Medical Device Clinical Trial Protocol

Protocol Number: PF109

A Real-world Study of the FARAPULSE Pulsed Field Ablation System in A Chinese Population with Paroxysmal Atrial Fibrillation

Investigational Device: FARAPULSE™ Pulsed Field Ablation System

Specifications and Models:

Component Name	Model
FARASTAR Pulsed Field Ablation Generator System	
FARASTAR Pulsed Field Ablation Generator	61M401
FARASTAR Recording System Module (RSM)	61M407
FARASTAR Stimulation Module Cable	61M404
FARASTAR EGM Cable	61M405
FARASTAR Stimulation Module Auxiliary Cable	61M408
FARASTAR Cable Set	61M406
FARASTAR Stimulation Module Male Cable	61M409
FARASTAR Stimulation Module Female Cable	61M410
FARASTAR Stimulation Module Y-Cable, Long	61M411
FARASTAR Stimulation Module Y-Cable, Short	61M412
FARASTAR Recording System Module Catheter Pin Cable	61M413
FARASTAR Recording System Module ECG Trunk Cable	61M415
FARASTAR Recording System Module ECG Output Module	61M416
FARASTAR Recording System Module EGM Input Module	61M417
FARAWAVE Pulsed Field Ablation Catheter	
FARAWAVE Pulsed Field Ablation Catheter, 35mm	41M402
FARAWAVE Pulsed Field Ablation Catheter, 31mm	41M401
FARASTAR Catheter Connection Cable	41M404
FARADRIVE Steerable Sheath	21M402

Class III medical device requiring clinical trial: Yes☐ No☒

Protocol version and date: Ver C, June 15th, 2022

Clinical trial site：Boao Super Hospital

Principal Investigator: Chen Minglong

Sponsor: BSC International Medical Trading (Shanghai) Co., Ltd, ("BSC China")

A Real-world Study of the FARAPULSE Pulsed Field Ablation System in A Chinese Population with Paroxysmal Atrial Fibrillation

(REPLACE Study)

PF109

CLINICAL INVESTIGATION PLAN

Sponsored By

BSC International Medical Trading (Shanghai) Co., Ltd, ("BSC China")
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200131

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Vendors/Labs	Vendors/Labs involved in this study may refer to the operating manual

Original Release: November, 18th, 2021

Current Version: June, 15th, 2022

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
Ver A	**November 18th 2021**	**92120219_ Rev/Ver G**	**NA**	**NA**	**Initial Release**
Ver B	**December 22nd 2021**	**92120219_ Rev/Ver G**	**Cover Page**	**Delete "Co-Priciple Investigator: Fang Pihua"**	**Investigator Change**
Ver B	**December 22nd 2021**	**92120219_ Rev/Ver G**	**Table Contact Information**	**Delete "Co-Priciple Investigator(s) Fang Pihua"**	**Investigator Change**
Ver B	**December 22nd 2021**	**92120219_ Rev/Ver G**	**Section 10.1**	**Delete "for PV dimensions"**	**PV dimension may not be present in the cardiac CT report.**
Ver B	**December 22nd 2021**	**92120219_ Rev/Ver G**	**Section 10.4**	**Revise "establishing PV dimensions" to "assessing PV"**	**PV dimension may not be present in the cardiac CT report.**
Ver B	**December 22nd 2021**	**92120219_ Rev/Ver G**	**Section 11.2**	**Revise sequence number**	**Sequence number error**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Throughout**	**To comply updated BSC template Version.**	**Per BSC procedures**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 15.2, Section 18.2, Section 18.3,**	**To comply updated Chinese GCP implemented since May 1st, 2022**	**To comply with updated Chinese GCP**

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			Section 18.6, Section 26		
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Cover page, Section 2. Section 5**	**Delete "FARADRIVE Steerable Sheath (Opaque Shaft)"**	**This model will be halted and will not be used in this study.**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 2, Section 8.3**	**Revise "valve area < 1.5 cm" to "valve area < 1.5 cm2"**	**Typo**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 6.2 Section 11.1 Section 25.2**	**Add supplementary intrudction to AAD withdrew after blanking period**	**Accurate definition**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 8.1**	**Revise "8.4" to "8.3"**	**Typo**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 10.1**	**Delete the "X" represented for Device Deficiency in Baseline visit**	**Typo**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 10.1, Section 10.4**	**The indication for pregnancy test is revised to be females of childbearing potential**	**Safety cosideration**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 10.3**	**Individuals that can sign ICF are revised to be the subject or legal representative competent and/or an authorized designee.**	**To be consistent with context in Section 19.**

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 10.14**	**Delete "IRB"**	**Not appliable**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 11.1, Section 25.2**	**The definition for total procedure time is revised to be from the initiation of interventional venous access puncture to all devices remove from the body.**	**Specify the definition for the total procedure time.**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 12.1**	**Revise "Medidata" to "iMedidata"**	**Typo**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 20.1**	**Add "Safety Monitoring Process" Section"**	**Be consistent with Chinese Version**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 25**	**Add eCRF, GCPand NMPA; Delete IRB and REB**	**Abbreviation Revision**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Section 25.2**	**Revise the definition of Pulmonary edema**	**To be consistent with the definition in Section 6.2.**
Ver C	**June 15th 2022**	**92120219_ Rev/Ver H**	**Throughout**	**Standard the wording for "eCRF" and "EDC system"**	**Accurate terminology**

2. Protocol Synopsis

<table>
<tr><td colspan="2">A Real-world Study of the FARAPULSE Pulsed Field Ablation System in A Chinese Population with Paroxysmal Atrial Fibrillation
(REPLACE Study)</td></tr>
<tr><td>Study Objective</td><td>To observe the safety and effectiveness of the FARAPULSE Pulsed Field Ablation System for treatment of recurrent, symptomatic Paroxysmal Atrial Fibrillation (PAF) in a Chinese population in the real world.</td></tr>
<tr><td>Indication for Use</td><td>FARAPULSE Pulsed Field Ablation System is intended for the isolation of pulmonary veins for the treatment of PAF.</td></tr>
<tr><td>(Commercial) Device/System applied as Standard of Care and sizes, if applicable</td><td>
<table>
<tr><th>Component Name</th><th>Model</th></tr>
<tr><td colspan="2">FARASTAR Pulsed Field Ablation Generator System</td></tr>
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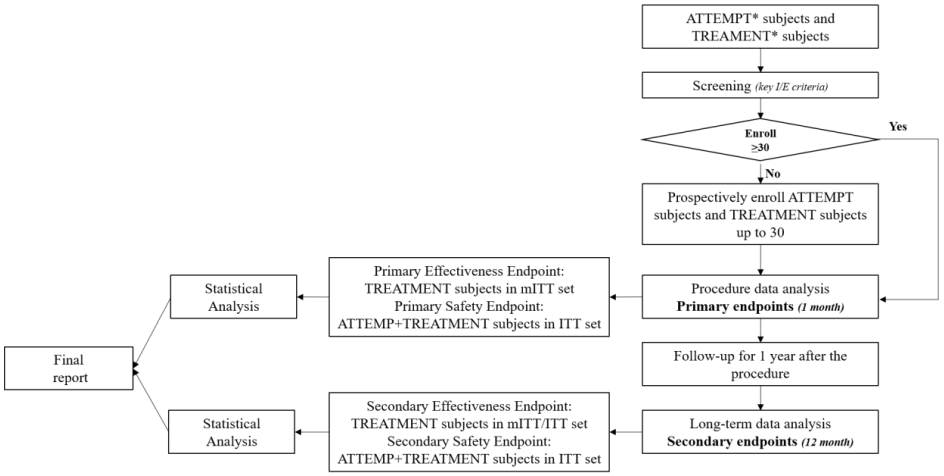
</table>
</td></tr>
<tr><td>Study Design</td><td>This is a retrospective and/or prospective single-center single-arm observational study.</td></tr>
</table>

A Real-world Study of the FARAPULSE Pulsed Field Ablation System in A Chinese Population with Paroxysmal Atrial Fibrillation (REPLACE Study)	
	 ******The definitions of ATTEMPT and TREATMENT refer to Section 9.4* **Figure 7.1-1: REPLACE Study Design**
Planned Number of Subjects	At least 30 ATTEMPT and TREATMENT subjects
Planned Number of Sites / Countries	1 site
Primary Endpoint	**Primary Effectiveness Endpoint:** Acute Procedural Success: Proportion of subjects that achieve electrical isolation* of all pulmonary veins (PVs) using FARAPULSE Pulsed Field Ablation system only. ** Electrical isolation of a PV is recommended to be demonstrated by entrance block after a 20-minute waiting period at least if the subject is enrolled prospectively, otherwise the way to confirm electrical isolation should be recorded, including whether there is a waiting period and its duration. If exit block testing is performed, the PV will only be considered isolated if both entrance and exit block testing was successful.* **Primary Safety Endpoint:** Occurrence of the acute serious procedure-related and/or device-related adverse events at 7 days post index procedure:

A Real-world Study of the FARAPULSE Pulsed Field Ablation System in A Chinese Population with Paroxysmal Atrial Fibrillation (REPLACE Study)	
	• Death • Myocardial infarction • Stroke/ Transient ischemic attack (TIA) • Peripheral or organ thromboembolism • Cardiac tamponade/perforation • Pulmonary edema • Vascular access complications • Heart block* • Gastric motility/pyloric spasm disorders • Pericarditis • Atrial esophageal fistula • Severe PV stenosis • Phrenic nerve palsy **Heart block not attributable to medication effect or vasovagal reaction.*
Secondary Endpoints	**Secondary Effectiveness Endpoints:** 1. Chronic Success: Proportion of subjects that free from effectiveness events defined as failure as below at 12 months post-procedure. Effectiveness events determining a failure are defined as: a) Fail to achieve electrical isolation of all PVs using FARAPULSE Pulsed Field Ablation system only. b) After the Blanking Period (90 days post the procedure) to 12-month after the procedure: • Occurrence of any Detectable atrial fibrillation (AF), atrial flutter (AFL)* or atrial tachycardia (AT) captured by one of the following methods: ≥ 30 seconds in duration recording from 24-hour Holter Monitor or ≥ 10 seconds recording from 12-lead Electrocardiography (ECG); • Any cardioversion for AF, AFL* or AT; • Use of any Class I or Class III antiarrhythmic drugs (AADs) for the treatment of AF, AFL* or AT.

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	c) At any time through 12 months after the procedure: • Re-ablation for AF, AFL* or AT; • Use of amiodarone, except intra-procedurally to control an arrhythmia. 2. Proportion of PVs that achieve electrical isolation by using the FARAPULSE Pulsed Field Ablation System only. 3. Chronic success allowing AADs. **excluding cavotricuspid isthmus (CTI)-dependent flutter confirmed by electrophysiology study* **Secondary Safety Endpoint:** Proportion of subjects that free from primary safety events defined as above through 7 days after the procedure and free from the following serious procedure-related and/or device-related adverse events at any time through the completion of 12-month follow-up visit. • Atrial esophageal fistula • Severe PV stenosis • Persistent phrenic nerve palsy* **The study will collect information on phrenic nerve palsy observed before the end of the index procedure and, in case of occurrence, will track information for potential recovery during data collection at the study visits.*
Method of Assigning Patients to Treatment	This is a real-world study, subjects who sign the consent form and meet all key eligibility criteria will be enrolled.

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Follow-up Schedule	This is a retrospective and/or prospective observational study. For retrospectively enrolled subjects, data will be collected from each patient's scheduled and unscheduled follow-up visits for 12 months post-procedure per the standard of care follow-up schedule as defined by their center that performs the clinical follow-up visits. For prospectively enrolled subjects, data collection at the following visits are recommended: • Baseline Visit • Procedure • 7 days after the procedure (7-10 days) Telephone contact • 1 month after the procedure (30 ±7 days) Telephone contact • 3 months after the procedure (91-104 days) Clinic visit • 6 months after the procedure (180 ± 30 days) Clinic visit • 12 months after the procedure (365 ± 30 days) Clinic visit
Study Duration	This is a retrospective and/or prospective study. The 12-month follow-up data will be collected after the procedure. The study duration is estimated up to 18 months depending on the precent of subjects enrolled prospectively.
Participant Duration	The study duration for subjects enrolled prospectively is expected to be approximately 12 months, and up to 12months after the procedure for the subjects enrolled retrospectively.
Key Inclusion Criteria	1. Subjects who are ≥ 18 and ≤ 75 years of age on the day of enrollment; 2. Subjects whose preoperative diagnosis is PAF confirmed by the clinician; 3. De novo ablation procedure for PAF with Class I or IIa recommendations* according to 2018 Chinese expert consensus on atrial fibrillation therapy; 4. Subjects who are able and willing to provide the defined observational data and/or participate in baseline and follow-up evaluations for the full study;

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	5. Subjects who are willing and capable of providing informed consent. ** In 2018 Chinese expert consensus on atrial fibrillation therapy, subjects with recurrent, symptomatic PAF and refractory or intolerant to at least one class I or class III antiarrhythmic medication are recommended to accept ablation therapy under Class I recommendation; Subjects with recurrent, symptomatic PAF are recommended to accept ablation therapy as the first line therapy under Class IIa recommendation.*
Key Exclusion Criteria	1. Subjects who, in the judgment of the investigator, have a life expectancy of less than one year before the procedure; 2. Women of childbearing potential who are, or plan to become, pregnant during the time of the study; 3. Subjects with any known contraindication to AF ablation with FARAPULSE Pulsed Field Ablation system, anticoagulation therapy, or contrast media in the judgment of the investigator or subjects unwillingness to use systemic anticoagulation 4. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study.
Additional Exclusion Criteria for modified Intent-to-Treat (mITT) set	1. AF that is any of the following: • Persistent (both early and longstanding) by diagnosis or continuous duration > 7 days • Requires four or more direct-current cardioversions in the preceding 12 months before the procedure. • Secondary to electrolyte imbalance, thyroid disease, alcohol or other reversible/ non-cardiac causes 2. Any of the following atrial conditions: • Left atrial anteroposterior diameter ≥ 5.5 cm (by MRI, CT or transthoracic echocardiography [TTE]*) • Any prior atrial endocardial or epicardial ablation procedure, other than right sided CTI ablation or for right sided supraventricular tachycardia • Any prior atrial surgery

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	• Intra-atrial septal patch or interatrial shunt • Atrial myxoma • Current left atrium (LA) thrombus[#] • LA appendage closure, device or occlusion, past or anticipated • Any PV abnormality, stenosis or stenting (common and middle PVs are admissible) [¥] 3. At any time, one or more of the following cardiovascular procedures, implants or conditions: • Sustained ventricular tachycardia or any ventricular fibrillation • Hemodynamically significant valvular disease: a) Valvular disease that is symptomatic b) Valvular disease causing or exacerbating congestive heart failure c) Aortic stenosis: if already characterized, valve area < 1.5 cm^2 or gradient > 20 mmHg d) Mitral stenosis: if already characterized, valve area < 1.5 cm^2 or gradient > 5 mmHg e) Aortic or mitral regurgitation associated with abnormal LV function or hemodynamic measurements • Hypertrophic cardiomyopathy • Any prosthetic heart valve, ring or repair including balloon aortic valvuloplasty • Pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices • Any inferior vena cava (IVC) filter, known inability to obtain vascular access or other contraindication to femoral access • History of rheumatic fever

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	• History of congenital heart disease with any residual anatomic or conduction abnormality 4. Any of the following procedures, implants or conditions: • At baseline or assessment before the procedure: a) New York Heart Association (NYHA) Class III/IV b) Left ventricular ejection fraction (LVEF) < 40% c) Symptomatic hypotension or Uncontrolled hypertension (Systolic blood pressure > 160 mmHg or Diastolic blood pressure > 95 mmHg on two blood pressure measurements at baseline assessment) d) Symptomatic resting bradycardia e) Implantable loop recorder or insertable cardiac monitor • Within the 3 months preceding the procedure: a) Myocardial infarction or Unstable angina or Percutaneous coronary intervention b) Heart failure hospitalization c) Treatment with amiodarone d) Pericarditis or symptomatic pericardial effusion e) Gastrointestinal bleeding • Within the 6 months preceding the procedure: a) Heart surgery b) Stroke, TIA or intracranial bleeding c) Any thromboembolic event d) Carotid stenting or endarterectomy 5. Diagnosed disorder of blood clotting or bleeding diathesis 6. Subject who is not on anticoagulation therapy for at least 3 weeks prior to the ablation procedure 7. Medical conditions assessed before the procedure that would prevent participation in the study, interfere with assessment or

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	therapy, significantly raise the risk of study participation, or modify outcome data or its interpretation, including but not limited to: • Body Mass Index (BMI) > 40.0 kg/m^2 • Solid organ or hematologic transplant, or currently being evaluated for an organ transplant • Severe lung disease, pulmonary hypertension, or any lung disease involving abnormal blood gases or requiring supplemental oxygen • Renal insufficiency with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, or any history of renal dialysis or renal transplant • Active malignancy or history of treated malignancy within 24 months of enrollment (other than cutaneous basal cell or squamous cell carcinoma) • Clinically significant gastrointestinal problems involving the esophagus or stomach including severe or erosive esophagitis, uncontrolled gastric reflux, gastroparesis, esophageal candidiasis or active gastroduodenal ulceration • Active systemic infection • COVID-19 disease a) Current confirmed, active COVID-19 disease b) Current positive test for SARS-CoV-2 c) Confirmed COVID-19 disease not clinically resolved at least 3 months prior to the procedure • Other uncontrolled medical conditions that may modify device effect or increase risk, including uncontrolled diabetes mellitus (HgbA1c > 8.0% if test result already obtained), untreated obstructive sleep apnea or active alcohol abuse 8. Clinically significant psychological condition that in the Investigator's opinion would prohibit the subject's ability to meet the protocol requirements 9. Employees/family members of:

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	• Boston Scientific or any of its affiliates or contractors • The Investigator, sub-Investigators, or their medical office or practice, or healthcare organizations at which study procedures may be performed 10. Subjects known to require or have accepted ablation outside the PV region during the procedure except CTI region ablation. **TTE obtained ≤ 6 months prior to procedure will be acceptable, unless a cardiac event has occurred (e.g. MI, acute heart failure or acute onset heart failure) between the date of the exam and the procedure. In this case, a new TTE is needed to confirm eligibility for mITT. The most recent report before the procedure will be used. LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used.* *[#]The absence of thrombus must be confirmed by means of a trans-esophageal echocardiogram (TEE) within 48 hours prior to the procedure or Intracardiac Echography (ICE) during the procedure.* *[¥] Cardiac CT/MRI obtained ⩽ 3 months prior to procedure will be acceptable.*
Statistical Methods	
Primary Statistical Hypothesis	There are no formal hypotheses testing in this small sample size observational study.
Statistical Test Method	Descriptive statistics will be conducted for the endpoint events. Explorative statistical analysis might be produced if appropriate, such as Bayesian estimation of the study results using ADVENT data as the prior. Primary effectiveness endpoints will be summarized for TREATMENT subjects in modified Intent-to-Treat (mITT) set. Secondary effectiveness endpoints will be summarized for TREATMENT subjects in Intent-to-Treat (ITT) set and mITT set respectively. Primary and secondary safety endpoints will be summarized for ATTEMPT and TREATMENT subjects in ITT set. The additional endpoints will be summarized for TREATMENT subjects in ITT set.
Sample Size Parameters	No formal sample size calculation is performed because there is no

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formal hypothesis testing in the study. The following table provides a 95% confidence interval (exact methods) for a sample size of 30 if there are 0 ~ 3 primary safety events.

