stenosis: • 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.
Roll-In Subjects	Roll-In Subjects are defined in **Section 4.1.1**, **Section 4.2** and ADVANTAGE Phase 1 Protocol **Section 6.6.2.**
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.
Source data **Ref: ISO 14155**	All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation This includes source data initially recorded in an electronic format.
Source document **Ref: ISO 14155**	Original or certified copy of printed, optical, or electronic document containing source data, including TSFs.
Treatment Failure	Treatment Failure is the absence of Treatment Success due to one or more protocol-stipulated reasons.
Treatment Subjects	Treatment Subjects are defined in **Section 6.6.5** of the ADVANTAGE Phase 1 Protocol.
Treatment Success	Treatment Success is defined in **Section 3.4**

Term	Definition
Vulnerable Subject **Ref: ISO 14155**	Individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response

24 Bibliography – ADVANTAGE AF Phase 2

1. Josephson M. Atrial Flutter and Fibrillation. In: Clinical Cardiac Electrophysiology: Techniques and Interpretation. Vol 2nd Edition. Melvern, Pennsylvania: Lea & Febiger; 1993:275-311.
2. Cosio FG, Arribas F, Lopez-Gil M, Gonzalez HD. Atrial flutter mapping and ablation II. Radiofrequency ablation of atrial flutter circuits. Pacing Clin Electrophysiol. 1996;19(6):965-975.
3. Da Costa A, Romeyer-Bouchard C, Dauphinot V, et al. Cavotricuspid isthmus angiography predicts atrial flutter ablation efficacy in 281 patients randomized between 8 mm- and externally irrigated-tip catheter. Eur Heart J. 2006;27(15):1833-1840.
4. Perez FJ, Schubert CM, Parvez B, Pathak V, Ellenbogen KA, Wood MA. Long-term outcomes after catheter ablation of cavo-tricuspid isthmus dependent atrial flutter: a meta-analysis. Circ Arrhythm Electrophysiol. 2009;2(4):393-401.
5. Nath S, Mounsey JP, Haines DE, DiMarco JP. Predictors of acute and long-term success after radiofrequency catheter ablation of type 1 atrial flutter. Am J Cardiol. 1995;76(8):604-606.
6. Waldo AL, Feld GK. Inter-relationships of atrial fibrillation and atrial flutter mechanisms and clinical implications. J Am Coll Cardiol. 2008;51(8):779-786.
7. Celikyurt U, Knecht S, Kuehne M, et al. Incidence of new-onset atrial fibrillation after cavotricuspid isthmus ablation for atrial flutter. Europace. 2017;19(11):1776-1780.
8. Brembilla-Perrot B, Girerd N, Sellal JM, et al. Risk of atrial fibrillation after atrial flutter ablation: impact of AF history, gender, and antiarrhythmic drug medication. J Cardiovasc Electrophysiol. 2014;25(8):813-820.
9. Candeias R, Adragcao P, Cavaco D, et al. Atrial fibrillation ablation: importance of cavotricuspid isthmus block. Rev Port Cardiol. 2009;28(10):1031-1040.
10. Moreira W, Timmermans C, Wellens HJ, et al. Can common-type atrial flutter be a sign of an arrhythmogenic substrate in paroxysmal atrial fibrillation? Clinical and ablative consequences in patients with coexistent paroxysmal atrial fibrillation/atrial flutter. Circulation. 2007;116(24):2786-2792.
11. Passman, RS. Monitoring for AF: Identifying the Burden of Atrial Fibrillation and Assessing Post-Ablation. J. Innov Cardiac Rhythm Manage. 2017; 8(1):2575-2582
12. Kim SH, Oh YS, Choi Y, et al. Long-Term Efficacy of Prophylactic Cavotricuspid Isthmus Ablation during Atrial Fibrillation Ablation in Patients Without Typical Atrial Flutter: a Prospective, Multicentre, Randomized Trial. Korean Circ J. 2021;51(1):58-64.