Events	Rates (n=30)	Lower 95%CI	Upper 95%CI
0	0%	0%	11.6%
1	3.3%	0.1%	17.2%
2	6.7%	0.8%	22.1%
3	10%	2.1%	26.5%

3. Table of Contents

3.1. *Table of Figures*

3.2. *Table of Tables*

4. Introduction

4.1. *Background*

4.1.1. *Background and Rationale*

AF is the most common sustained cardiac arrhythmia, affecting approximately 33.5 million people worldwide estimated at 2010[1]. The currently estimated prevalence of AF in adults is between 2% and 4%, and a 2.3-fold rise is expected, owing to extended longevity in the general population and intensifying search for undiagnosed AF[2]. According to the atrial fibrillation prevalence survey of adults in China in 2021, it is estimated that there are about 7.9 million patients with atrial fibrillation in China[3] . The annual risk of AF-related stroke is 5% per year and 1 of every 6 strokes diagnosed occurs in the presence of AF[4]. 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 LA, tachycardia-induced cardiomyopathy and reduced left ventricular function (heart failure). AF remains a significant cause of morbidity and mortality in industrialized societies.

At present, radiofrequency ablation and cryoablation are the main energy forms for atrial fibrillation ablation, but both ablation mechanisms rely on heat conduction and have no tissue selectivity. If the ablation is insufficient, the prevalence of electrical reconnection of pulmonary vein is high; if the ablation is excessive, there is a risk of adjacent injury. According to 2018 Chinese expert consensus statement on atrial fibrillation therapy, the incidence of complications after radiofrequency ablation of atrial fibrillation is about 6.29%, and the late recurrence rate of atrial arrhythmia is about 25%-40%[1]. Thus, it has become a mission for cardiac electrophysiologists to find a strategy to improve the safety and efficacy of atrial fibrillation ablation.

4.1.2. *Irreversible Electroporation*

In 2007, Al-Sakere, et al.[5] 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 [6,7,8,9] . IRE ablation typically spares the extracellular matrix, which facilitates rapid wound healing[10,11,12,13,14].
In 2011, Thomson, et al.[15] reported a case-series study (N=38) assessing the safety of IRE for treating liver, kidney or lung cancers in humans. The first four patients showed signs of transient ventricular arrhythmia, so subsequent patients were all treated using ECG-synchronized delivery of electroporation pulses. There were 2 further arrhythmias and 2 cases of inadvertent damage to neighboring organs. Approximately 68% of tumors were completely ablated. The authors concluded that IRE is safe for clinical use, provided ECG-synchronized delivery is used.

A research group led by FHM Wittkampf in Utrecht investigated the potential effectiveness and safety of epicardial electroporation in AF ablation procedures using porcine models. In 2011, Wittkampf, et al. [16] (N=10) used a circular ablation catheter and showed that PVI was

achieved in all animals, with no sign of stenosis at 3-week follow-up. In 2014, Van Driel, et al.[17] (N=6) confirmed this result out to 3-month follow-up. In 2014, Neven, et al [18] (N=5) showed that electroporation lesion depth depended on the level of electrical energy applied, reaching 8 mm at 300 joules. In 2015, Van Driel, et al.[19] (N=20) showed that electroporation could create deep lesions close to the phrenic nerve without damage to the nerve. In 2014, Neven, et al.[20] similarly showed that neighboring coronary arteries were undamaged by electroporation (N= 5). These animal studies suggest that IRE can safely create deep lesions in heart tissue without harming adjacent tissues.

4.1.3. *Summary of Clinical Studies about FARAPULSE Pulsed Field Ablation System used for PAF*

The FARAPULSE Pulsed Field Ablation system has accumulated large amount of clinical data. Its pre-market studies include IMPULSE, PEFCAT, PEFCAT II and ADVENT studies (**Table 4.1-1**). In addition, there are also some observational trials with small sample size published aiming to observe its clinical safety and efficacy.

In these clinical studies, the primary safety endpoint was defined as the occurrence of predefined serious adverse events at 7 or 30 days after the procedure. The acute procedural success, PVI durability, long-term success and therapeutic success were often designed as the primary or secondary efficacy endpoints. Acute procedural success rate was defined as the proportion of subjects that achieved PVI with FARAPULSE Pulsed Field Ablation system only; PVI durability was defined as proportion of subjects with durable PVI in the remapping evaluation at 2-3 months after the procedure; Long-term success rate was defined as proportion of subjects free from post-blanking AF, AFL or AT; Therapeutic success rate was defined as the proportion of subjects free from post-blanking AF, AFL or AT, post-blanking electrical cardioversion, post-blanking ablation for AF, AFL or AT, and at any time ablation with a non-study device.

IMPULSE study

The IMPULSE study was a prospective multi-center single-arm study, aiming to observe the safety and efficacy of the FARAPULSE Pulsed Field Ablation system in the treatment of PAF[21]. Forty patients with drug-refractory PAF accepted FARAPULSE Pulsed Field Ablation system ablation. All subjects received electrophysiological remapping at 3 months after the procedure to assess PVI durability and were then followed up for 12 months. The primary safety endpoint was the incidence of serious adverse events within 7 days after the procedure, and the primary efficacy endpoint was acute procedural success rate. The secondary efficacy endpoints included chronic procedural success rate at 12 months after the procedure. The results showed that the occurrence of serious adverse events was 2.5% (1/40), including one subject reporting asymptomatic pericardial effusion. The acute procedural success rate was 100% (40/40), the PVI durability at 3 months after procedure was 41.2% (14/34), and the long-term success rate was 77.5% (31/40). This study provided preliminary data of the safety and efficacy of the FARAPULSE Pulsed Field Ablation system in clinical use and provide references for optimizing the ablation parameters.

PEFCAT and PEFCAT II studies

The PEFCAT study was a prospective multi-center single-arm study, aiming to further observe the safety and efficacy of the FARAPULSE Pulsed Field Ablation system in the treatment of

PAF with optimized parameters[22]. Seventy-one patients with drug-refractory PAF accepted FARAPULSE Pulsed Field Ablation system ablation. Invasive remapping was performed at 75 days after the procedure, and reconnected PVs were reisolated with PFA or radiofrequency ablation. After a 90-day blanking period, arrhythmia recurrence was assessed over 1-year follow-up. The primary safety endpoint was the incidence of serious adverse events within 30 days after the procedure, the primary efficacy endpoint was the acute procedural success rate, and the secondary efficacy endpoints included the PVI durability at 75 days and the long-term success rate at 1 year. The results showed that the incidence of serious adverse events was 2.8% (2/71), including 1 pericardial tamponade and 1 arteriovenous fistula. The acute procedural success rate was 100% (71/71), the PVI durability at 75 days was 75.8% (50/66), and the long-term success rate at 1 year was 77.9% (53/68). Additional analysis showed that the therapeutic success was 66.2% (45/68).

The PEFCAT II study was an extending study of the PEFCAT study[23]. It had the same trial design with PEFCAT study, except allowing the physicians to use the FARAFLEX catheter (another ablation catheter developed by FARAPULSE, Inc) to create focal lesion or tricuspid isthmus ablation. Ten patients with PAF were enrolled and the results showed that the primary safety endpoint was 0% (0/10), the acute procedural success rate was 100% (10/10), the PVI durability at 75 days was 77.8% (7/9), the long-term success rate at 1 year was 90% (9/10), and the therapeutic success rate was 80% (8/10).

Since the PEFCAT and PEFCATII studies have similar study design, the clinical team conducted a consolidated analysis to apply CE certification[24]. In this consolidated analysis with 81 subjects, the primary safety endpoint was defined as device and/or procedure related serious adverse events within 30 days, and the analysis set was the ITT population (81 cases), which was defined as all enrolled eligible subjects except those who terminated their participation prior to the beginning of the Index Procedure. The primary efficacy endpoint was the long-term success rate at 1 year after the procedure, and the analysis set was the mITT population (64 cases), which was defined as those ITT subjects who did not undergo radiofrequency re-ablations (at any time) or post-blanking PFA ablations. The primary efficacy endpoint was statistically analyzed using Kaplan-Meier method. The results showed that the primary safety endpoint was 1.2% (1/81), and the primary efficacy endpoint was 82.4% (95%CI: 70.5%-89.9%). Other analysis showed the acute procedural success rate was 100% (81/81), the PVI durability at 2-3 months after the procedure was 76% (57/75), and the long-term success rate at 1 year was 79.2% (95% CI: 68.3%-86.7%) in ITT analysis set.
In summary, the perioperative complications after FARAPULSE Pulsed Field Ablation system ablation were rare, and the acute procedural success rate was 100%. PVI durability and long-term success rate are also quite considerable.

ADVENT Study

The ADVENT study (the FDA IDE study) is a prospective multi-center randomized controlled non-inferiority adaptive study, aiming to compare the FARAPULSE Pulsed Field Ablation system with standard of care ablation with force-sensing radiofrequency catheters and cryoballoon catheters indicated for the treatment of PAF[25]. Patients with PAF who meet the inclusion and exclusion criteria will be randomly assigned to the PFA group or thermal ablation group with a ratio of 1:1, and then be followed up for 1 year. The primary safety endpoint is the occurrence of device and/or procedure related serious adverse events within 7 days after

the procedure, and the analysis set is the PP population, which is defined as eligible subjects who has had a study ablation catheter inserted into the body at an Index/Rescheduled Index Procedure. The primary efficacy endpoints include the acute procedural success rate and the long-term therapeutic success at 1 year after the procedure in the absence of Class I/III AADs treatment after the blanking period, and the analysis set is mITT population, which is defined as the eligible subjects who have accepted energy delivery from FARAPULSE Pulsed Field Ablation system for PVI. The statistical assumption is that the primary safety endpoint and primary efficacy endpoint of the PFA group are not inferior to those of the thermal ablation group, and the sample size calculated under non-inferiority model and adaptive design results in 900 cases at most. The trial is currently ongoing.

Table 4.1-1. Summary of FARAPULSE clinical trials for PAF

Study name	Sample Size	Trial design	Primary endpoints and results	Other endpoints and results
IMPULSE	40 subjects with PAF	A prospective multicenter single-arm cohort study	Safety: Serious adverse events at 7 days: 2.5% (95%CI: 0.1%-13.2%) Efficacy: Acute success rate: 100% (95%CI: 89.6%-100%)	Durable PVI rate at 3 months: 41.2% (95%CI: 24.6%-95.3%)
PEFCAT+ PEFCAT II	81 subjects with PAF	A prospective multicenter single-arm cohort study	Safety: Serious adverse events in ITT population at 30 days: 1.2% (95%CI: 0.0%-6.7%) Efficacy: Freedom from AF/AFL/AT from blanking period to 12 months after the procedure in mITT population: 82.4% (95%CI: 70.5%-89.9%)	ITT analysis set: Acute success rate: 100% (95%CI: 95.5%-100%); Durable PVI rate at 75 days: 76.0% (95%CI: 64.7%-85.1%); Long-term success rate from blanking period to 12 months: 79.2% (95%CI: 68.3%-86.7%) mITT analysis set: Long-term success rate after single PFA ablation from blanking period to 12 months: 69.9% (95%CI: 56.9%-79.6%)
ADVENT (In progress)	900 subjects with PAF	A prospective multicenter randomized controlled non-inferiority adaptive study	Safety: Serious adverse events at 7 days Efficacy: Freedom from AF/AFL/AT from blanking period to 12 months after the procedure in absent of Class I/III AADs, additional ablation and electric cardioversion after blanking period.	Acute success rate Therapeutic success rate

In 2019, Reddy VY et al.[26] summarized and reported the preliminary data from IMPULSE and PEFCAT studies. The data from 81 subjects showed that the durable PVI rate after PFA varied with different phases or parameters (18%-100%), and the durable PVI rate after ablation with optimized waveform (biphasic wave; 1800-2000V) was the highest. In 2021, Reddy VY et al.[27] summarized and reported the 1-year follow-up data of 121 subjects in the IMPULSE study, PEFCAT and PEFCAT II studies, and they also performed subgroup analysis based on whether the subjects treated with optimized PFA parameters or not. The statistical results

showed that the incidence of the primary safety endpoint (device and/or procedure related serious adverse events within 7 days for IMPULSE/within 30 days for PEFCAT) was 2.5% (3/121; 2 pericardial effusion and 1 arteriovenous fistula), and no esophagus injury, phrenic nerve damage or stroke events were reported. The PVI durability at 2-3 months after the procedure was present in 84.1% of patients treated with optimized waveform. At 1 year, the Kaplan-Meier estimate for freedom from AF, AFL or AT was 78.5±3.8% and 84.5±5.4% for the entire cohort or PFA-optimized waveform cohort, respectively.

Other studies

The safety and efficacy of the FARAPULSE Pulsed Field Ablation system in the treatment of PAF have also been verified in some other clinical literatures. In 2018, Reddy VY et al.[28] first reported the postoperative data of 15 patients with PAF who received the endocardial ablation with FARAPULSE Pulsed Field Ablation system. The acute success rate was 100% and no adverse events were reported, which initially proved the safety and efficacy of FARAPULSE Pulsed Field Ablation system in the treatment of PAF.

In 2020, Kuroki K et al.[29] compared the changes in PV ostial diameters after radiofrequency ablation (RFA) and PFA in 80 patients with PAF (PFA group: 37 cases, RFA group: 43 cases). All subjects received left atrial CT evaluations at baseline and 3 months after the procedure, and PV ostial diameter was quantitatively and qualitatively analyzed by 2 physicians. The results showed the changes in the PV ostial diameters in the PFA group were significantly slighter than those in RFA group (PFA vs RFA: Long axis: 0.9%±8.5% vs -11.9% ±16.3%, P<0.001; short axis: 3.4%±12.7% vs -12.9%±18.5%, P<0.001). In the RFA group, pulmonary vein stenosis was diagnosed as Mild (30% - 49%), Moderate (50% - 69%), or Severe (70% - 100%) at 9.0%, 1.8%, and 1.2% of patients, respectively, while in the PFA group, only 0.8% patents were diagnosed as mild pulmonary vein stenosis. The results of qualitative analysis showed that 12% of patients in RFA group and 0% of patients in PFA group were diagnosed as ablation related pulmonary vein stenosis. This study indicates that unlike after RFA, the incidence and severity of PV narrowing/stenosis after PV isolation is virtually eliminated with PFA.

In 2021, Cochet H et al.[30] and Nakatani Y et al.[31] respectively evaluated the adjacent tissue injury and the atrial compliance in 41 PAF patients (PFA group: 18 cases accepted PFA, thermal ablation group: 16 cases accepted RFA, 7 cases accepted cryoballoon ablation). All subjects accepted MRI evaluation at baseline, acute phase (<3 h) and 3 months after ablation. Late gadolinium enhanced (LGE) imaging was used to evaluate adjacent tissues injury, and the phrenic nerve damage was evaluated intraoperatively by pacing. No diaphragmatic paralysis was reported during ablation in both groups. In the acute phase after ablation, 43% of patients in the thermal ablation group showed esophageal lesions adjacent to the ablation site, while no esophageal lesion was detected in the PFA group ($P < 0.001$). Additionally, the volume of LGE accumulation after PFA was 60% larger than that after thermal ablation ($P < 0.001$), which aligned with the effect of PFA electroporation, however the volume of myocardial edema in the PFA group revealed by T2 imaging was 20% smaller than thermal ablation group ($P = 0.002$). There was no sign of microvascular injury or intramural hemorrhage in the ablation zone after PFA ablation. The MRI T2 imaging examination performed at 3 months after the procedure showed that the majority of acute myocardial LGE had disappeared after PFA, while most LGE persisted after the thermal ablation, indicating

that the PFA ablation has a specific reparative process involving less chronic fibrosis. In addition, the maximum strain on PV antra, the left atrial expansion index, and the left atrial emptying fraction declined acutely after PFA and thermal ablation but recovered at chronic stage only with PFA.

In summary, the FARAPULSE Pulsed Field Ablation system has a satisfied efficacy in the ablation of PAF. The acute success rates of PVI in different trials were all 100%. The PVI durability at 2-3 months after the procedure was present in 84.1% of patients treated with optimized waveform. Long-term outcome at 1 year was also comparable with exiting data. In addition, the FARAPULSE Pulsed Field Ablation system potentially improved the safety of the procedure. The incidence of perioperative serious adverse events was about 0 - 2.5%. No esophageal injury, phrenic nerve damage, or stroke were reported. Some clinical studies showed that, compared with thermal ablation, FARAPULSE Pulsed Field Ablation system had potential advantages in avoiding pulmonary vein stenosis, reducing damage to adjacent tissues, and sparing of the left atrial myocardium compliance.

4.2. *Study Rationale*

Catheter ablation for PAF with a variety of energy sources and catheter configurations has been demonstrated to be a safe and effective procedure. The FARAPULSE Pulsed Field Ablation System has undergone preclinical and clinical testing to demonstrate its preliminary safety and effectiveness for isolating PVs quickly and with minimal complications, using a standard catheter-based endocardial procedure. The System has undergone preclinical testing in representative models to demonstrate that it can isolate PVs quickly, durably and with minimal complications, using a standard catheter-based endocardial procedure. Clinical data from 121 endocardial ablated human subjects demonstrates the creation durable lesions when assessed at 75-day remapping procedures, and the Kaplan-Meier estimate for freedom from AF, AFL or AT was 84.5±5.4% for the PFA-optimized waveform cohort with quite few complications, which showed the excellent effectiveness and safety of FARAPULSE Pulsed Field Ablation System.

FARAPULSE Pulsed Field Ablation system has produced a large amount of oversea data, and the ongoing FDA IDE trial, ADVENT study is a prospective multicenter randomized adaptive study, which will produce more clinlical data. The REPLACEstudy will be conducted to generate local clinical evidence to support FAREAPULSE Pulsed Field system regulatory approval in China**.**

5. (Commercial) Device Description (part of Standard of Care)

5.1. *Commercial Device Under Study*

5.1.1. *Names of Investigational Devices*

The FARAPULSE™ Pulsed Field Ablation system is comprised of the following:

- FARAWAVE™ Pulsed Field Ablation Catheter：
  - FARAWAVE™ Pulsed Field Ablation Catheter, 31mm
  - FARAWAVE™ Pulsed Field Ablation Catheter, 35mm

- FARASTAR™ Catheter Connection Cable
- FARASTAR™ Pulsed Field Ablation Generator System:
  - FARASTAR™ Pulsed Field Ablation Generator
  - FARASTAR™ Recording System Module and associated modules and cables
  - FARASTAR™ Stimulation Module Cable and associated cables
  - Other cables
- FARADRIVE™ Steerable Sheath

5.1.2. *Intended Use*

FARAPULSE Pulsed Field Ablation system is intended for the isolation of pulmonary veins for the treatment of paroxysmal atrial fibrillation.

5.1.3. *FARAPULSE Pulsed Field Ablation System*

The components, sub-components and model numbers of FARAPULSE Pulsed Field Ablation system are listed in **Table 5.1-1** and depicted in **Figure 5.1-1.**

Table 5.1-1 FARAPULSE Pulsed Field Ablation System Components

Component Name	Model
FARASTAR Pulsed Field Ablation Generator System	
FARASTAR Pulsed Field Ablation Generator	61M401
FARASTAR Recording System Module (RSM)	61M407
FARASTAR Stimulation Module Cable	61M404
FARASTAR EGM Cable	61M405
FARASTAR Stimulation Module Auxiliary Cable	61M408
FARASTAR Cable Set	61M406
FARASTAR Stimulation Module Male Cable	61M409
FARASTAR Stimulation Module Female Cable	61M410
FARASTAR Stimulation Module Y-Cable, Long	61M411
FARASTAR Stimulation Module Y-Cable, Short	61M412
FARASTAR Recording System Module Catheter Pin Cable	61M413
FARASTAR Recording System Module ECG Trunk Cable	61M415
FARASTAR Recording System Module ECG Output Module	61M416
FARASTAR Recording System Module EGM Input Module	61M417
FARAWAVE Pulsed Field Ablation Catheter	
FARAWAVE Pulsed Field Ablation Catheter, 35mm	41M402
FARAWAVE Pulsed Field Ablation Catheter, 31mm	41M401
FARASTAR Catheter Connection Cable	41M404
FARADRIVE Steerable Sheath	21M402

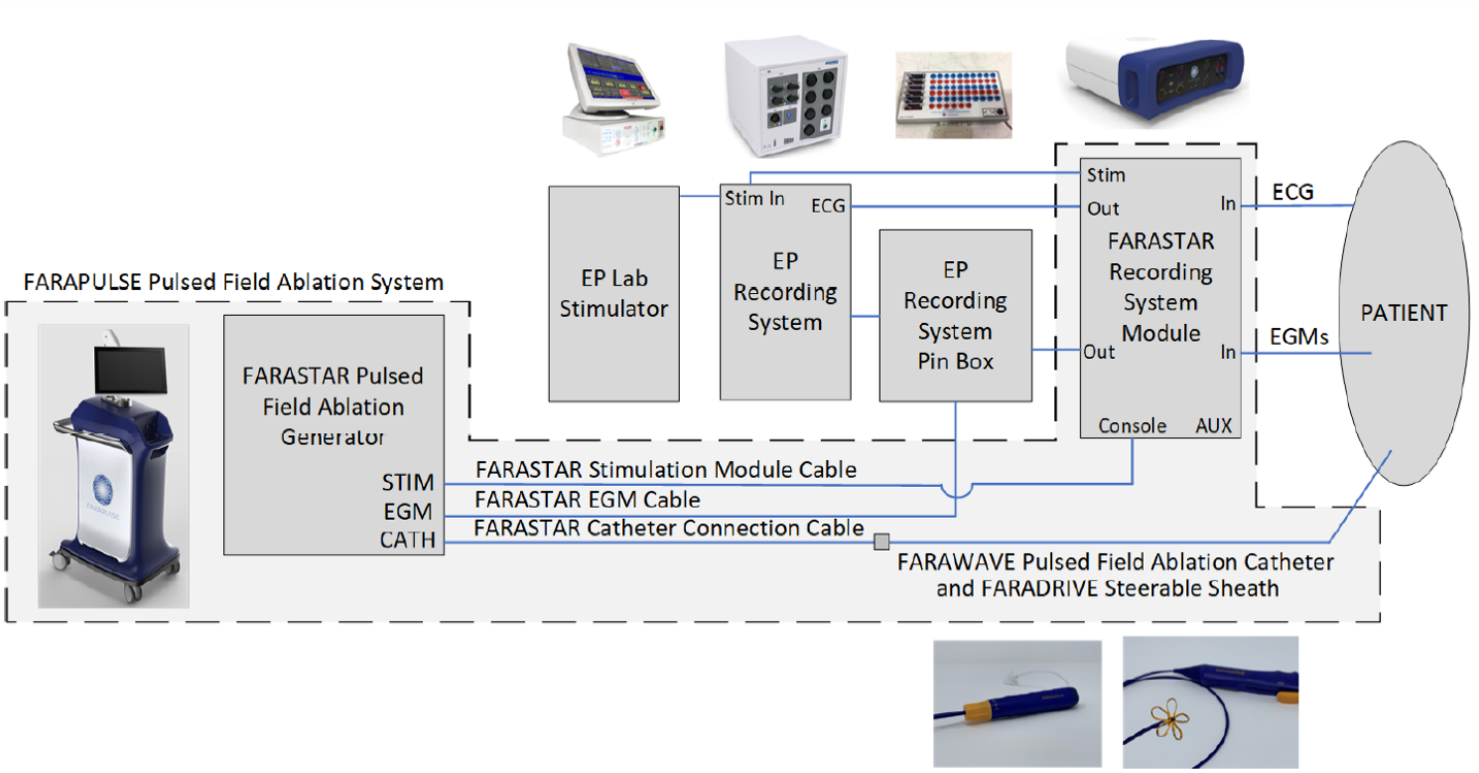


Figure illustrates how the main FARAPULSE Pulsed Field Ablation system components are connected in a typical Electrophysiology Lab. The blocks labeled EP Lab Stimulator, EP Recording System, and EP Recording System Pin Box are not included with the FARAPULSE Pulsed Field Ablation System and are components provided by the Electrophysiology Lab.

Figure 5.1-1: FARAPULSE Pulsed Field Ablation System Components

5.1.3.1. FARAWAVE Pulsed Field Ablation Catheter

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

The FARAWAVE Pulsed Field Ablation Catheter is offered in 2 different sizes (31-mm and 35-mm fully deployed diameters) to accommodate varying PV anatomy. Selection of either catheter will be at the Investigator's discretion. The FARAWAVE Pulsed Field Ablation Catheter is a multi-electrode catheter that connects electrically to the FARASTAR Pulsed Field Ablation Generator (**Figure 5.1-2**). It consists of a distal section with electrodes arranged on splines, a shaft section and a proximal handle with a manually operated deployment control.

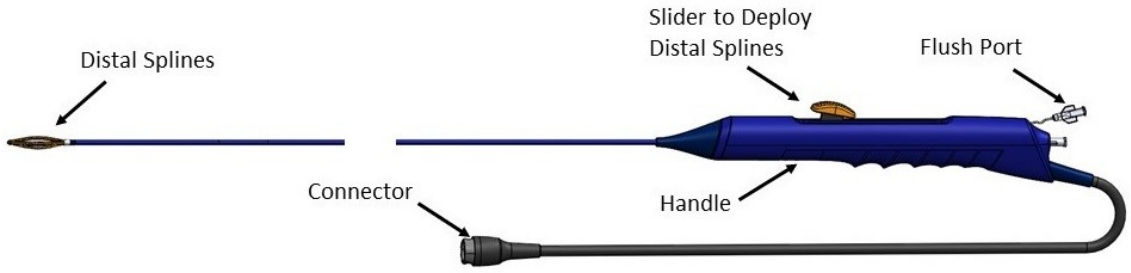


Figure 5.1-2: FARAWAVE Pulsed Field Ablation Catheter

The FARAWAVE Pulsed Field Ablation Catheter has five variably deployable splines. The five splines are undeployed during insertion and removal and during use can deploy continuously from an undeployed state through a basket-shaped configuration to a fully deployed flower-shaped configuration with five petals (**Figure 5.1-3**).

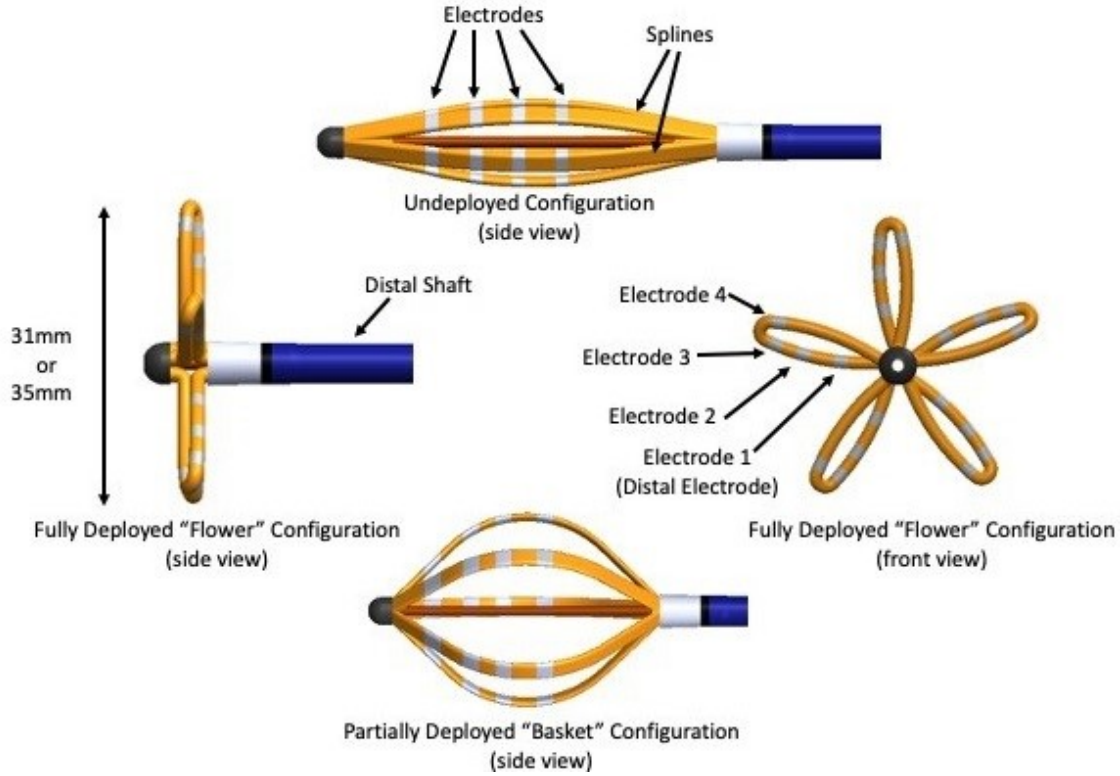


Figure 5.1-3: FARAWAVE Pulsed Field Ablation Catheter - Deployed States

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

5.1.3.2. FARASTAR Pulsed Field Ablation Generator system

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

- FARASTAR Pulsed Field Ablation Generator
- FARASTAR Stimulation Module Cable
- FARASTAR EGM Cable
- FARASTAR Recording System Module
- FARASTAR Stimulation Module Auxiliary Cable
- 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

- FARASTAR Recording System Module Catheter Pin Cable
- FARASTAR Recording System Module ECG Trunk Cable
- FARASTAR Recording System Module ECG Output Module
- FARASTAR Recording System Module EGM Input Module

The FARASTAR Pulsed Field Ablation Generator is a 12 channel Pulsed Electric Field Generator (PEF) unit that is used with the FARAWAVE Pulsed Field Ablation Catheter for cardiac tissue ablation. The FARASTAR contains a two channel cardiac stimulator that can be used for optional synchronous energy delivery.

The primary function of the FARASTAR Pulsed Field Ablation Generator is to produce and deliver PEF energy to the FARAWAVE Pulsed Field Ablation Catheter. The PEF energy is delivered in the form of discrete highvoltage pulses using a proprietary algorithm that controls the pulse timing, duration and sequencing that is applied to the FARAWAVE Pulsed Field Ablation Catheter. The output waveform is biphasic consisting of pulses of equal amplitude and opposite polarity that is delivered in a proprietary bipolar sequence between splines of the FARAWAVE Pulsed Field Ablation Catheter. The only waveform parameter that can be adjusted by the user through the FARASTAR control interface is the pulse voltage which ranges from 1.8 kV to 2.0 kV in increments of 0.1 kV.

5.1.3.3. FARADRIVE Steerable Sheath

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

The FARADRIVE Steerable Sheath consists of two 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 5.1-4**). Details regarding the sheath are provided in the FARADRIVE Steerable Sheath IFU.

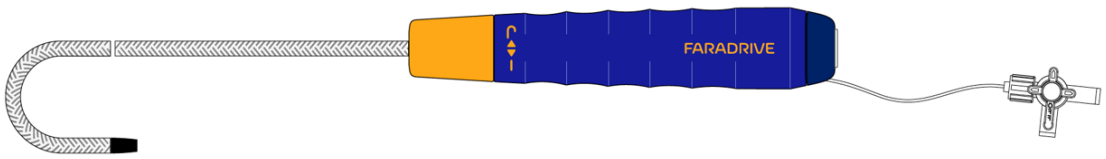


Figure 5.1-4: FARADRIVE Steerable Sheath

This is a real-world study. Boston Scientific will not conduct investigational device accountability as required per ISO 14155 as all study devices are commercially available products and are being used within their approved indication. The study devices shall be maintained per each institution's standard practice.

5.2. *Required Medical Equipment*

The FARAPULSE Pulsed Field Ablation System must be used with additional ancillary products to complete an EP ablation procedure, including compatible EP lab stimulator, EP recording system and EP recording system Pin Box. Any compatible commercial use equipment can be used during the procedure at the investigator's discretion under standard of care at the investigational site.

The pre-ablation and post-ablation voltage mapping are not required for the PFA procedure. It can be done at the investigator's discretion with any mapping system and catheter available for commercial use under standard of care at the investigational site.

5.3. *Required Procedures*

5.3.1. *TEE/ICE*

According to Chinese experts consensus statement on AF ablation, transesophageal echocardiography (TEE) within 48 hours of the procedure or intracardiac echocardiography (ICE) during the procedure is recommended to be utilized prior to transseptal puncture for exclusion of LA thrombus.

5.3.2. *Pulsed Field Ablation for PVI*

Physician who is specialists trained, experienced in cardiac ablation procedures to treat cardiac arrhythmias, and have been trained with the use of FARAPULSE Pulsed Field Ablation system will be selected as the investigator. The PFA workflow is recommended as below but can be adjusted based on institutional practice within the scope of approved IFUs.

Subjects will undergo sedation/anesthesia according to institutional protocol. They will then be prepared in conventional sterile fashion for a cardiac catheterization procedure. Femoral vein access will be obtained via Seldinger technique. A heparin bolus will be delivered prior to or immediately after transseptal puncture. Procedural activated clotting times (ACTs) will be regularly monitored. A procedural ACT between 300 seconds and 450 seconds should be maintained until all devices are withdrawn from the left atrium. Commercially approved diagnostic catheters may be placed before or after transseptal access is established at the Investigator's discretion. Transseptal access to the LA will be obtained using commercially approved devices, establishing guidewire access to the LA. The FARADRIVE Steerable Sheath will be prepared and advanced via guidewire to the LA.The FARAWAVE Pulsed Field Ablation Catheter will then be prepared and advanced to the LA through the FARADRIVE Steerable Sheath. After confirming an ACT of 300 or greater, ablation of the PVs to achieve isolation will be performed according to the approved IFU documents and institutional practice.
PVI ablation may be repeated at the Investigator's discretion. Each addressable PV will be ablated in turn. The isolating effect of the PVI ablation(s) will be checked periodically and then finally twenty minutes after the last PVI ablation. Adenosine may be used for the final assessment but is not required. At the conclusion of the PVI ablation procedure, the FARAWAVE Pulsed Field Ablation Catheter will be undeployed and withdrawn from the

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

5.3.3. *Additional Ablation*

Ablation of the CTI may be performed during the procedure using any approved catheter in subjects with a past history of CTI-dependent AFL, subjects who manifest typical AFL during a procedure or within the Blanking Period, or subjects who have inducible typical flutter. Bidirectional block is recommended to be demonstrated after the last CTI ablation.

5.4. *Required Medications*

5.4.1. *Anti-Arrthythmic Drugs (AADs)*

5.4.1.1. AADs prior to index procedure

This is a retrospective and/or prospective real-world study with no key criteria for AADs use. Prior AADs therapy will be collected in the Electronic data capture (EDC) system. If applicable, administration of amiodarone and stop date will be entered in EDC system.

5.4.1.2. AADs post Index Procedure during the 90-day blanking period

Blanking period is defined as the time between Index procedure and 90 calendar days post Index procedure. Post-procedure AADs are allowed per physician's discretion during the blanking period. If treatment with AADs is prescribed during the blanking period, it is recommended that AADs be selected according to the guidelines or expert consensus statements for the Management of Patients with AF. AADs therapy during the blinding period will be collected in the EDC system.

5.4.1.3. AADs post blanking period

Post-blanking AADs use is determined by per physician's discretion based on the real-world condition of the subject. If the investigator determines that the subject must be prescribed any dose of AAD* for treatment of any atrial tachyarrhythmia after the blanking period, the subject will be considered a Secondary Effectiveness Failure.
**AADs for endpoint will consist of all Class I/III medications taken for control of AF/AT/AFL recurrence. Treatment with and AAD for conditions other than control of atrial arrhythmia recurrence is permitted and will be documented.*

5.4.2. *Anticoagulation*

5.4.2.1. Pre-ablation

Physicians is highly recommended to follow guidelines or expert consensus statements for the management of Patients with AF for adequate systemic anticoagulation. For patients with anticoagulation therapy before the procedure, an uninterrupted anticoagulation approach is recommended.

5.4.2.2. Intra ablation

Physicians is highly recommended to follow guidelines or expert consensus statements for the management of Patients with AF and FARAPULSE Pulsed Field Ablation IFUs for adequate anticoagulation during procedure. It is recommended that heparin be administered prior to or immediately following transseptal puncture or use of the mapping catheter (if available) during AF ablation procedures and the heparin is adjusted to achieve and maintain an ACT of at least 300 seconds. A procedural ACT between 300 seconds and 450 seconds should be maintained until all devices are withdrawn from the left atrium.

5.4.2.3. After ablation

Adherence to AF anticoagulation guidelines is recommended for subjects who have undergone an AF ablation procedure, regardless of the apparent success or failure of the procedure. Warfarin or NOAC anticoagulation is recommended for using for at least 2 months after ablation. Whether to continue anticoagulation after 2 months is determined by the clinician based on the patient's condition.

6. Study Objectives and Endpoints

6.1. *Study Objectives*

The objective of the study is to observe the safety and effectiveness of the FARAPULSE Pulsed Field Ablation system for treatment of recurrent, symptomatic PAF in a Chinese population in the real world. The overview of primary and secondary objectives and endpoints are summarized in **Table 6.1-1**.