13. Pontoppidan J, Nielsen JC, Poulsen SH, et al. Prophylactic cavotricuspid isthmus block during atrial fibrillation ablation in patients without atrial flutter: a randomised controlled trial. Heart. 2009;95(12):994-999.
14. Shah DC, Sunthorn H, Burri H, Gentil-Baron P. Evaluation of an individualized strategy of cavotricuspid isthmus ablation as an adjunct to atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2007;18(9):926-930.
15. Yamaji H, Higashiya S, Murakami T, et al. Rates of atrial flutter occurrence and cavotricuspid isthmus reconduction after prophylactic isthmus ablation performed during atrial fibrillation ablation: a clinical study, review, and comparison with previous findings. J Interv Card Electrophysiol. 2021.
16. Tohoku S, Fukunaga M, Nagashima M, et al. Clinical impact of eliminating nonpulmonary vein triggers of atrial fibrillation and nonpulmonary vein premature atrial contractions at initial ablation for persistent atrial fibrillation. J Cardiovasc Electrophysiol. 2021;32(2):224-234.
17. BSC. CS1796 Rev A, PersAFOne II Interim Progress Report. 2022.
18. Reddy V. et al. Coronary Arterial Spasm During Pulsed Field Ablation to Treat Atrial Fibrillation. Circulation. 2022 146(24): 1808-1819.
19. Aguilar M. at al. Influence of Monitoring Strategy on Assessment of Ablation Success and Postablation Atrial Fibrillation Burden Assessment: Implications for Practice and Clinical Trial Design. Circulation 2022; 145:21-30.
20. Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Heart Rhythm. 2017;14(10):e275-e444.
21. 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 in Collaboration With the Society of Thoracic Surgeons. Circulation. 2019;140(2):e125-e151.
22. Schiavone,M, Gasperetti A, Montemeralo E., et al. Long-term comparisons of atrial fibrillation ablation outcomes with a cryoballoon or laser-balloon: A propensity-matched analysis based on continuous rhythm monitoring. Hellenic J Cardiol . 2022 May-Jun;65:1-7.
23. Baimbetov AK; Bizahanov K, Jukenova AM, et al. Comparative Effectiveness and Safety of Cryoablation Versus Radiofrequency Ablation Treatments for Persistent Atrial Fibrillation. Am J Cardiol. 2022 Dec 1;184:22-30.
24. Rovaris G, Ciconte G, Schiavone M. et al Second-generation laser balloon ablation for the treatment of atrial fibrillation assessed by continuous rhythm monitoring: the LIGHT-AF study. Europace. 2021 Sep 8;23(9):1380-1390.
25. Gessler N, Willems S, Steven D et al. Supervised Obesity Reduction Trial for AF ablation patients: results from the SORT-AF trial. Europace. 2021 Oct 9;23(10):1548-1558.
26. Dulai R, Sulke N, Furniss S, et al. The effect of second-generation cryoablation without electrical mapping in persistent AF using continuous monitoring. J Interv Card Electrophysiol. 2021 Mar;60(2):175-182.

27. Forkmann M, Schwab C, Edler D, et al. Characteristics of early recurrences detected by continuous cardiac monitoring influencing the long-term outcome after atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2019 Oct;30(10):1886-1893.
28. Wechselberger S, Kronborg M, Huo Y, . Continuous monitoring after atrial fibrillation ablation: the LINQ AF study. Europace. 2018 Nov 1;20(FI_3):f312-f320.
29. Heeger CH, Tscholl V, Salloum O, et al. What is the real recurrence rate after cryoballoon-based pulmonary vein isolation? Lessons from rhythm follow-up based on implanted cardiac devices with continuous atrial monitoring. Heart Rhythm. 2018 Dec;15(12):1844-1850.
30. Dekker LR, Pokushalov E, Sanders P, et al . Continuous Cardiac Monitoring around Atrial Fibrillation Ablation: Insights on Clinical Classifications and End Points. Pacing Clin Electrophysiol. 2016 Aug;39(8):805-13.
31. Andrade J, Chamnpagne J, Deyell MW, et al. Cryoballoon or Radiofrequency Ablation for Atrial Fibrillation Assessed by Continuous Monitoring A Randomized Clinical Trial. Circulation. 2019;140:1779–1788.
32. Andrade J, Wells G , Deyell MW, et al. Cryoablation or Drug Therapy for Initial Treatment of Atrial Fibrillation. N Engl J Med. 2021 Jan 28;384(4):305-315.
33. Andrade J, Deyell MW, et al. Healthcare utilization and quality of life for atrial fibrillation burden: the CIRCA-DOSE study. Eur Heart J. 2023 Mar 1;44(9):765-776.
34. Schiavone, M, Gasperetti A, Montemeralo E., et al. Long-term comparisons of atrial fibrillation ablation outcomes with a cryoballoon or laser-balloon: A propensity-matched analysis based on continuous rhythm monitoring. Hellenic J Cardiol . 2022 May-Jun;65:1-7.
35. Rovaris G, Ciconte G, Schiavone M. et al Second-generation laser balloon ablation for the treatment of atrial fibrillation assessed by continuous rhythm monitoring: the LIGHT-AF study. Europace. 2021 Sep 8;23(9):1380-1390.
36. Gessler N, Willems S, Steven D et al. Supervised Obesity Reduction Trial for AF ablation patients: results from the SORT-AF trial. Europace. 2021 Oct 9;23(10):1548-1558.
37. Dulai R, Sulke N, Furniss S, et al. The effect of second-generation cryoablation without electrical mapping in persistent AF using continuous monitoring. J Interv Card Electrophysiol. 2021 Mar;60(2):175-182.
38. Forkmann M, Schwab C, Edler D, et al. Characteristics of early recurrences detected by continuous cardiac monitoring influencing the long-term outcome after atrial fibrillation ablation. J Cardiovasc Electrophysiol. 2019 Oct;30(10):1886-1893.
39. Wechselberger S, Kronborg M, Huo Y, . Continuous monitoring after atrial fibrillation ablation: the LINQ AF study. Europace. 2018 Nov 1;20(FI_3):f312-f320.
40. Heeger CH, Tscholl V, Salloum O, et al. What is the real recurrence rate after cryoballoon-based pulmonary vein isolation? Lessons from rhythm follow-up based on implanted cardiac devices with continuous atrial monitoring. Heart Rhythm. 2018 Dec;15(12):1844-1850.
41. Poole JE, Bahnson TD, Monahan KH, Johnson G, Rostami H, Silverstein AP, et al. Recurrence of atrial fibrillation after catheter ablation or antiarrhythmic drug therapy in the CABANA trial. J Am Coll Cardiol 2020;75:3105–3118.