Table 6.1-1: Overview of Primary and Secondary Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary Endpoints		
Observe the acute safety of the FARAPULSE Pulsed Field Ablation system	The primary safety endpoint is defined as occurrence of the acute serious procedure-related and/or device-related adverse events at 7 days post index procedure. Primary safety events will consist of a composite of serious procedure and/or device-related adverse events.	The list of events contributing to the primary safety endpoints was selected from those typically associated with catheter ablation of AF.
Observe the acute procedural success of the FARAPULSE Pulsed Field Ablation system	The primary effectiveness endpoint is acute Procedural Success, defined as proportion of subjects that achieve electrical isolation of all PVs using FARAPULSE Pulsed Field Ablation system only.	This is the acute effectiveness endpoint recommended in the Chinese guidelines for cardiac radiofrequency catheter Registration.

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Secondary Endpoints		
Evaluate the 12-month safety of FARAPULSE Pulsed Field Ablation system	The secondary safety endpoint is defined as the safety event-free rate at 12 months post-procedure. Secondary safety events will consist of a composite of serious procedure and/or device-related adverse events.	The list of events contributing to the long-term safety endpoints was selected from those typically associated with catheter ablation of AF detected in the long-term period.
Observe the 12-month effectiveness of the FARAPULSE Pulsed Field Ablation system	One of the secondary effectiveness endpoints is the chronic success, defined as the proportion of subjects that free from Failure events.	This is the chronic success recommended in the Chinese guidelines for cardiac radiofrequency catheter Registration.
Observe the 12-month effectiveness of the FARAPULSE Pulsed Field Ablation system allowing AADs	One of the secondary effectiveness endpoints is the chronic success allowing AADs.	This is an analysis to assess chronic success allowing AADs.
Observe the acute procedural success of the FARAPULSE Pulsed Field Ablation system	One of the secondary effectiveness endpoints is the proportion of PVs that achieve electrical isolation using FARAPULSE Pulsed Field Ablation system only.	This is an analysis to assess acute procedural success by proportion of PVs.
Other endpoints		
Observe the improvement of AF symptoms	Descriptive analysis of atrial fibrillation symptoms at baseline versus 12 months after the procedure.	This is an analysis to assess AF symptoms
Observe procedureal parameters	Other endpoints included total procedure time, PVI ablation time, left atrial dwell time and fluoroscopy time.	This is an analysis to assess procedureal parameters

6.2. *Study endpoints*

6.2.1. *Primary Endpoints*

6.2.1.1. Primary Effectiveness Endpoint

The primary effectiveness endpoint is the acute procedural success, defined as the proportion of subjects that achieve electrical isolation* of all PVs using FARAPULSE Pulsed Field Ablation system only.

** Electrical isolation of a PV is demonstrated by entrance block after a 20-minute waiting period if the subject is enrolled prospectively, otherwise the way to confirm electrical isolation should be recorded, including whether there is a waiting period and its duration. If exit block testing is performed, the PV will only be considered isolated if both entrance and exit block testing was successful.*

6.2.1.2. Primary Safety Endpoint

The primary safety endpoint is defined as the occurrence of the acute serious procedure-related and /or device-related adverse events at 7 days post index procedure based on the definitions contained in **Table 6.2-1.**

- Death
- Myocardial infarction
- Stroke/ TIA
- Peripheral or organ thromboembolism
- Cardiac tamponade / perforation
- Pulmonary edema
- Vascular access complications
- Heart block*
- Gastric motility/pyloric spasm disorders
- Pericarditis
- Atrial esophageal fistula
- Severe PV stenosis
- Phrenic nerve palsy

**Heart block not attributable to medication effect or vasovagal reaction.*

Table 6.2-1：Composite Safety Endpoint Definitions

Related SAE	Description/Criteria
Death	AE resulting in subject death

Related SAE	Description/Criteria
Myocardial infarction	Defined as the presence of any one of the following criteria: • detection of ECG changes indicative of new ischemia (new ST- T wave changes or new LBBB) that persist for more than 1 hour • development of new pathological Q waves on an ECG • imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Phrenic nerve palsy	Defined as absent phrenic nerve function as assessed by a change from baseline in the elevation of a hemidiaphragm, persisting beyond the end of the procedure that is: • Demonstrated radiographically by either an inspiration /expiration chest X-ray or fluoroscopic sniff test • Not due to a demonstrable pulmonary process such as atelectasis or pleural disease. Unresolved phrenic nerve palsy at 1-month follow-up visit will be involved in primary safety events. Phrenic nerve palsy will be evaluated at every follow-up visit thereafter and record the recovery time. Persistent: Unresolved phrenic nerve palsy at 1-month follow-up visit will be reassessed during each follow-up visit. Unresolved phrenic nerve palsy at the 12-monthfollow-up visit will be considered as persistent phrenic nerve palsy
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.

Related SAE	Description/Criteria
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.
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 atrium-ventricular 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.
Severe pulmonary vein stenosis	>70% reduction of an ablated measured PV diameter compared to the baseline CT/MRI scan, as determined by the CIL.
Atrio-esophageal fistula	Confirmation of a fistulous connection between the atrium and the lumen of the esophagus by radiographic, endoscopic or post-mortem examination

AV = atrioventricular, **CIL** = Cardiac Imaging Laboratory, **CT** = computed tomography, **ECG** = electrocardiographic, **LBBB** = left bundle branch block, **MRI** = magnetic resonance imaging, **PV** = pulmonary vein, **SAE** = serious adverse event.

6.2.2. *Secondary Endpoints*

6.2.2.1. Secondary Effectiveness Endpoints

1. Chronic Success: Proportion of subjects that free from effectiveness events defined as failure as below at 12 months post-procedure.

Effectiveness events determining a failure are defined as:

- Fail to achieve electrical isolation of all PVs using FARAPULSE Pulsed Field Ablation system only.
- After the Blanking Period (90 days post the procedure) to 12-month after the procedure:

1) Occurrence of any Detectable AF, AFL* or AT captured by one of the following methods: ≥ 30 seconds in duration recording from 24-hour Holter Monitor or ≥ 10 seconds recording from 12-lead ECG, or
2) Any cardioversion for AF, AFL* or AT, or
3) Use of any Class I or Class III AADs[#] for the treatment of AF, AFL* or AT.

- At any time through 12 months after the procedure:

1) Re-ablation for AF, AFL* or AT, or
2) Use of amiodarone, except intra-procedurally to control an arrhythmia.

2. Proportion of PVs that achieve electrical isolation by using the FARAPULSE Pulsed Field Ablation system only.
3. Chronic success allowing AADs.

[#]*It won't be considered as a failure if the subject has three-month visit happened after 90 days post the procedure, but still in the window (<=104 day) with AADs on, and physicians decide to take AADs off after this visit.*

**excluding CTI-dependent flutter confirmed by EP study*

6.2.2.2. Secondary Safety Endpoints

Proportion of subjects that free from primary safety events defined as above through 7 days after the procedure and free from the following serious procedure-related and/or device-related adverse events at any time through the completion of 12-month follow-up visit. based on the definitions contained in **Table 6.2-1.**

- Atrial oesophageal fistula
- Severe PV stenosis
- Persistent phrenic nerve palsy*

**The study will collect information on phrenic nerve palsy observed before the end of the index procedure and, in case of occurrence, will track information for potential recovery during the study visits*

6.2.3. *Other Endpoints*

1. AF Symptom Assessment: AF symptoms will be assessed at baseline and 12 months.

2. Procedural parameters:

- Total procedure time (initiation of venous access to venous access closure)
- Left atrial dwell time (total time an ablation catheter is in the left atrium [LA])
- Total PVI ablation time (first ablation to last ablation for PVI)
- Fluoroscopy time (total duration of exposure)

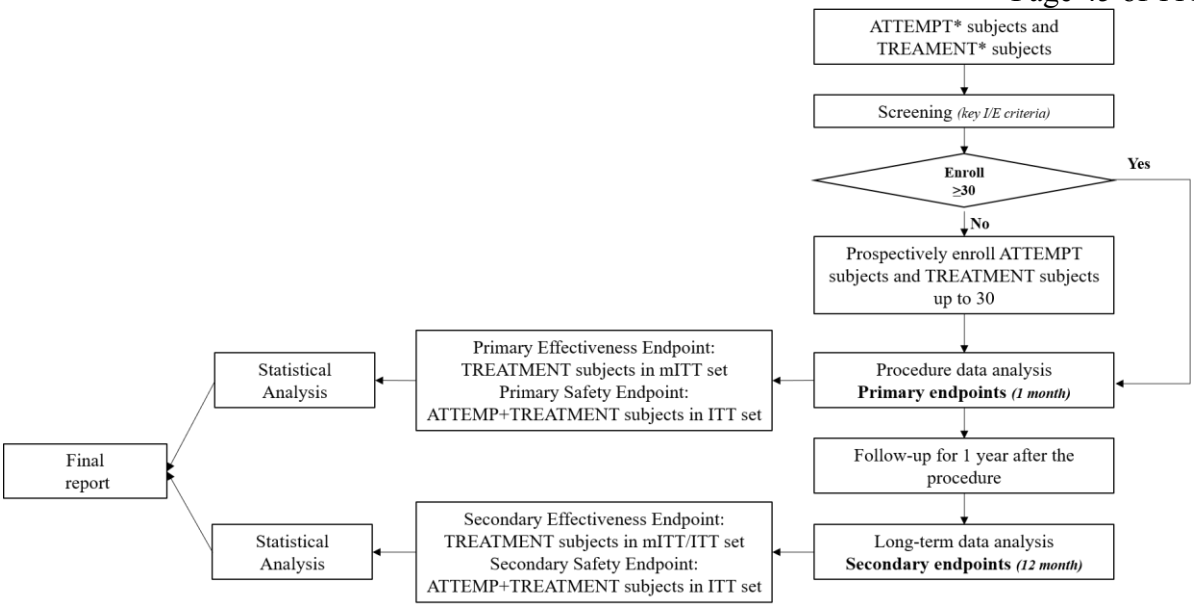
7. Study Design

The REPLACE study is a retrospective and/or prospective single-center single-arm observational real-world study to observe the safety and effectiveness of the FARAPULSE Pulsed Field Ablation system for treatment of recurrent, symptomatic PAF in a Chinese population in the real world. Primary endpoints analysis is planned to be conducted after all enrolled subjects have completed data collection at 1-month follow-up visit. All the subjects underwent study device treatment will be followed up to 12 months after the procedure, and the secondary and other endpoints will be analyzed then. The final report will be completed then too.

7.1. *Scale and Duration*

Thirty ATTEMPT and TREATMENT subjects will be enrolled in this study. The enrollment period for this study is expected up to 6 months depending on the precent of patients enrolled prospectively. Each subject will be followed under standard of care after the ablation procedure with a follow-up duration of 12 months. The study duration is estimated up to 18 months. Primary endpoints analysis is planned to be conducted after all enrolled subjects have completed data collection at 1-month follow-up visit. All the subjects underwent study device treatment will be followed up to 12 months after the procedure, and the secondary and other endpoints will be analyzed then. The final report will be completed then too.

All the subjects will be enrolled from 1 site.



*The definitions of ATTEMPT and TREATMENT refer to Section 9.4.

Figure 7.1-1: REPLACE Study Design

7.2. *Treatment Assignment*

This is a single arm real-world study. All screened subjects who sign the informed consent form (ICF) and satisfied with all the key criteria will be considered enrolled.

7.2.1. *Target and Non-target Lesions*

The pulmonary vein isolation for treatment of PAF will be the target lesion. Ablation of the CTI may be performed with any approved catheter in subjects who manifest typical AFL during a procedure or subjects who have inducible typical flutter. The order to ablate will be decided by the operator based on the patient condition.

7.3. *Justification for the Study Design*

The study device, FARAPULSE Pulsed Field Ablation system has got CE mark and accumulated amount of clinical safety and effectiveness data. The ongoing ADVENT study, a prospective multicenter randomized control study, is powered for non-inferior safety and effectiveness margin, which will produce more clinical data. Boston Scientific China asserts that this real-world study with about 30 cases is reasonable to obtain local data to support FARAPULSE Pulsed Field Ablation system registration in China.

7.4. *Method to control biases*

This is a real-world study. Selection of patients will be made from the Investigational site's routine patients. All patients meeting the key eligibility criteria and having signed the ICF will be eligible for enrollment in the study. Control and reduction of potential bias associated with

a single-arm study design have been taken into account by defining key inclusion and exclusion criteria to represent a population similar to the patients with AF ablation in the real world, and defining a mITT set with population similar to the subjects enrolled in ongoing ADVENT trial and other trial about AF ablation.

Every effort will be undertaken to minimize missing or incorrect data. However, some missingness is inevitable. The reasons for missing or incorrect data will be described in detail and evaluated for assessment of possible bias if appropriate.

8. Subject Selection

8.1. *Study Population and Eligibility*

Subjects enrolled in the REPLACE study will be clinically indicated for an ablation procedure for the treatment of symptomatic, recurrent PAF with Class I or IIa recommendations according to 2018 Chinese expert consensus statement on atrial fibrillation therapy. Subjects must meet the key inclusion/exclusion criteria as outlined below in **Section 8.2** and **8.3**. Subjects assigned to modified ITT set must meet all the key criteria and additional criteria as outlined below in **Section 8.3** The subjects selected for participation will be from the investigational site's general patient population. The investigator or its designee has the responsibility for screening all potential subjects and selecting those who meet study eligibility criteria.

8.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see **Table 8.2-1**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see **Section 8.3**) is met.

Table 8.2-1: Inclusion Criteria

Key Inclusion Criteria	1. Subjects who are ≥ 18 and ≤ 75 years of age on the day of enrollment; 2. Subjects whose preoperative diagnosis is PAF confirmed by the clinician; 3. De novo ablation procedure for PAF with Class I or IIa recommendations* according to 2018 Chinese expert consensus on atrial fibrillation therapy; 4. Subjects who are able and willing to provide the defined observational data and/or participate in baseline and follow-up evaluations for the full study; 5. Subjects who are willing and capable of providing informed consent. ** In 2018 Chinese expert consensus on atrial fibrillation therapy, subjects with recurrent, symptomatic PAF and refractory or intolerant to at least one class I or class III antiarrhythmic medication are recommended to accept ablation therapy under Class I recommendation; Subjects with recurrent, symptomatic PAF are recommended to accept ablation therapy as the first line therapy under Class IIa recommendation.*

8.3. *Exclusion Criteria*

Subjects who meet any one of the following key exclusion criteria in **Table 8.3-1** cannot be included in this study or will be excluded from this clinical study. No vulnerable populations will be enrolled in this study. See **Section 25.2** for the definition of a vulnerable subject. Subjects who meet any one of the following additional exclusion criteria in **Table 8.3-1** cannot be included in the mITT set or will be excluded from mITT set.

Table 8.3-1: Exclusion Criteria

Key Exclusion Criteria	1. Subjects who, in the judgment of the investigator, have a life expectancy of less than one year before the procedure; 2. Women of childbearing potential who are, or plan to become, pregnant during the time of the study; 3. Subjects with any known contraindication to AF ablation with FARAPULSE Pulsed Field Ablation system, anticoagulation therapy, or contrast media in the judgment of the investigator or subjects unwillingness to use systemic anticoagulation 4. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study.
Additional Exclusion Criteria for mITT set	1. AF that is any of the following: • Persistent (both early and longstanding) by diagnosis or continuous duration > 7 days • Requires four or more direct-current cardioversions in the preceding 12 months before the procedure. • Secondary to electrolyte imbalance, thyroid disease, alcohol or other reversible/ non-cardiac causes 2. Any of the following atrial conditions: • Left atrial anteroposterior diameter ≥ 5.5 cm (by MRI, CT or transthoracic echocardiography [TTE]*) • Any prior atrial endocardial or epicardial ablation procedure, other than right sided CTI ablation or for right sided supraventricular tachycardia • Any prior atrial surgery • Intra-atrial septal patch or interatrial shunt • Atrial myxoma • Current left atrium (LA) thrombus# • LA appendage closure, device or occlusion, past or anticipated • Any PV abnormality, stenosis or stenting (common and middle PVs are admissible) ¥ 3. At any time, one or more of the following cardiovascular procedures, implants or conditions:

- Sustained ventricular tachycardia or any ventricular fibrillation
- Hemodynamically significant valvular disease:
  a) Valvular disease that is symptomatic
  b) Valvular disease causing or exacerbating congestive heart failure
  c) Aortic stenosis: if already characterized, valve area < 1.5 cm^2 or gradient > 20 mmHg
  d) Mitral stenosis: if already characterized, valve area < 1.5 cm^2 or gradient > 5 mmHg
  e) Aortic or mitral regurgitation associated with abnormal LV function or hemodynamic measurements
- Hypertrophic cardiomyopathy
- Any prosthetic heart valve, ring or repair including balloon aortic valvuloplasty
- Pacemaker, implantable cardioverter defibrillator or cardiac resynchronization therapy devices
- Any inferior vena cava (IVC) filter, known inability to obtain vascular access or other contraindication to femoral access
- History of rheumatic fever
- History of congenital heart disease with any residual anatomic or conduction abnormality

4. Any of the following procedures, implants or conditions:
   - At baseline or assessment before the procedure:
     a) New York Heart Association (NYHA) Class III/IV
     b) Left ventricular ejection fraction (LVEF) < 40%
     c) Symptomatic hypotension or Uncontrolled hypertension (Systolic blood pressure > 160 mmHg or Diastolic blood pressure > 95 mmHg on two blood pressure measurements at baseline assessment)
     d) Symptomatic resting bradycardia
     e) Implantable loop recorder or insertable cardiac monitor
   - Within the 3 months preceding the procedure:

	a) Myocardial infarction or Unstable angina or Percutaneous coronary intervention b) Heart failure hospitalization c) Treatment with amiodarone d) Pericarditis or symptomatic pericardial effusion e) Gastrointestinal bleeding • Within the 6 months preceding the procedure: a) Heart surgery b) Stroke, TIA or intracranial bleeding c) Any thromboembolic event d) Carotid stenting or endarterectomy 5. Diagnosed disorder of blood clotting or bleeding diathesis 6. Subject who is not on anticoagulation therapy for at least 3 weeks prior to the ablation procedure 7. Medical conditions assessed before the procedure that would prevent participation in the study, interfere with assessment or therapy, significantly raise the risk of study participation, or modify outcome data or its interpretation, including but not limited to: • Body Mass Index (BMI) > 40.0 kg/m^2 • Solid organ or hematologic transplant, or currently being evaluated for an organ transplant • Severe lung disease, pulmonary hypertension, or any lung disease involving abnormal blood gases or requiring supplemental oxygen • Renal insufficiency with an estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2, or any history of renal dialysis or renal transplant • Active malignancy or history of treated malignancy within 24 months of enrollment (other than cutaneous basal cell or squamous cell carcinoma) • Clinically significant gastrointestinal problems involving the esophagus or stomach including severe or erosive esophagitis, uncontrolled gastric reflux, gastroparesis, esophageal candidiasis or active gastroduodenal ulceration • Active systemic infection • COVID-19 disease a) Current confirmed, active COVID-19 disease

	b) Current positive test for SARS-CoV-2 c) Confirmed COVID-19 disease not clinically resolved at least 3 months prior to the procedure • Other uncontrolled medical conditions that may modify device effect or increase risk, including uncontrolled diabetes mellitus (HgbA1c > 8.0% if test result already obtained), untreated obstructive sleep apnea or active alcohol abuse 8. Clinically significant psychological condition that in the Investigator's opinion would prohibit the subject's ability to meet the protocol requirements 9. Employees/family members of: • Boston Scientific or any of its affiliates or contractors • The Investigator, sub-Investigators, or their medical office or practice, or healthcare organizations at which study procedures may be performed 10. Subjects known to require or have accepted ablation outside the PV region during the procedure except CTI region ablation. **TTE obtained ≤ 6 months prior to procedure will be acceptable, unless a cardiac event has occurred (e.g. MI, acute heart failure or acute onset heart failure) between the date of the exam and the procedure. In this case, a new TTE is needed to confirm eligibility for mITT. The most recent report before the procedure will be used. LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used.* *[#]The absence of thrombus must be confirmed by means of a trans-esophageal echocardiogram (TEE) within 48 hours prior to the procedure or Intracardiac Echography (ICE) during the procedure.* *[¥] Cardiac CT/MRI obtained ≤ 3 months prior to procedure will be acceptable.*

9. Subject Accountability

9.1. *Point of Enrollment*

Subjects satisfied with all the key criteria will be considered enrolled into the clinical study at the time of the study-specific ICF execution. No data collection of study-related testing, procedures, etc. can take place until the ICF is signed and dated by the subject.
It is the investigative site's responsibility to assess eligibility criteria before obtaining the ICF and to document them for each screened patient in the study Screening and Enrollment Log. It is the responsibility of the delegated physician investigator to assess final eligibility criteria prior to data collection. If the subject is found to be ineligible prior to data collection, it must be documented.

9.2. *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 device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical study.
Reasons for withdrawal include but are not limited to physician discretion, subject choice to withdraw consent, lost to follow-up or death. While study withdrawal is discouraged, subjects may voluntarily withdraw from the study at any time, with or without reason, and without prejudice to further treatment. In the event a subject decides to withdraw from the study, or an investigator withdraws a subject due to investigator discretion, every effort should be made to obtain full information on any on-going reportable Adverse Events/Serious Adverse Events up to the point of withdrawal. Additional data may no longer be collected after the point at which the 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 for study analysis, unless local regulations apply which require removal of the data. All applicable, electronic case report forms (eCRFs) up to the point of subject withdrawal and a "Subject End of Study" form (or equivalent) must be completed.
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 closed or chronic.

9.3. *Lost to Follow-Up*

A participant will be considered lost to follow-up if he/she fails to complete the routine follow-up visits scheduled visits and is unable to be contacted by the study site staff.
The following actions must be taken if a participant fails to return to the clinic for a required standard of care visit:

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

9.4. *Subject Status and Classification*

As subjects are evaluated, enrolled and treated in the study, they will be grouped into one of the following four categories and analyzed by predefined sets. Categorization will help determine how data gathered from them will be stored and evaluated.
It is the investigational site's responsibility to list all screened subjects, Screening failure, INTENT, ATTEMPT and TREATMENT subjects on the Screening and Enrollment Log.

9.4.1. *Screening Failure*

A subject who has signed informed consent but is later determined to not meet key eligibility criteria will be classified as "Screening Failure". Subjects not meeting key eligibility criteria due to oversight (i.e., I/E violation) will be considered 'Screening Failure'. There are no follow-up reporting requirements for Screening Failure subjects. Subjects determined to be Screening Failure will not be used for analysis of the endpoints and do not count toward the enrollment ceiling. The original signed Informed Consent must be maintained in the site's subject file. A subject Identification Number (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
  - Relevant eCRFs for study visits completed through consent ineligible determination, including device tracking, if applicable.
- Adverse Event forms for any reportable event, as defined in **Section 18.1** for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal

9.4.2. *INTENT*

A subject who signs informed consent, meets key eligibility criteria, but does not have any study devices inserted into the body will be classified as "INTENT." For prospectively enrolled subjects that are enrolled in the study but do not undergo ablation procedure within 30 days from consent signature date must not be reconsented and will be withdrawn from the study and classified as "INTENT." These subjects won't be allowed to be re-enrolled in the study.
There are no follow-up requirements for INTENT subjects. INTENT subjects will not count for analysis of the endpoints and do not count toward the enrollment ceiling. The original signed ICF must be maintained in the center's patient file. A subject ID will be assigned in the EDC system.
For INTENT subjects, at the minimum the following forms must be completed:

- Enrollment and baseline forms such as, but not limited to informed consent, enrollment information and other related forms.
- End of Study form;
- Adverse Event forms for any reportable event, as defined in **Section 18.1** for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal

9.4.3. *ATTEMPT*

An ATTEMPT subject is one who signs informed consent, meets eligibility criteria, and has any study device inserted into the body but does not receive ablation (PFA energy) with the FARAPULSE Pulsed Field Ablation System for PVI. ATTEMPT subjects will be used for analysis of the primary and secondary safety endpoints and count toward the enrollment ceiling.
The original signed Informed Consent and any relevant documentation must be maintained in the site's subject file. A subject ID will be assigned in the EDC system. ATTEMPT subjects are not allowed to be re-enrolled in the study.
Prospectively enrolled ATTEMPT subjects will be followed up to 30 days for safety. For

retrospectively enrolled ATTEMPT subjects, one-month follow-up data will be collected. ATTEMPT subjects will not need to complete data collection of the post-procedure arrythmia. All applicable eCRFs, per the protocol, will be completed.
For ATTEMPT subjects, at the minimum the following forms must be completed:

- Enrollment and baseline forms such as, but not limited to: ICF, enrollment information and other related forms.
- End of Study form.
- Protocol Deviation form
- Adverse Event forms for any reportable event, as defined in Section 18.1 for any adverse event that occurs after signing the ICF, up to the point of subject withdrawal

9.4.4. *TREATMENT*

Any subject that signs the ICF, meets key eligibility criteria and has the specified study device inserted into the body and receives PFA ablation with the FARAPULSE Pulsed Field Ablation system will be classified as "TREATMENT". The data collection of these subjects will be performed in accordance with the follow-up schedule and are included in all study analyses. A subject ID will be assigned in the EDC system.
All applicable eCRFs, per the protocol, must be completed for TREATMENT subjects. TREATMENT subjects do count towards the enrollment ceiling and will be used for analyses of the endpoints. The original signed ICF and any relevant documentation must be maintained in the center's patient file.

9.5. *End-of-Study Definition*

A clinical trial is considered completed when the last participant's last study data collection has occurred.

A subject is considered to have completed the study if he/she has completed all data collection including the last visit or assessment as shown in the Data Collection Schedule shown in **Table 10-1**.
The end of the study is defined as completion of data collection shown in the Data Collection Schedule including the 12-month follow-up visit.

9.6. *End of Study Action Plan*

This is a real-world study. All the subjects will continue to accept routine follow-up under standard of care.

10. Study Methods

10.1. *Data Collection*

The data collection schedule is shown in **Table 10.1-1**.

Table 10.1-1 Data Collection Schedule

Data Collection	Baseline Visit Clinic Visit	Procedure Visit (Day 0) Clinic Visit	Follow-up (FU) Visits					
			7 days FU (7-10 days) Telephone interview	1 M FU (30±7 Days) Telephone interview	3 M FU (91-104 Days) Clinic Visit	6 M FU (180±30 Days) Clinic Visit	12 M FU (365±30 Days) Clinic Visit	Unscheduled FU Clinic Visit
Informed consent	X							
Baseline information including demographics information	X							
Eligibility Criteria	X							
Pregnancy test	X[1]							
Medical history	X							
Physical Assessment	X							
Related Blood Tests	X							
Transthoracic echocardiogram (TTE)	X[2]							
Cardiac CT/MRI	X[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
TEE/ICE to exclude LA thrombus	X[4]	X[4]						
Procedural Data		X						
Phrenic Nerve Palsy Assessment		X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]
AF Symptom Assessment	X						X	
AADs and anticoagulant medications	X	X	X	X	X	X	X	X
Documentation of intervention AF/AFL/AT			X	X	X	X	X	X

12-lead ECG	X[7]				X	X	X	X[7]
24h Holter	X[7]				X[7]	X	X	X[7]
Neuro assessment	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]	X[6]
Adverse events	X	X	X	X	X	X	X	X
Device Deficiency Assessment		X	X	X	X	X	X	X
Protocol Deviations	X	X	X	X	X	X	X	X

[1] Females of childbearing potential.
[2] TTE obtained ≤ 6 months prior to procedure will be acceptable, unless a cardiac event has occurred (e.g., MI, acute heart failure or acute onset heart failure) between the date of the exam and the procedure. In this case, a new TTE is needed. The most recent report before the procedure will be used.
[3] Cardiac CT/MRI obtained ⩽ 3 months prior to procedure will be acceptable. Cardiac CT/MRI scan may be considered post-procedure if PV stenosis is suspected at the physician's discretion.
[4] The absence of thrombus must be confirmed by means of a trans-esophageal echocardiogram (TEE) within 48 hours prior to the procedure or Intracardiac Echography (ICE) during the procedure.
[5] Phrenic Nerve Palsy Assessment at discharge and at follow-up visits is only applicable for subjects who had phrenic nerve palsy detected during the index or repeat procedure. Subjects should be assessed per standard of care; suggested means of assessment include a sniff test or an inhalation-exhalation chest radiography of the diaphragm.
[6] If there is a clinical suspicion of stroke/TIA by the physician, then the data of neuro assessment, including but not limited to specialist consultation and brain MRI, will be collected.
[7] Collect results if applicable, the absent of this assessment is not Protocol Deviation.

10.2. *Study Candidate Screening*

Investigators are responsible for screening all subjects and selecting those who are appropriate for study inclusion. The investigator is expected to follow standard of care testing to diagnose and screen subjects for inclusion in the study. A Screening and Enrollment Log will be maintained to document select information about candidates who fail to meet the general and specific selection criteria, including those enrolled in the study and classified either as Screen Failure, INTENT, ATTEMPT or TREATMENT subjects.

10.2.1. *Strategies for Recruitment and Retention*

The subjects selected for participation should be from the investigation site's general patient population, and all the eligible subjects will be ablated and followed up under standard of care based on the care as defined by their center that performs the follow-up visits.

10.3. *Informed Consent*

Subjects who are satisfied with all the key eligible criteria and have signed and dated the ICF are considered enrolled in the study. In order to determine eligibility of a subject, the investigator or designee needs to implement the consent process as well as verify and document the subject meets final eligibility criteria prior to collect the predefined data by the protocol. Informed consent is required for all subjects prior to their participation in the study. No study-specific data collection can be conducted prior to the subject providing his/her consent.
The subject will be given ample time to consider participation and ask questions if necessary. An approved ICF shall be signed and personally dated by the subject or legal representative competent and/or an authorized designee. The original, signed consent must be kept with the subject's file and a copy must be provided to the subject.
The index procedure must be performed within 30 days post ICF signature for the subjects enrolled prospectively. In case the index procedure has not been performed within this time period, the subject will be classified as INTENT (see **Section 9.4.2**). The same subject cannot be considered for re-enrollment as re-enrollment is not allowed for any subjects in this study. The site will ensure that originally signed ICFs are filed in subjects' binders and the ICF process is properly documented in the medical file. Originally signed ICFs and the ICF process will be made available for review at Monitoring Visits (MVs).

10.4. *Baseline Visit*

Enrolled subjects will have baseline data collected within 30 days of Enrollment. The Baseline Visit may be conducted in the same day as the Enrollment, however the Informed Consent must be signed and dated prior to data collection. In-person at investigational site is recommended.
The data collection at the Baseline Visit includes:

- Visit date, time and way to collect the data
- Check of eligibility criteria
- Demographics including age at time of the procedure, gender, height, weight, race
- Pertinent medical and cardiovascular history, including, but not limited to:

a) Underlying cardiovascular disease, if any; including but not limited to hypertension, dyslipidemia, coronary artery disease
b) Prior surgical interventions and/or cardiac procedures
c) Detailed history of all arrhythmias
d) History of other disease

- AADs and Anticoagulation medication history and most recent dose prior to enrollment; stop date of amiodarone (if applicable)
- Cardiovascular/Pulmonary Exam at Baseline must be completed by someone qualified to perform the physical assessment i.e., physician/medical doctor, nurse practitioner (NP) and/or Physician Assistant (PA) and include at least:
  a) Lung auscultation (includes respiratory rate and respiratory rhythm)
  b) Heart auscultation
- Pregnancy test (women of child-bearing potential)
- Pertinent blood test for screening, including eGFR
- COVID-19 testing by site if available:
  a) PCR for SARS-CoV-2 virus or equivalent testing, or
  b) Confirmation of successful vaccination with National Medical Products Administration (NMPA)-approved vaccine
- 12-lead ECG and/or Holter before the procedure if applicable
- The following cardiac image will be performed and/or data from existing information will be collected:
  a) TTE establishing LVEF, left atrial diameter
  b) Cardiac CT or MRI assessing PV
  c) TEE assess left atrial thrombus (if ICE is not planned during procedure)
- NYHA Classification
- CHA2DS2-VASc score
- AF symptom assessment
- Reportable Adverse Events, if applicable
- Protocol Deviations, if applicable

10.5. *Procedure Visit*

The Index Procedure and/or data collection must occur after all activities and/or data collection required for the Baseline Visit are completed. For eligible subjects enrolled retrospectively, data collection in **Section 10.5.2** may occur in the same day as the Baseline Visit data collection. For eligible subjects enrolled prospectively, the procedures in **Section 10.5.1** are recommended and data collection in **Section 10.5.2** will occur as the data collection schedule.

10.5.1. *Index procedure*

The details in workflow can be found in related IFUs. The following manipulations are recommended but can be adjusted based reasonable institutional protocol.

10.5.1.1. Pulmonary vein isolation

Use of the FARAWAVE Pulsed Field Ablation system should be restricted to those physicians who are specialists trained, experienced in cardiac ablation procedures to treat cardiac arrhythmias, and have been trained with the use of these devices.

Subjects will undergo sedation/anesthesia according to institutional protocol. They will then be prepared in conventional sterile fashion for a cardiac catheterization procedure. Femoral vein access will be obtained via Seldinger technique. A heparin bolus will be delivered prior to or immediately after transseptal puncture. Patients should be anticoagulated to an ACT between 300 seconds to 450 seconds prior to insertion of the FARAWAVE Pulsed Field Ablation Catheter into the blood pool to avoid thrombus formation. A procedural ACT between 300 seconds and 450 seconds should be maintained until all devices are withdrawn from the left atrium. Pre-ablation and post-ablation voltage map are not required. Commercially approved diagnostic catheters may be placed before or after transseptal access is established at the Investigator's discretion. Transseptal access to the LA will be obtained using commercially approved devices, establishing guidewire access to the LA. TEE within 48 hours of the procedure or ICE during the procedure will be utilized prior to transseptal puncture for exclusion of LA thrombus. If the study reveals atrial thrombus, the investigational procedure will not begin or will be terminated, no ablation will be performed, and the subject will be rescheduled. The FARADRIVE Steerable Sheath will be prepared and advanced via guidewire to the LA. The FARAWAVE Pulsed Field Ablation Catheter will then be prepared and advanced to the LA through the FARADRIVE Steerable Sheath. After confirming an ACT of 300 or greater, ablation of the PVs to achieve isolation will be performed according to the approved IFU documents and institutional practice. PVI ablation may be repeated at the Investigator's discretion. Each addressable PV will be ablated in turn.

10.5.1.2. Pulmonary vein isolation validation

The isolating effect of the PVI ablation(s) will be checked periodically and then finally 20 minutes after the last PVI ablation. PVI can be confirmed using the physician's standard workflow. If additional ablations are required to seal up gaps or to ablate potential gaps, then isolation will be confirmed post additional ablations. Electrical isolation of the veins is recommended to be demonstrated by the absence of electrical propagation through the ablation lines. Electrical Isolation is recommended to be demonstrated and documented using Entrance Block for each pulmonary vein following at least a 20-minute waiting period from the last application in each location. Exit block verification is also recommended and may be performed per center's standard of care. If Exit Block verification is attempted, a vein will only be considered isolated if Exit Block is also demonstrated and documented on the appropriate eCRF. If Exit Block is not attempted, it must be documented on the appropriate eCRF and in that case, verification via Entrance Block is sufficient to confirm isolation. If isolation is not confirmed after the 20-minute waiting period, the Investigator must perform additional ablations to treat any gaps. Entrance Block is recommended to be re-assessed after any additional ablations and another 20-minute waiting period is required. Adenosine may be used for the final assessment but is not required.

10.5.1.3. Pulmonary vein isolation conclusion

At the conclusion of the PVI ablation procedure, the FARAWAVE Pulsed Field Ablation Catheter will be undeployed and withdrawn from the FARADRIVE Steerable Sheath. The functional status of both phrenic nerves will be assessed before the study is concluded. If phrenic nerve palsy is detected, it will be documented on the appropriate eCRF. All subjects presenting with phrenic nerve palsy at the end of the index or repeat procedure will be re-assessed at the follow-up visits for phrenic nerve palsy.

10.5.1.4. Additional ablations

CTI ablation: Ablation of the CTI may be performed using any approved catheter in subjects with a past history of CTI-mediated (typical) AFL, subjects who manifest typical AFL during a procedure or within the Blanking Period, or subjects who have inducible typical flutter. Bidirectional block should be demonstrated after the last CTI ablation. The CTI ablation data will be documented in the eCRF and does not constitute a Treatment Failure.

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

If the subject presents with AF after all ablations are complete, cardioversion should be performed and will be noted. Cardioversions during the Index procedure do not signify procedural failures and are not to be reported as adverse events. Induction of or spontaneous conversion to AF during the procedure will not be considered an adverse event. If at any time during the ablation procedure the investigator is unable to continue the ablation with the designated investigational catheter (for the PV isolation), the investigator may consider the case a procedural failure and complete the case with a device determined best for the subject. The point at which failure was determined as well as the rationale must be documented. A protocol deviation will be documented in the EDC system.