42. Worck R, Sorensens SK, Johannessen A et al. Posterior wall isolation in persistent atrial fibrillation. Long-term outcomes of a repeat procedure strategy. J Interv Card Electrophysiol 2023 Jun;66(4):971-979

43. Sirico G, Sirico D, Montisci A et al. Contact-Force Guided Posterior Wall Isolation as an Adjunctive Ablation Strategy for Persistent Atrial Fibrillation. J Atr Fibrillation. 2021 Aug 31;14(2):20200475.

44. O'Neill L, Almorad A, El Haddad M et al. Impact of Catheter Ablation on Arrhythmia Burden in Patients With Shock-Resistant Persistent Atrial Fibrillation. JACC Clin Electrophysiol. 2023 9(10):2071-2081.

45. Verma A, Haines DE, Boersma LV et al. Influence of monitoring and atrial arrhythmia burden on quality of life and health care utilization in patients undergoing pulsed field ablation: A secondary analysis of the PULSED AF trialHeart Rhyhtm 20(9): 1238-1245.

46. Van Gelder IC, Healey JS, Crijins et al. Duration of device-detected subclinical atrial fibrillation and occurrence of stroke in ASSERT. Eur Heart J . 2017, 38(17):1339-1344.

47. Glotzer TV, Daoud EG, Wyse DG, et al. The relationship between daily atrial tachyarrhythmia burden from implantable device diagnostics and stroke risk: the TRENDS study. Circ Arrhythm Electrophysiol. 2009 Oct;2(5):474-80.

Appendix B: ADVANTAGE AF Study - LUX-Dx Sub-Study

ADVANTAGE AF Study LUX-Dx sub-study (Appendix B) may only be implemented by sites who are participating in Phase 2 of the ADVANTAGE AF Study.

APPENDIX B - LUX-Dx Sub-Study

Note: Data from this sub-study will not be required to be included in the standard FDA reports, including s-PMA applications and the ADVANTAGE AF final report.

The elements defined in this sub-study Appendix are intended to be applied and followed in addition to the elements described within APPENDIX A of the ADVANTAGE AF Phase 2 protocol.

Background

Post-ablation assessment of arrhythmia recurrence over time is an important aspect to determine the chronic success of ablation therapy. An insertable cardiac monitor (ICM) is a device able to monitor the heart rhythm over an extended period. The LUX-Dx™ ICM System is inserted subcutaneously to provide long term, continuous monitoring over multiple years. The ICM has the advantage of automatically capturing and transmitting arrhythmia episodes, independent from the patient's symptoms.

The ICM also captures the AF burden for each patient, which is the proportion of time an individual spends in AF during a period (typically expressed as a percentage per day). Additional evidence is needed to determine the relationship of AF burden with AF-related outcomes.