10.5.2. *Data collection during procedure visit*

The following data related to the procedure will be collected:

- Visit date, time and way to collect the data
- Date of procedure
- Peri-procedural anticoagulation data:
  a) For subjects on a NOAC whether NOAC therapy was interrupted for procedure
  b) For subjects on warfarin, a pre-treatment international normalized ratio (INR) value
  c) Heparin administration and timing if available
- Identification of devices:
  a) FARAPULSE Pulsed Field Ablation system
  b) Identification of non-study devices if applicable
- Presenting rhythm at the beginning of the procedure

- Method of delivering sedation or anesthesia for the procedure
- Total Procedure Time
- Total LA dwell time if available*
- Total fluoroscopy time if available*
- Total Ablation Time for PVI if available*
- Total Number of PFA applications for each pulmonary vein
- Cardioversion performed during the procedure, if applicable
- Lesion set data

**For eligible subjects enrolled retrospectively, these data may not be available, this should not be Protocol Deviations.*

At the end of the PVI ablation(s), PVI is recommended to be confirmed by entrance block as a minimum. The following information related to PVI validation will be collected:

- Methods to confirm PVI, including the waiting period
- If Adenosine was administered
- If Isoproterenol was administered
- Acute Isolation Result per PV (Entrance Block at a minimum, and Exit Block, if tested)
- Final rhythm at the end of the procedure
- Post-ablation 3D electroanatomical maps (at Investigator discretion)
- Post-ablation fluoroscopic examination of diaphragm motion to assess phrenic nerve response if available
- Reportable Adverse Events, if any
- Device deficiencies and malfunctions, if any
- Protocol Deviations, if any

For subjects who undergo CTI ablation as part of the Index Procedure, the following information will be collected:

- Identification of devices
- Total Ablation Time for the CTI if available
- Reportable Adverse Events, if any
- Demonstration of bidirectional block across the CTI with Methodology used (e.g., differential pacing or vMap)
- Additional ablation parameters (included but not limited to: RF duration, RF power, autotag parameters, contact force)

10.6. *Seven Day Follow-up Visit (7-10 days)*

Discharged subjects will be assessed by a telephone contact 7 days (7-10 days) post-Index Procedure. If the patient is still hospitalized, follow-up will be performed as in-hospital visit. For eligible subjects enrolled retrospectively, the Seven Day Follow-up Visit data collection may occur in the same day as Procedure Visit data collection. For eligible subjects enrolled prospectively, the Seven Day Follow-up Visit should occur within 7-10 days post Index Procedure. The data collection at the Seven Day Follow-up Visit includes:

- Date and time of visit, way to visit
- Date of discharge (if discharge)
- Rhythm at time of discharge (if discharge, by means of 12-lead ECG and/or Holter if applicable)

- Recurrent arrhythmia, cardioversions, ablations or hospital admissions including occurrence, date, indication and outcome of any intervention after the procedure
- Any Stroke Evaluation for Neurologic Assessment, if applicable
- Subjects with unresolved phrenic nerve palsy detected at the discharge visit must be re-assessed per center's standard of care to evaluate if the event resolved
- Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period
- Medication information, including new, discontinued or changes in study-collected medication information (e.g., AADs and NOAC)
- Reportable Adverse Events, including resolution of ongoing events, if applicable
- Protocol Deviations, if applicable

10.7. *One Month Follow-up Visit (30 ± 7 days)*

Discharged subjects will be assessed by a telephone contact one month (30 ± 7 days) post-Index Procedure. If the patient is still hospitalized, follow-up will be performed as in-hospital visit. For eligible subjects enrolled retrospectively, the One-month Follow-up Visit data collection may occur in the same day as Seven Day Follow-up Visit data collection. For eligible subjects enrolled prospectively, the One Month Follow-up Visit should occur within 30 ± 7days post Index Procedure. The data collection at the One-Month Follow-up Visit includes:

- Date and time of visit, way to visit
- Date of discharge (if not discharge within 7 days after the procedure)
- Rhythm at time of discharge (by means of 12-lead ECG and/or Holter if applicable)
- Recurrent arrhythmia, cardioversions, ablations or hospital admissions including occurrence, date, indication and outcome of any intervention after the procedure
- Any Stroke Evaluation for Neurologic Assessment, if applicable
- Subjects with unresolved phrenic nerve palsy detected at the discharge visit must be re-assessed per center's standard of care to evaluate if the event resolved
- Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period
- Medication information, including new, discontinued or changes in study-collected medication information (e.g., AADs and NOAC)
- Reportable Adverse Events, including resolution of ongoing events, if applicable
- Protocol Deviations, if applicable

10.8. *Three Month Follow-up Visit (91-104 days)*

Discharged subjects will be assessed in person 3 months (91-104 days) post-Index Procedure. For eligible subjects enrolled retrospectively, the Three-Month Follow-up Visit data collection may occur at the same day as One Month Follow-up Visit data collection. For eligible subjects enrolled and/or followed up prospectively, the Three-Month Follow-up Visit should occur within 91-104 days post Index Procedure. The data collection at the Three-Month Follow-up Visit includes:

- Date and time of visit, way to collect the data

- Cardiac physical assessment performed as standard of care including, heart rhythm, heart rate, systolic and diastolic blood pressure.
- 12-lead ECG
- 24-hour Holter Monitor if applicable
- Recurrent arrhythmia, cardioversions, ablations or hospital admissions including occurrence, date, indication and outcome of any intervention
- Any Stroke Evaluation for Neurologic Assessment, if applicable
- Subjects with unresolved phrenic nerve palsy detected at the discharge visit must be re-assessed per center's standard of care to evaluate if the event resolved
- Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period
- Medication information, including new, discontinued or changes in study-collected medication information (e.g., AAD and NOAC)
- Reportable Adverse Events, including resolution of ongoing events, if applicable
- Protocol Deviations, if applicable

AADs Treatment: Class I/III AADs are recommended be stopped after blanking period, if they have not already been discontinued. If the investigator determines that the subject must be prescribed any dose of Class I/III AAD for treatment of AF/AFL*/AT after the 3 month follow-up visit, the subject will be considered a Secondary Effectiveness Failure.

* *excluding cavotricuspid isthmus (CTI)-dependent flutter confirmed by electrophysiology study*

10.9. *Six Month Follow-up Visit (180 ± 30 days)*

Discharged subjects will be assessed in person 6 month (180 ± 30 days) post-Index Procedure. For eligible subjects enrolled retrospectively, the Six-Month Follow-up Visit data collection may occur at the same day as Three-Month Follow-up Visit data collection. For eligible subjects enrolled prospectively, the Six Month Follow-up Visit should occur within 180 ± 30 days post Index Procedure. The data collection at the Six-Month Follow-up Visit includes:

- Date and time of visit, way to collect the data
- Cardiac physical assessment performed as standard of care including, heart rhythm, heart rate, systolic and diastolic blood pressure.
- 12-lead ECG
- 24-hour Holter Monitor
- Recurrent arrhythmia, cardioversions, ablations or hospital admissions including occurrence, date, indication and outcome of any intervention
- Any Stroke Evaluation for Neurologic Assessment, if applicable
- Subjects with unresolved phrenic nerve palsy detected at the discharge visit must be re-assessed per center's standard of care to evaluate if the event resolved
- Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period
- Medication information, including new, discontinued or changes in study-collected medication information (e.g., AADs and NOAC)
- Reportable Adverse Events, including resolution of ongoing events, if applicable
- Protocol Deviations, if applicable

10.10. *Twelve Month Follow-up Visit (365 ± 30 days)*

Discharged subjects will be assessed in person 12 month (365 ± 30 days) post-Index Procedure. For eligible subjects enrolled retrospectively, the Twelve-Month Follow-up Visit data collection may occur in the same day as Six-Month Follow-up Visit data collection. For eligible subjects enrolled prospectively, the Twelve Month Follow-up Visit should occur within 365 ± 30 days post Index Procedure. The data collection at the Twelve-Month Follow-up Visit includes:

- Date and time of visit, way to collect the data
- Cardiac physical assessment performed as standard of care including, heart rhythm, heart rate, systolic and diastolic blood pressure.
- 12-lead ECG and/or Holter
- Apply the 24-hour Holter monitor on the subject and instruct subject to submit their heart rhythm
- Recurrent arrhythmia, cardioversions, ablations or hospital admissions including occurrence, date, indication and outcome of any intervention
- Any Stroke Evaluation for Neurologic Assessment, if applicable
- AF symptom assessment
- Subjects with unresolved phrenic nerve palsy detected at the discharge visit must be re-assessed per center's standard of care to evaluate if the event resolved
- Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period
- Medication information, including new, discontinued or changes in study-collected medication information (e.g., AAD and NOAC)
- Reportable Adverse Events, including resolution of ongoing events, if applicable
- Protocol Deviations, if applicable

10.11. *Unscheduled Visit*

An Unscheduled Follow-up Visit is any subject visit triggered by subject symptoms indicative of complications that may be associated with the catheter ablation procedure or cardiac arrythmia. In addition to determining the best course of action for the subject (i.e., repeat ablation, medication adjustment), during the visit, the following will be collected:

- Date and time of visit, way to collect the data
- Cardiac physical assessment performed as standard of care including, heart rhythm, heart rate, systolic and diastolic blood pressure.
- Rhythm at time of visit by means of 12-lead ECG and/or Holter per investigator's discretion
- Recurrent arrhythmia, cardioversions, ablations or hospital admissions including occurrence, date, indication and outcome of any intervention
- Any Stroke Evaluation for Neurologic Assessment, if applicable
- Perform Cardiac CT/MRI if PV stenosis is suspected at any time throughout the follow-up period
- Medication information, including new, discontinued or changes in study-collected medication information (e.g., AAD and NOAC)
- Reportable Adverse Events, including resolution of ongoing events, if applicable

- Protocol Deviations, if applicable

10.12. *Re-ablation Procedure*

Re-ablation under this protocol requires documentation of detectable AF, AFL or AT. When performed, PVI re-ablation will be performed utilizing the study ablation catheter or any approved catheter at investigator discretion. Any re-ablation procedure for AF, AFL or AT during study follow-up constitutes a Secondary Effectiveness Failure, and therefore during such procedures other sites may be ablated at investigator discretion. CTI ablation or re-ablation for right-sided typical AFL may be performed at any time during the study follow-up and does not constitute a Secondary Effectiveness Failure. Other sites may be ablated at investigator discretion using a commercially available ablation system.

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

- Date and time of visit, way to collect the data
- Date and time of Re-ablation
- Reason for Re-ablation
- During any re-ablation procedure in which LA access is performed, a mapping procedure is recommended to be performed to characterize the reconnection status for each originally treated PV to characterize lesion durability.
- For subjects who received ablation of the CTI, the persistence of nonconductivity in targeted tissue will be evaluated with either pacing maneuvers or electroanatomical mapping.
- Lesion set data

10.13. *Study Completion*

Each Treatment subject will be followed until the Twelve-Month Follow-Up Visit is completed. The end of the study is defined as completion of the last visit shown in the Data Collection Schedule.
ATTEMPT subjects will be followed up to the One Month Follow-Up Visit. However, ATTEMPT subjects will not need to complete post-procedure arrythmia monitoring.
Even though a subject's participation in the clinical study has ended, physicians may wish to continue standard of care visits outside of the study.
In case of premature termination of the study, please refer to **Section 9**. Following termination/completion of the study, subjects will be managed according to local institution practice.
Site must complete the "End of Study" eCRF to signify study completion.

10.14. *Unforeseen Circumstances (Natural Disaster/Global Pandemic)*

There may be unforeseen circumstances that occur during the course of the study, such as a natural disaster (e.g., hurricanes, tornadoes) or a global pandemic (e.g., COVID-19) that prevents a subject from attending study visits 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 EC approved.

In the event that study data must be collected remotely, every effort should be made to collect the data within the study visit window, if possible. Critical data collected during the study includes any procedure or device related adverse events, recurrence of any AF/AT/AFL, and a Cardiac CT or MRI (if PV stenosis is suspected). ECG and 24- hour Holter monitors can be used to detect any recurrence of AF/AT/AFL. If a Cardiac CT or MRI is required because PV stenosis is suspected, the Cardiac CT or MRI may be performed at another healthcare facility and the window to conduct this test data collection may be extended by up to one month (30 days) following the normal study visit window. If the subject is not able to have his/her heart rhythm assessed via a 12-lead ECG, it will not be a protocol deviation.

10.15. *Source Documents*

Table 10.15-1 summarizes all source data requirements for this protocol. 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 10.15-1.**

Table 10.15-1: Source Documentation Requirements

Requirement	**Disposition**
Screening and Enrollment Log	Retain at Center
Informed consent documentation process and investigator eligibility assessment	Retain at Center
Medical history documents pertaining to eligibility criteria	Retain at Center
Documentation of demographics data	Retain at Center
Pregnancy test, if applicable	Retain at Center
Physical assessment	Retain at Center
Cardiovascular/pulmonary examination, including but is not limited to: • Cardiac CT/MRI • TEE/TTE • 12-lead ECG • 24-hour Holter	Retain at Center
Medication Regimen and Changes	Retain at Center
Medical history	Retain at Center

Table 10.15-1: Source Documentation Requirements

Requirement	Disposition
Electrocardiographically documented episodes of AF/AFL/AT can include, but is not limited to: • ECG • 24-hour or longer Holter • Rhythm Strip – note that if the irregular heart rhythm was captured via a wearable, the investigator must review the rhythm strip, document confirmation of atrial fibrillation and sign and date the printed rhythm strip. If the rhythm strip is not printed, documentation of investigator review, and confirmation of the atrial fibrillation must be located in the EMR system.	Retain at Center
Neurological consultation, assessment and/or examination, if applicable	Retain at Center
Labs	Retain at Center
EP lab procedure report	Retain at Center
Signed Technical Source Form (TSF)	Retain at Center
Adverse events	Retain at Center
In the event of a patient death: • Death narrative • Relevant medical records • Death certificate • Autopsy report, if applicable • Relevant medical records	Retain at Center

10.16. *Local vendor documentation*

This study requires a vendor. Appropriate certifications and documentation records are required to be maintained at the site for vendor.

11. Statistical Considerations

11.1. *Endpoints*

11.1.1. *Primary Endpoints*

11.1.1.1. Primary Safety Endpoint

The primary safety endpoint at 30 days consists of acute primary safety endpoint events as defined in **Section 6**, which will be assessed after all the enrolled subjects finishing One-month Visit data collection.

11.1.1.1.1 Hypothesis

This is an observational real-world study with small sample size, no formal hypothesis is performed in this study.

11.1.1.1.2 Sample Size

There is no formal hypothesis for this study, thus no sample size calculation is performed in this study. The study device has achieved CE mark and accumulated a large amount of clinical data. This trial with 30 PAF subjects will be used to produce data in Chinese population.

The following table provides a 95% confidence interval (exact methods) for a sample size of 30 if there are 0 ~ 3 primary safety events.

Safety Events	Rates (n=30)	Lower 95%CI	Upper 95%CI
0	0%	0%	11.6%
1	3.3%	0.1%	17.2%
2	6.7%	0.8%	22.1%
3	10%	2.1%	26.5%

11.1.1.1.3 Statistical Methods

Descriptive statistics will be conducted for the safety endpoint events. The number, incidence (amount of events/number of subjects) and its 95% confidence interval (exact methods) will be calculated. The primary safety endpoints will be analyzed for ATTEMPT and TREATMENT subjects in the ITT set. Explorative statistical analysis might be produced if appropriate, e.g., Bayesian estimation of the study results using FARAPULSE IDE data as the prior.

11.1.1.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint is the acute procedural success, defined as proportion of subjects that achieved PVI with FARAPULSE Pulsed Filed Ablation system only, which will be assessed after all the enrolled subjects finishing One-month Visit data collection.

11.1.1.2.1 Hypothesis

This is an observational real-world study with small sample size; thus, no formal hypothesis is performed in this study.

11.1.1.2.2 Sample Size

There is no formal hypothesis for this study, thus no sample size calculation is performed in this study. The study device has achieved CE mark and accumulated a large amount of clinical data. This trial with 30 PAF subjects will be used to produce data in Chinese population.

11.1.1.2.3 Statistical Methods

Descriptive statistics will be conducted for the effectiveness endpoint events. The number, incidence (amount of events/number of subjects) and its 95% confidence interval (exact methods) will be calculated. The primary effectiveness endpoints will be analyzed for TREAMENT subjecs in the mITT set. Explorative statistical analysis might be produced if appropriate, e.g., Bayesian estimation of the study results using FARAPULSE IDE data as the prior.

11.1.2. *Secondary Endpoints*

11.1.2.1. Secondary Safety Endpoints

The secondary safety endpoint will evaluate the proportion of subjects that free from primary safety events defined in **Section 6** through 7 days after the procedure and free from the following serious procedure-related and/or device-related adverse events at any time through the completion of 12-month follow-up visit, which will be assessed at the time of the twelve-month analysis:

- Atrial esophageal fistula
- Severe PV stenosis
- Persistent phrenic nerve palsy*

**The study will collect information on phrenic nerve palsy observed before the end of the index procedure and, in case of occurrence, will track information for potential recovery during the study visits.*

11.1.2.2. Secondary Effectiveness Endpoint 1

The first secondary effectiveness endpoint will evaluate the chronic success, which is defined as proportion of subjects that free from effectiveness events defined as failure as below at twelve months post-procedure.

Effectiveness events determining a failure are defined as:

- Fail to achieve electrical isolation of all PVs using FARAPULSE Pulsed Filed Ablation system only.
- After the Blanking Period to 12-month after the procedure:

a) Occurrence of any Detectable AF, AFL* or AT captured by one of the following methods: ≥ 30 seconds in duration recording from 24-hour or longer Holter Monitor or ≥ 10 seconds recording from 12-lead ECG.

b) Any cardioversion for AF, AFL* or AT.

c) Use of any Class I or Class III AADs[#] for the treatment of AF, AFL* or AT.

- At any time through 12 months after the procedure:

a) Re-ablation for AF, AFL* or AT.

b) Use of amiodarone, except intra-procedurally to control an arrhythmia.

[#]*It won't be considered as a failure if the subject has three-month visit happened after 90 days post the procedure, but still in the window (<=104 day) with AADs on, and physicians decide to take AADs off after this visit.*

**excluding CTI-dependent flutter confirmed by EP study*

11.1.2.3. Secondary Effectiveness Endpoint 2

The second secondary effectiveness endpoint will evaluate the proportion of PVs that achieve electrical isolation by using the FARAPULSE Pulsed Field Ablation system only.

11.1.2.4. Secondary Effectiveness Endpoint 3

The third secondary effectiveness endpoint will evaluate the chronic success when allowing AADs, which is defined as proportion of subjects that free from effectiveness events defined as failure as below at 12 months post-procedure.

Effectiveness events determining a failure are defined as:

a) Fail to achieve electrical isolation of all PVs using FARAPULSE Pulsed Field Ablation system only.

b) After the Blanking Period to 12-month after the procedure:

- Occurrence of any Detectable AF, AFL* or AT captured by one of the following methods: ≥ 30 seconds in duration recording from 24-hour or longer Holter Monitor or ≥ 10 seconds recording from 12-lead ECG.
- Any cardioversion for AF, AFL* or AT.

c) At any time through 12 months after the procedure:

- Re-ablation for AF, AFL* or AT.

**excluding CTI-dependent flutter confirmed by EP study*

11.1.3. *Additional Endpoints*

1. AF symptoms assessment: Descriptive analysis of atrial fibrillation symptoms at baseline versus 12 months after the procedure.
2. Procedural parameters:

- Total procedure time (initiation of interventional venous access puncture to all devices remove from the body)
- Left atrial dwell time (total time an ablation catheter is in the left atrium)
- Total ablation time (first ablation to last ablation for PVI)
- Fluoroscopy time (total duration of exposure)

11.2. *General Statistical Methods*

Descriptive statistics will be conducted for the primary, secondary and other endpoint events. When descriptive statistics are used, continuous variables will be summarized using standard quantitative statistics: number of available observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values) and its 95% confidence interval. Categorical variables will be summarized using the number, incidence (amount of events/number of subjects) and its 95% confidence interval (exact methods).

Explorative statistical analysis might be produced if appropriate, e.g., Bayesian estimation of the study results using FARAPULSE IDE data as the prior.

11.2.1. *Analysis Sets*

ITT set will involve subjects who have signed informed consent and satisfied with all key criteria.Primary effectiveness endpoints will be summarized for TREATMENT subjects in mITT set.

Secondary effectiveness endpoints will be summarized for TREATMENT subjects in ITT set and mITT set respectively.

Primary and secondary safety endpoints will be summarized for ATTEMPT and TREATMENT subjects in ITT set.

The additional endpoints will be summarized for TREATMENT subjects in ITT set.

11.2.2. *Control of Systematic Error/Bias*

This is a real-world study. Selection of patients will be made from the Investigational site's routine patients. All patients meeting the key eligibility criteria and having signed the ICF will be eligible for enrollment in the study. Control and reduction of potential bias associated with a single-arm study design have been taken into account by defining key inclusion and exclusion criteria to represent a population similar to the patients with AF ablation in the real world and defining a mITT group with population similar to the subjects enrolled in ongoing ADVENT trial and other trials about AF ablation.

11.2.3. *The Method of Handling Missing Value and Outliers*

Every effort will be undertaken to minimize missing or incorrect data. However, some missingness is inevitable. The reasons for missing or incorrect data will be described in detail and evaluated for assessment of possible bias if appropriate. The distribution of missing and/or

incorrect data will be analyzed too, which will be separately analyzed based on whether the data is collected prospectively or not.

For the missing data, only the missing primary endpoint indicators will be carried forward during analysis, and the specific carry forward method will be explained in SAP. Sensitivity analyses will be performed on the primary safety and effectiveness endpoints to assess the impact of missing data on study results. In addition to worst-case missing data filling, Tipping Point Analysis will be performed as a post-hoc Analysis to assess the impact of different missing data filling methods on the results.

Error and unreasonable data will be checked and confirmed during data cleansing prior to statistical analysis. Error data will be corrected before analysis, and sensitivity analyses will be performed to assess the impact of unreasonable data on the stability of the results if appropriate.

11.2.4. *Number of Subjects per Investigative Site*

Thirty ATTEMPT or TREATMENT subjects will be enrolled from one site.

11.3. *Data Analyses.*

11.3.1. *Primary Endpoints/Measurements*

The primary safety and effectiveness endpoints will be analyzed after all the enrolled subjects finishing One-month Visit data collection. The primary safety endpoint will be analyzed for ATTEMPT and TREATMENT subjects in ITT set. The primary effectiveness endpoint will be analyzed for TREATMENT subjects in mITT set. Descriptive statistics will be conducted for the effectiveness endpoint events. The number, incidence (amount of events/number of subjects) and its 95% confidence interval will be calculated (exact methods). Explorative statistical analysis might be produced if appropriate, e.g., Bayesian estimation of the study results using FARAPULSE IDE data as the prior.

11.3.2. *Secondary Endpoints/Measurements*

The primary safety and effectiveness endpoints will be analyzed after all TREATMENT subjects finishing Twelve-month Visit data collection. The secondary safety endpoint will be analyzed for ATTEMPT and TREATMENT subjects in ITT set. The secondary effectiveness endpoint will be analyzed for TREATMENT subjectsin mITT set and ITT set respectively. Descriptive statistics will be conducted for the effectiveness endpoint events. The number, incidence (amount of events/number of subjects) and its 95% confidence interval will be calculated (exact methods). The final report will be finished then.

11.3.3. *Additional Endpoints/Measurements*

The additional endpoints will be analyzed after all TREATMENT subjects finishing Twelve-month Visit data collection. The additional endpoints will be analyzed for TREATMENT subjects in ITT set. Descriptive statistics will be conducted for the effectiveness endpoint

events. The number, incidence (amount of events/number of subjects) and its 95% confidence interval will be calculated (exact methods).

11.3.4. *Interim Analyses*

There is no formal statistical hypothesis test in this study, thus interim analysis can be made according to actual needs.

11.3.5. *Subgroup Analyses*

The primary and secondary endpoints will be sub analyzed based on the following variables,including but not limited to:

- gender
- Whether ablation is performed as first-line therapy.
- Whether the subject is enrolled prospectively.

11.3.6. *Univariable Analyses*

Univariable analyse will be performed to assess the impact of potential baseline data and clinical characteristics on the primary endpoints.

11.3.7. *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

12. Data Management

12.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure EDC system.

The clinical database will reside on a production server hosted by iMedidata 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. 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 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 Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

All access to the clinical database will be changed to "Read only" after all data is either "Hard Locked" or "Entry Locked". Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. Once all of the closeout activities are completed a request to IT is submitted to have the "Database Locked" or Decommissioned and all database access revoked.

12.2. *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 Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

12.3. *Technical Source Forms*

A TSF is developed by Boston Scientific or by the investigational site to capture protocol required data elements that are not duplicated in any other source documents. This form is to be used by the study sites as a source document. A Boston Scientific representative may complete the TSF at the request of the Principal Investigator. The TSF will be reviewed and signed for approval by the Principal Investigator or his/her designee at the end of each procedure. For eligible subjects enrolled retrospectively, the TSF may not be available, this should not be a Protocol Deviation.

The protocol trained Boston Scientific representative may only use study specific TSFs provided and approved by the Boston Scientific study team. 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.

Collection and completion of all information on the TSF is the responsibility of the appropriate personnel as defined on the TSF. If available, the protocol trained FARAPULSE Pulsed Field Ablation system specialist or other protocol trained Boston Scientific representative will provide the delegated site personnel with the study related data collected during the case directly from FARAPULSE Pulsed Field Ablation system.
At the conclusion of the procedure, the completed TSF must be signed (and initialed as needed) by the following people:

- Delegated Site Personnel completing the forms
- Delegated Investigator conducting and/or supervising the case
- BSC personnel supporting the visit

13. Amendment

The investigator should adhere to clinical trial protocol approved by Ethics Committee (EC). Any Amendment to the protocol (management information or study process modification, etc.) should be completed and reviewed by the sponsor during the study, then should be submitted to the EC for approval via the investigator. Only the amendment of protocol is approved by EC, the amended ptotocol should be implemented.

14. 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 and the reviewing EC, 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 eCRF. Sites may also be

required to report deviations to the EC, and the regulatory authority, per local guidelines and national/government regulations.

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

The sponsor will not approve protocol waivers.

15. Compliance

15.1. *Statement of Compliance*

This clinical investigation is financed by the study 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 related parts in ISO14155, ICH-GCP, ethical principles that have their origins in the Declaration of Helsinki, and applicable Chinese laws and regulations. The study shall not begin until the required approval/favorable opinion from the EC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

15.2. *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/, the spirit of ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing EC, 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 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 eCRFs 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 sponsor, clinical trial institution, the EC any SAEs , and follow up visit will be conducted and reported per protocol according to China regulations.
- Report to sponsor, clinical trial institution and EC when the clinical trial risks are identified to outweigh the possible benefits and it is necessary to suspend or terminate the clinical trial. Inform subjects of the risk immediately, ensuring that the subjects could receive appropriate treatment and follow-up visits.
- 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 EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local EC 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 ICF.
- Inform the subject of the nature and possible cause of any adverse events experienced.
- 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, including decoding procedures for blinded/masked clinical investigations, as needed.
- 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.

15.2.1. 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, are competent to perform the tasks they have been delegated and adequate supervision of 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.

15.3. *Ethics Committee*

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

A copy of the written EC 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. 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 EC before the changes are implemented to the study. All changes to the ICF will be EC approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.
Annual EC approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or EC requirements. Copies of the study reports and the EC continuance of approval must be provided to the sponsor.

15.4. *Sponsor Responsibilities*

All information and data sent to Boston Scientific (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.

15.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during procedure, 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 the FARAPULSE Pulsed Field Ablation system and other support equipment).
At the request of the investigator and while under investigator supervision, trained BSC personnel may operate equipment during ablation procedure, 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:

- Setting up, calibrating and/or operating parameters to investigator-requested settings of the FARAPULSE Pulsed Field Ablation system during the procedure.
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel.
- Interaction with Boston Scientific noninvasive equipment and interpretation of information contained therein to support the collection of required information by the delegated site staff.
- Provide original to clinical site as source documentation, if appropriate.
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.
- Assisting with the collection of study data from the BSC equipment/devices, if appropriate.
- Entering technical data on TSF as long as the responsible investigator verifies and signs the completed form.

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 clinical protocol compliance.
- Reviewing collected data and study documentation for completeness and accuracy.

Boston Scientific 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 without the approval and presence of the investigator
- Independently collect critical study data (defined as primary or secondary endpoint data) without review and approval of the investigator
- Enter data in EDC systems or on paper case report forms

15.5. *Insurance*

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

16. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies 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/institution guarantees 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 is devoted to the process.

17. Potential Risks and Benefits

17.1. *Instructions for Use*

Please refer to the Instructions for Use for an overview of anticipated adverse (device) effects, and risks associated to the commercial device(s).

17.2. *Risks associated with Participation in the Clinical Study*

This is a real-world observational study. There are no specific tests outside of standard practice required by this clinical study protocol. During follow-up visits, the ECG and 24-hour Holter pre-defined in the protocol align with routine clinical procedures and guidelines. Therefore, there is no foreseen increased risk to subjects for participating in the REPLACE Study.

17.3. *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.

17.4. *Anticipated Benefits*

This is a real-world observational study; subjects may not receive any benefit from participating in this study compared to the current standard of care. However, aligning with these follow-up schedules will allow physicians to have better knowledge about the patient's condition and adjust treatment plans accordingly. Moreover, the data collected in this study will be used to support the FARAPULSE Pulsed Field Ablation system registration in China, thus more PAF patients will benefit from PFA treatment in the future.

18. Safety Reporting

18.1. *Reportable Events by investigational site to Boston Scientific*

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

- All adverse events
- All serious adverse events
- All Adverse Events related to FARAPULSE Pulsed Field Ablation system
- All Serious Adverse Events related to FARAPULSE Pulsed Field Ablation system
- All Adverse Events related to the Procedure
- All Serious Adverse Events related to the Procedure
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects
- 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

The following clinical events will not be considered adverse events for this clinical study:

- 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.

- Pre-planned hospitalizations before the index procedure or for a pre-existing condition.
- AF/AFL/AT episodes with medical intervention or hospitalization due to arrhythmia recurrence during the blanking period.
- If an additional ablation procedure is required, this additional ablation procedure should only be considered an AE if it is associated with subject worsening condition or a new diagnosis. The ablation would be considered a corrective action.

If the subject experiences a new or worsening arrhythmia between the index procedure and the end of study, and the investigator considers this AE to be study related, it needs to be reported. Refer to Investigator's Brochure or IFU as appropriate for the known risks associated with the study device(s).

Any reportable event, experienced by the study subject after informed consent, whether prior to, during or subsequent to the 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 18.2-1** for AE definitions).

Refer to Instructions for Use for the known risks associated with the study device(s).

18.2. *Definitions and Classification*

Adverse event definitions are provided in **Table 18.2-1**. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR Part 812, ISO 14155, GCP issued by NMPA and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 18.2-1: Safety Definitions

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 study medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the study 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 study medical device.

Table 18.2-1: Safety Definitions

Term	Definition
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of the study medical device **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 study medical device. **NOTE 2**: This definition includes any event resulting from use error or from intentional misuse of the study 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) fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
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

Table 18.2-1: Safety Definitions

Term	Definition
	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 device under study.
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)

Table 18.2-1: Safety Definitions

Term	Definition
	• 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) **NOTE 1**: If complications or AEs occur during an elective/planned (i.e., planned prior to signing ICF) hospitalization after signing ICF, the complications and AEs must be reported as AEs or SAEs if they meet the protocol-specified definitions, However, the original elective/planned hospitalization(s) itself should not be reported as an SAE.
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 criterion.

18.3. *Relationship to Study Device(s) and/or Study Procedure*

The Investigator must assess the relationship of the reportable AE to the study device(s), and/or study procedure. See criteria in **Table 18.3-1:**

Table 18.3-1 : Criteria for Assessing Relationship of Study Device(s) or Procedure to Adverse Event

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 study device, or the procedures related to the use of the study 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 study 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 study 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 study device or, comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.

Table 18.3-1 : Criteria for Assessing Relationship of Study Device(s) or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MDCG 2020-10/1*	The serious event is associated with the study device, 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 the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to. -the study 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 study 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 event.

Please refer to **Section 26** Appendices for Relationship Criteria that to be used in sponsor expediting reporting.

18.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Table 18.4-1.**

Considering that this study is a real-world observational study conducted in Boao, Hainan province, and the time limit for reporting adverse events for subjects enrolled retrospectively is not stipulated by the current regulations, the sponsor has stipulated the time limit for reporting adverse events according to the characteristics and practical operation of this study and applicable national regulations.

Table 18.4-1: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event for data collected prospectively. • Within 5 working days of first becoming aware of the event for data collected retrospectively. • Terminating at the end of the study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor.
Serious Adverse Event including serious adverse effects	Complete AE eCRF page with all available new and updated information.	• Within 24 hours of first becoming aware of the event for data collected prospectively. • Within 5 working days of first becoming aware of the event for data collected retrospectively. • Reporting required through end of study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
Device Deficiencies (including but not limited to malfunctions, use errors, and inadequacy in information supplied by the manufacturer, including labelling)	Complete eCRF with all available new and updated information.	• Within 24 hours of first becoming aware of the event for data collected prospectively. • Within 5 working days of first becoming aware of the event for data collected retrospectively. • Reporting required through the end of the study

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (*EU MDR 2017/745, MDCG 2020-10/1*MEDDEV 2.12/1: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
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.	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
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.	• In a timely manner but recommend within 10 business days after becoming aware of the information • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor

18.5. *Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) associated with the study devices (FARAPULSE Pulsed Field Ablation system) will be documented and reported to BSC. All other ablation or diagnostic catheters may be disposed of per standard EP practice. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency, would be recorded as an adverse event on the appropriate eCRF.

18.6. *Reporting to ECs/ Investigators*

Boston Scientific is responsible for reporting adverse events and device deficiencies (if applicable) to all participating investigators, clinical trial institutions, ethic committees and regulatory authorities in compliance with the current Medical Device Good Clinical Practice. Please refer to **Section 26** Appendices for Template of Report Form for Serious Adverse Events.

Investigator is responsible for reporting all SAEs to the sponsor, the clinical trial institution, and the EC within 24 hours of first becoming aware of the event. Investigator shall also follow up the SAE according to the study protocol and submit a follow-up report.

BSC shall notify all participating Chinese study centers if SAEs/SADEs occur which imply a possible increase in the anticipated risk of the procedure or use of the device or if the occurrence of certain SAEs/SADEs demands changes to the protocol or the conduct of the study in order to further minimize the unanticipated risks.

18.7. *Subject Death Reporting*

A subject death during the study should be reported to Boston Scientific as soon as possible and, in any event, within three (3) calendar days of site notification. The site's EC must be notified of any deaths in accordance with that site's EC 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 (if not already submitted to Boston Scientific)
- Death certificate (if available)

19. 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 study devices, study-required procedures and/or 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, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's EC, or central IRB, if applicable.

Boston Scientific 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 EC. Any modification requires acceptance from BSC prior to use of the form. 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 consent forms must also have EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form 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 sign, 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 document and any other written information must be given to the person signing the form.

Failure to obtain subject 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., EC), 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 EC. The new version of the ICF must be approved by the EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site’s EC. The EC will determine the subject population to be re-consented.

There are special circumstances in which the willingness of individual subjects to participate in the study could be unduly influenced or unknown.

Subject Needing Legally Authorized Representative:

- Informed consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation (e.g., infant, child and juvenile, seriously ill or unconscious subject, mentally ill person, mentally handicapped person). In such cases, the subject shall also be informed about the clinical study within his/her ability to understand.
- Where the subject's mental and/or physical capacity may deteriorate over the course of the subject's participation in the study rendering the subject incapable of rendering reliable responses to study activities, the subject may appoint/designate at the initial informed consent, an individual to provide responses in the case of incapacity, deterioration or death of the subject.

Unable to Read or Write:

- Informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent and impartial witness shall be present throughout the process. The written ICF and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, either one shall sign and personally date the ICF. The witness also signs and personally dates the ICF attesting that the information was accurately explained, and that informed consent was freely given.

20. Committees

20.1. *Safety Monitoring Process*

The BSC personnel from the Medical Safety and Safety Trial Operation group 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 cardiac electrophysiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

20.2. *Steering Committee*

A Steering Committee composed of the sponsor's Clinical Management and the study Principal Investigator 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.

21. Suspension or Termination

21.1. *Premature Termination of the Study*

Boston Scientific 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 ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

21.1.1. *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 bby the EC 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 Boston Scientific to suspend or discontinue development/marketing of the device.

21.2. *Termination of Study Participation by the Investigator or Withdrawal of EC Approval*

Any investigator, or associated EC or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to Boston Scientific. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

21.3. *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 site(s) by Boston Scientific. The EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

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

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 Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents, unless this action would jeopardize the rights, safety, or welfare of the subjects.

21.4. *Criteria for Suspending/Terminating a Study Site*

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 3 months after site initiation, 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, all study-related documents will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The EC and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

22. Study Registration and Results

22.1. *Study Registration*

To comply with applicable laws and regulations, the study will be registered on a publicly accessible database.

22.2. *Clinical Investigation Report*

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

22.3. *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 may submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific 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 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 Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

23. Reimbursement and Compensation for Subjects

23.1. *Subject Reimbursement*

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.

23.2. *Compensation for Subject's Health Injury*

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

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25. Abbreviations and Definitions

25.1. *Abbreviations*

Abbreviations are shown in **Table 25.1-1**.

Table 25.1-1: Abbreviations

Abbreviation/Acronym	Term
AAD	Anti-Arrhythmic Drug

Table 25.1-1: Abbreviations

Abbreviation/Acronym	Term
ACT	Activated Clotting Time
AF	Atrial Fibrillation
AFL	Atrial Flutter
AT	Atrial Tachycardia
AV	Anterio-Venous
BMI	Body Mass Index
CABG	Coronary Artery Bypass Grafting
CRF	Case Report Form
CRO	Contract Research Organization
CRT	Cardiac Resynchronization Therapy
CTI	Cavotricuspid Isthmus
CVA	Cerebral Vascular Accident
DFU	Directions for Use
DMS	Diaphragm Movement Sensor
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiography
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
eGFR	Estimated Glomerular Filtration Rate
EP	Electrophysiology
GCP	Good Clinical Practice
HRS	Heart Rhythm Society
IB	Investigator's Brochure
ICD	Implantable Cardioverter Defibrillator
ICE	Intracardiac echocardiography
ICF	Informed Consent Form
ID	Identification Number
IFU	Instructions for Use
INR	International Normalized Ratio
IVC	Inferior Vena Cava
LA	Left Atrium
LGE	Late Gadolinium Enhance
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
MVs	Monitoring Visits
NMPA	National Medical Products Administration
NOAC	New oral anticoagulants
NYHA	New York Heart Association
PAF	Paroxysmal Atrial Fibrillation
PE	Pulmonary Embolism
PFA	Pulse Field Ablation
PTCA	Percutaneous transluminal coronary angioplasty

Table 25.1-1: Abbreviations

Abbreviation/Acronym	Term
PV	Pulmonary Veins
PVI	Pulmonary Vein Isolation
RFA	Radiofrequency Ablation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SCE	Silent Cerebral Event
SCL	Silent Cerebral Lesion
TEE	Trans-esophageal echocardiography
TIA	Transient Ischemic Attack
TSF	Technical Source Form
TTE	Transthoracic Echocardiography
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

25.2. *Definitions*

Terms are defined in **Table 25.2-1**.