Accordingly, the use of an ICM may identify a novel standard for arrhythmia detection, AF burden quantification, and could be considered the gold standard for clinical trials in the future. Since this is a novel method of assessment in the context of AF ablation trials (in particular, persistent AF), the standards for the determination of a successful treatment in terms of arrhythmia rates and distribution (time to first recurrence, minimal duration, and AF burden) still need to be established in clinical trials. Continuing to collect long-term data on AF, AT, and AFL recurrence with the LUX-Dx device in the ADVANTAGE AF study will provide insights into the long-term effectiveness of ablative intervention of persistent AF with the FARAPULSE PFA System.

Sub-Study Objectives

The objectives of this sub-study are to:

1. Characterize the long-term effectiveness of the FARAPULSE PFA System for treatment of persistent atrial fibrillation as assessed by the LUX-Dx ICM device.
2. Characterize AF burden as determined by the LUX-Dx device.

Subject Selection

Subjects will be selected for the LUX-Dx sub-study based upon their willingness to agree to provide access to their medical record data or medical claims data and LUX-Dx ICM device data following completion of the Day 360 assessment visit in Phase 2 of the ADVANTAGE AF study.

Inclusion Criteria:

1. Subjects enrolled in Phase 2 of the ADVANTAGE AF study with an active LUX-Dx ICM device.

Exclusion Criteria:
None

Sub-Study Procedures

No additional study procedures or follow-up assessments are required for subjects that agree to participate in the LUX-Dx sub-study. The LUX-Dx ICM device will continue to be programmed as defined within the ADVANTAGE AF Phase 2 protocol or as determined most appropriate to assess the subjects' heart condition per physician assessment. Subjects will continue to use their myLUX patient application to complete manual transmissions when experiencing symptoms and remain connected to the LATITUDE Clarity™ system throughout the duration of the trial.

Data Collection and Analysis

Once a LUX-Dx subject completes their Day 360 assessment, they will continue to be remotely monitored via LATITUDE Clarity for up to a total of 3 years (36 months) from the ADVANTAGE AF index ablation procedure. There is no additional data collection that will need to be entered in the study database after the Day 360 assessment.

Subjects will need to maintain connection between their device and the myLUX patient app to ensure continuous arrythmia monitoring. It is recommended that subjects do not stay disconnected for more than two (2) weeks to ensure no data is overwritten.

No additional study procedures or follow-up assessments are required for subjects that agree to participate in the LUX-Dx sub-study, however, participating subject's electronic medical records or health care claims may be reviewed to assess for clinical events associated with ablation efficacy (e.g., cardioversions, re-ablations, hospitalizations).

Adverse events will not be reported through the clinical study database after the subject completes their active participation (i.e., Day 360 assessment visit) in Phase 2 of the

ADVANTAGE AF Study. Adverse events will be reported through normal commercial channels/complaint processes as applicable by sites.

1.1 LUX-Dx Recordings

Recurrence episodes captured by the LUX-Dx ICM may be analyzed by cardiac algorithm for rhythm determination. An independent reviewer may also be used to verify recurrences captured by the LUX-Dx.

1.2 Data Analysis

There are no pre-specified hypotheses for the sub-study objectives. The purpose of the sub-study is to characterize the occurrence of atrial arrhythmia events as well as the overall AF burden experienced by subjects up to a total of three (3) years post-AF ablation for persistent AF using the FARAPULSE PFA System. All subjects enrolled in the sub-study that transmit their LUX-Dx data will be included in the analyses.

Risks and Potential Benefits

1.3 Risks

There are no increased risks as it relates to continued participation in the LUX-Dx sub-study that haven't already been defined within the ADVANTAGE AF Phase 2 protocol and described within the ADVANTAGE AF Phase 2 informed consent form (ICF).

1.4 Potential Benefits

Subjects that agree to participate in the LUX-Dx sub-study may not directly benefit from participating. The information gained from this sub-study may support future improvements in the management of post-atrial fibrillation ablation monitoring.

Reporting and Approval Requirements

Site and subject participation in the LUX-Dx sub-study is optional/not required. Institutional Review Board (IRB) approval of the ADVANTAGE AF Phase 2 LUX-Dx sub-study ICF are required prior to subjects participating in the sub-study and providing continued access to Boston Scientific to their LUX-Dx ICM data via the LATITUDE Clarity system.

There are no additional reporting requirements related to the sub-study from the Investigator or Investigational Site after all subjects complete their Day 360 Assessment per the ADVANTAGE AF Phase 2 protocol.