Table 25.2-1: Definitions

Term	Definition
Activated Coagulation/Clotting Time	ACT is a test that is used to monitor the effectiveness of high dose heparin therapy.
Acute Procedural Success	Achieve electrical isolation of all PVs using FARAPULSE Pulsed Field Ablation only.
Arterial-Venous Fistula	Abnormal communication between an artery and a vein.
Atrioesophageal Fistula	An atrioesophageal fistula is defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium, such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT scan or MRI scan is the most common method of documentation of an atrioesophageal fistula.
Attempt Subject	Any subject that signs the consent form, meets eligibility criteria and has any study device inserted into the body but does not receive any PFA application with the study device.
AV block	A conduction disturbance that results in the partial inability of an electrical impulse generated in the atria to reach the ventricles. Refers to AV block not attributable to medication effect or vasovagal reaction.
Blanking Period	90-day period between ablation procedure and the initiation of the Long-term Effectiveness Evaluation Period during which subjects can be prescribed antiarrhythmic drugs as determined necessary by the investigator.
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.

Table 25.2-1: Definitions

Term	Definition
	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.
Embolism	The sudden blocking of an artery by a clot or foreign material which has been brought to its site of lodgment by the blood current.
Enrolled Subject	A subject who is eligible for enrollment and signs an informed consent document to participate in the study.
Hematoma	A localized collection of blood, usually clotted, in an organ, space or tissue, due to a break in the wall of a blood vessel.
Intent Subject	Any subject that signs the consent form but does not have any study devices inserted into the body. Subjects who are enrolled in the study but do not undergo ablation procedure within 30 days from consent signature date may not be reconsented and will be withdrawn from the study.
In-patient Hospitalization	Hospitalizations ≥24 hours in duration or <24 hours with medical intravenous therapy or surgical intervention
Total procedure time	Initiation of interventional venous access puncture to all devices remove from the body
LA dwell time	Total time an ablation catheter is in the left atrium
Myocardial infarction (in the context of AF ablation)	The presence of any one of the following criteria: (1) detection of ECG changes indicative of new ischemia (new STT 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
Paroxysmal Atrial Fibrillation (PAF)	Recurrent symptomatic Atrial Fibrillation that terminates spontaneously or with intervention within seven days of onset.
Pericarditis	Inflammation of the pericardium surrounding the heart. Pericarditis should be considered a major complication following ablation if it 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.
Phrenic Nerve Palsy	Phrenic nerve palsy is defined as absent phrenic nerve function demonstrated radiographically. A phrenic nerve palsy is considered to be permanent when it is documented to be present 12 months or longer following ablation.
Pneumothorax	Collapse of the lung due to an abrupt change in the intrapleural pressure within the chest cavity.
Secondary Effectiveness Failure	A Treatment Subject with: • Fail to achieve electrical isolation of all PVs using FARAPULSE Pulsed Field Ablation system only. • After the Blanking Period (90 days post the procedure) to 12-month after the procedure:

Table 25.2-1: Definitions

Term	Definition
	1) Occurrence of any Detectable AF, AFL* or AT captured by one of the following methods: ≥ 30 seconds in duration recording from 24-hour or longer Holter Monitor or ≥ 10 seconds recording from 12-lead ECG, or 2) Any cardioversion for AF, AFL* or AT, or 3) Use of any Class I or Class III AADs[#] for the treatment of AF, AFL* or AT. • At any time through 12 months after the procedure: 1) Re-ablation for AF, AFL* or AT, or 2) Use of amiodarone, except intra-procedurally to control an arrhythmia. [#]*It won't be considered as a failure if the subject has three-month visit happened after 90 days post the procedure, but still in the window (<=104 day) with AADs on, and physicians decide to take AADs off after this visit.* **excluding cavotricuspid isthmus dependent (CTI)-dependent flutter confirmed by EP study*
Pseudoaneurysm	A dilation of an artery with disruption of one or more layers of its walls.
Pulmonary edema	Respiratory compromise resulting from cardiac dysfunction or volume overload leading to increased interstitial lung fluid requiring intubation or parenteral diuretics.
Severe Pulmonary Vein Stenosis	Severe pulmonary vein stenosis is defined as a reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as mild <50%, moderate 50%–70%, and severe ≥70% reduction in the diameter of the PV or PV branch. A severe PV stenosis will count towards the primary safety endpoint if it is confirmed by imaging.
Source Data *Ref: ISO 14155*	All information in original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical study (original records or certified copies).
Source Document *Ref: ISO 14155*	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, radiographs, records kept at the investigation site, and at the laboratories involved in the clinical study.
Vulnerable Population *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.
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

Table 25.2-1: Definitions

Term	Definition
	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.
Thrombus	An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing vascular obstruction at the point of its formation.
Thromboembolism	The blockage of a blood vessel lumen by air or solid material such as device fragments, blood clot or other tissues that have migrated from another anatomic site.
Transient Ischemic Attack (TIA)	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), always within 24 hours; neuroimaging without tissue injury
Treatment Subject	Any subject that signs the consent form, meets eligibility criteria and has the specified study devices inserted into the body and undergoes protocol specific treatment for the intended disease.
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.
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)，prolonging the hospital stay, or requiring hospital admission.

26. Appendices

Template of Report Form for

Serious Adverse Events in Clinical Trials of Medical Devices/In Vitro Diagnostic Reagents

Basic Information			
Name of the Clinical Trial			
Filing No. of the Clinical Trial			
Type of Report	□ Initial report □ Follow-up report □ Summary report	Date of Report	Date: （MM/DD/YYYY）
Sponsor			
Contact Address of the Sponsor			
Contact Person of the Sponsor		Sponsor's Contact Number/Mobile Number	
Clinical Trial Institution			
Filing No. of the Institution		Clinical Trial Specialty	
Principal Investigator		Title	
Contact Person		Contact Number	
Information of the Investigational Medical Device			
Name of Investigational Medical Device		Specification and Model/Packaging Specification	
Classification of Investigational Medical Device		Class III Medical Device Requiring Approval of Clinical Trial	□Yes □ No
Batch Number		Date of Production/Expiration Date	
Scope of Application or Intended Use			
Information of the Subject			
No.			
Gender	□Male □Female	Date of Birth	Date: （MM/DD/YYYY）

Comorbid Conditions and Treatment Description			
Information of Serious Adverse Events			
Name of Serious Adverse Event			
Use Date	Date: （MM/DD/YYYY）	Date of Onset	Date: （MM/DD/YYYY）
Date Investigator Became Aware of the Event	Date: （MM/DD/YYYY）	Date Sponsor Became Aware of the Event	Date: （MM/DD/YYYY）
Classification of Serious Adverse Events	□ Lead to death_____(DD/MM/YYYY) □ Fatal disease or injury □ Permanent defects in body structure or body function □ An in-patient or prolonged hospitalization □ Medical measures are required to avoid permanent defects to body structure or body function □ Lead to fetal distress, fetal death or a congenital abnormality or congenital defect □ Other_____		
Measures Taken on the Investigational Medical Device	□ Continue to use □ Reduce the use □ Resume after suspending use □ Stop using □ Other		
Outcome	□ Symptoms disappear (sequelae □Yes □No) □ Symptoms persist □ Symptoms relieved □ Symptoms worsening □ Death □ Other_____		
Relationship with the Investigational Medical Device	□ Definitely related □ Possibly related □ Possibly unrelated □ Definitely unrelated (Note: it shall not need to be reported to relevant regulatory department if it is possibly or definitely unrelated)		
Device Defects or Not	□Yes □ No	Expected or not	□Yes □ No
Other Serious Safety Risk Information or Not	□Yes □ No	Serious adverse events occurring on a large scale or other major safety issues	□Yes □ No
Detailed information of onset and treatment:			
Risk Control Measures Taken or to be Taken	□ Modify the clinical trial protocol □ Modify the informed consent form (ICF) and other information provided to the subjects □ Modify other relevant documents □ Continue to monitor risks and not take other measures temporarily □ Suspend clinical trials of medical devices □ Terminate clinical trials of medical devices □ Other_____		
Seal of Sponsor			

Note: The medical devices mentioned in this form include in vitro diagnostic reagents.

Completion Instructions:

I. This form is for sponsor of the clinical trial of medical device (including in vitro diagnostic reagents, the same below) to report individual cases of serious adverse events related to the investigational medical device during the clinical trial of medical device to the provincial drug regulatory departments in the place where the sponsor is located, the provincial regulatory departments and health administration departments in the place where the clinical trial institution of medical device is located. The written report shall be delivered by courier after being affixed with the official seal of the sponsor. The report form for the investigator to report serious adverse events shall be determined by the sponsor, information of which shall be covered at least in principle.

II. Serious adverse events related to the investigational medical device refer to the events that occur after subjects use the investigational medical device according to the clinical trial protocol and are believed to be possibly or definitely related to the investigational medical device through analysis.

III. The sponsor shall report serious adverse events (death or life-threatening) related to the investigational medical device within 7 days after being informed of them and report serious adverse events (non-death or non-life-threatening) related to the investigational medical device within 15 days after being informed of them. The day when the sponsor is notified of a serious adverse event is day 0.

IV. When serious adverse events related to the medical devices used in a blind trial occur, in order to identify the correlation between the serious adverse events and the medical devices used in the trial, the sponsor shall establish corresponding procedures. The unblinding of related individual cases shall only be made to individual special persons, but the "blindness" of the cases shall still be kept to those who are responsible for analyzing and elaborating on the efficacy results.

V. When other serious safety risks appear during clinical trials of medical devices, the sponsor shall fill in the applicable items in this form and elaborate on the control measures.

VI. When serious adverse events related to the medical devices used in clinical trials occur on a large scale or other major safety issues arise during clinical trials, the sponsor

shall tick the applicable items in this form, elaborate on the occurrence and handling, and take such risk control measures as suspending or terminating clinical trials of medical devices, etc.

VII. Filling Requirements

1. This form shall be filled in by the sponsor, the content of which shall be not only true, accurate and complete, but also consistent with source data of the clinical trial.

2. This form includes the following four parts: basic information, information of the investigational medical devices, information of subjects and information of serious adverse events.

3. Basic information

3.1 Name of the clinical trial: It refers to the name of the clinical trial of medical device stated on the *Filing Form for Clinical Trial of Medical Device*.

3.2 Filing No. of the clinical trial: It refers to the filing number stated on the *Filing Form for Clinical Trial of Medical Device*.

3.3 Report type

3.3.1 Initial report: It refers to the report submitted when the sponsor is informed of the serious adverse events related to the investigational medical device for the first time.

3.3.2 Follow-up report: It refers to the report submitted when important changes take place during follow-up of the serious adverse events.

3.3.3 Summary report: It refers to the last report after the disappearance/relief of serious adverse events.

3.4 Report date: It refers to the exact day when this form is filled in.

3.5 Sponsor: It refers to the sponsor who reports serious adverse events, which shall be consistent with that stated on the *Filing Form for Clinical Trial of Medical Device*. The official seal shall be affixed.

3.6 Contact address of the sponsor: It refers to the contact address of the entity which reports adverse events of medical device.

3.7 Contact person of the sponsor: It refers to the person who is responsible for monitoring adverse events in clinical trial of medical device and works for the sponsor that takes charge of reporting serious adverse events.

3.8 Sponsor's contact number/mobile number: It refers to the telephone number of the monitoring department which is responsible for monitoring adverse events in clinical trial of medical device and under jurisdiction of the sponsor that takes charge of reporting serious adverse events.

3.9 Clinical trial institution: It refers to the clinical trial institution of medical device that reports the onset of serious adverse events. And it shall be consistent with that stated on the *Filing Form for Clinical Trial of Medical Device*.

3.10 Filing No. of the institution: It refers to the filing number of the clinical trial institution of medical device that reports the onset of serious adverse events in the filing system of the drug regulatory departments. And it shall be consistent with that stated on the *Filing Form for Clinical Trial of Medical Device*.

3.11 Clinical trial specialty: It refers to the filing name of the clinical trial specialty where the reported serious adverse events occur in the filing system of the drug regulatory departments. And it shall be consistent with that stated on the *Filing Form for Clinical Trial of Medical Device*.

3.12 Principal investigator: It refers to the principal investigator from the clinical trial institution of medical device that reports the onset of serious adverse events. And it shall be consistent with that stated on the *Filing Form for Clinical Trial of Medical Device*.

3.13 Title: It refers to the title of the principal investigator of the clinical trial institution of medical device that reports the onset of serious adverse events.

3.14 Contact person: It refers to the contact person of the clinical trial institution of medical device that reports the onset of serious adverse events. The contact person can be either the principal investigator or clinician among investigators authorized by the principal investigator.

3.15 Contact number: It refers to the contact telephone number of the contact person from the clinical trial institution of medical device that reports the onset of serious adverse events.

4. Information of the investigational medical device

4.1 Name of investigational medical device: It refers to the name of the investigational medical device related to the reported serious adverse events. And it shall be consistent with that stated on the *Filing Form for Clinical Trial of Medical Device*.

4.2 Specification and model/packaging specification: It refers to the specification and model of the investigational medical device or the packaging specification of the investigational in vitro diagnostic reagent involved in the reported serious adverse events, which shall be consistent with the specification and model of the investigational medical device or the packaging specification of the investigational in vitro diagnostic reagent stated on the *Filing Form for Clinical Trial of Medical Device*.

4.3 Classification of investigational medical device: It refers to the classification of the investigational medical device related to the reported serious adverse events. And it shall be consistent with that stated on the *Filing Form for Clinical Trial of Medical Device*.

4.4 Class III medical device requiring approval of clinical trial: It refers to whether the investigational medical device related to the reported serious adverse events belongs to Class III medical device requiring approval of clinical trial. And it shall be consistent with that stated on the *Filing Form for Clinical Trial of Medical Device*.

4.5 Batch No.: It refers to the batch number of the investigational medical device related to the reported serious adverse events. And it shall be consistent with that stated on the label or packaging mark used for the investigational medical device.

4.6 Date of production/expiration date: It refers to the date of production and period during which the quality of the investigational medical device can be guaranteed under specified conditions. And it shall be consistent with that stated on the label or packaging mark used for the investigational medical device.

4.7 Scope of application or intended use: It refers to the scope of application or intended use of the investigational medical device.

When multiple investigational medical devices are involved, more lines can be added as appropriate.

5. Information of subjects

5.1 No.: It refers to the number of the subject involved in the reported serious adverse events in clinical trial.

5.2 Gender: It refers to the gender of the subjects involved in the reported serious adverse events.

5.3 Date of birth: It refers to the date of birth of the subject involved in the reported serious adverse events in clinical trial.

5.4 Comorbid conditions and treatment: It refers to the comorbid conditions and treatment of the subject involved in the reported serious adverse events in clinical trial, which shall be filled in according to the medical record of the subject. If the subject has no comorbid conditions and treatment, please fill in "None".

6. Information of serious adverse events

6.1 Name of serious adverse events: It refers to the name of the reported serious adverse event, which shall be a medical term with priority given to medical diagnosis.

6.2 Use date: It refers to the exact use date of the investigational medical device related to the reported serious adverse events.

6.3 Onset date: It refers to the onset date of the reported serious adverse event.

6.4 Date investigator became aware of the event: It refers to the exact date when the investigator becomes aware of the reported serious adverse events.

6.5 Date sponsor became aware of the event: It refers to the exact date when the investigator reports the serious adverse events to the sponsor.

6.6 Classification of serious adverse events: It refers to the classification of the reported serious adverse events. If "Other" is ticked, the specific situation shall be indicated.

6.7 Measures taken on the investigational medical device: They refer to the measures taken by investigators on the investigational medical device related to serious adverse events. If "Other" is ticked, the specific measures shall be indicated.

6.8 Outcome: It refers to the outcome of the subjects when this form is filled in. If "Symptoms disappear" is ticked, whether there are sequelae shall be further chosen. If "Other" is ticked, the specific situation shall be indicated.

6.9 Relationship with the investigational medical device: It refers to the correlation between the reported serious adverse events and the investigational medical device.

6.9.1 Related to the investigational medical device: (1) there is a reasonable time relationship between the two; (2) it belongs to the known risk of the investigational medical device or can be explained by the mechanism of the investigational medical device; (3) the injury is reduced or disappeared after stopping use; (4) the injury appears again after reuse; (5) it cannot be explained by other influencing factors. It shall be determined as "definitely related" when five of them are met at the same time and "possibly related" when two of them are met.

6.9.2 Unrelated to the investigational medical device: (1) there is no reasonable time relationship between the two; (2) this adverse event is a type of event that is unlikely to be caused by the investigational medical device; (3) this adverse event can be explained by combination of device/drug, disease progress of the patient and other treatment effects. It shall be determined as "definitely unrelated" when three of them are met at the same time and "possibly unrelated" when one of them is met.

6.10 Device defects or not: It refers to whether the reported serious adverse events are caused by device defects of the investigational medical device.

6.11 Expected or not: It refers to whether the reported serious adverse events are the expected serious adverse events of investigational medical device.

6.12 Other serious safety risk information: It refers to whether the reported content belongs to other serious safety risk information.

6.13 Serious adverse events occurring on a large scale or other major safety issues: It refers to whether it belongs to serious adverse events occurring on a large scale or other

major safety issues that require suspension or termination of clinical trials according to the clinical trial protocol, characteristics of medical devices, product risks, literature data, etc. in combination with the number of cases previously reported and their specific situation.

6.14 Detailed information of onset and treatment: It refers to the onset of the reported serious adverse events and the treatment conducted by the investigator.

6.14.1 It is necessary to describe the participation of subjects in clinical trial of medical device.

6.14.2 It is necessary to describe the use of the investigational medical device. For active and passive medical devices, the following shall be described: specific operation and use of the investigational medical device, unexpected results, (possible) injury to subjects, rescue measures taken and results, etc. For in vitro diagnostic medical devices, the following shall be described: patient diagnosis and treatment information (such as disease and medication), sample testing process and results, abnormal conditions found, measures taken, final result determination, and impact on clinical diagnosis and treatment.

6.14.3 The occurrence and handling of serious adverse events shall be described.

6.14.4 In case of any serious adverse events occurring on a large scale, the situation of the subjects involved in the serious adverse events shall be summarized in detail.

6.15 Risk control measures taken or to be taken: They refer to the risk control measures taken or to be taken for serious adverse events. If "Other" is ticked, the specific measures shall be described, such as strengthening the training of investigators, paying close follow-up visits, etc