AFIRE study
Protocol Number: BWI202107
APRIL 20, 2023 V2.2

A prospective, multicenter, single arm with performance goal study to evaluate sAfety and eFfectiveness of Multi-electrode Circular IRE Catheter and Multi-Channel IRE Generator in paroxysmal AF

In short: AFIRE study

Name of investigational medical device	BWI IRE system: CCI [redacted]
Model/specification	See section 4.2
Management category of investigational medical device	Class III medical device requiring clinical trial approval: Yes ☐ No ■ Predicate product in China: Yes ☐ No ■
Protocol No.	BWI202107
Protocol version No.	2.2
Protocol version date	Apr 20, 2023
Clinical study site	The First Affiliated Hospital of Zhengzhou University
Investigator	Jianzeng Dong
Sponsor	Biosense Webster, Inc., a division of Johnson & Johnson
Agent	Johnson & Johnson Medical (Shanghai) Ltd.

Revision History

Version	***Version date***	***Change description***
V 1.0	***Mar 10, 2022***	***Original Document***
V 2.0	***Jun 13, 2022***	***Update contents***
	Anticoagulation protocol prior to procedure related amendments	*The exclusion criteria listed in the **Study Synopsis** and **6.1.4.2** are modified as follows* *1. In Item 6 of Exclusion criteria, "**Documented left atrium (LA) thrombus within 48 hours prior to the index procedure by one of the following modalities TEE, ICE, CT, MRI**" was updated to "**Documented left atrium (LA) thrombus within 48 hours prior to the index procedure by TEE or CT (in case of TEE intolerance), or by ICE prior to the transeptal puncture by ICE during procedure**".* *2. In Item 10 of Exclusion criteria, the content "**History of a documented thromboembolic event (including TIA) within the past 12 months**" was updated to "**History of a documented thromboembolic event (including TIA) within the past 12 months, or history of a documented left atrial appendage (LAA) thrombus**".* *3. The following exclusion criteria were added from 31 to 34:* *31. **History of massive haemorrhage** within the past 6 months.* *32. **Blood test anomaly**: HGB ⩽90 g/L or PLT <100*10^9 /L.* *33. **Liver function anomaly**: Cirrhosis or bilirubin > 2 times the upper limit of the normal value or transaminase anomaly: AST/ALT/ALP > 3 times the upper limit of the normal value.* *34. **Renal function anomaly**: Dialysis, kidney transplant, Cr > 2.26 mg/d or > 200 μmol/L, CCR < 30 mL/ (min*1.73 m^2).*
		***6.3.1** Medication use, PRIOR to the procedure: "**Uninterrupted warfarin (INR 2.0 to 3.0) or NOAC therapy should be in place at least 3 weeks prior to ablation procedure**" was updated to "**Anticoagulation therapy (NOAC or low molecular weight heparin) MUST be in place at least 24 hours prior to ablation procedure**".*
		***6.3.1**Medication use, DURING the procedure:* *1) "Administer a heparin bolus **prior or post to** transseptal puncture" was updated to "Administer a heparin bolus **prior to** transseptal puncture"* *2) "Optimally target an ACT 350-400 seconds **prior to inserting the study catheter** and throughout the procedure." was updated to "Optimally target an ACT 350-400 seconds **prior to ablation** and throughout the procedure" according to the description of procedure workflow part of section 6.5.2*
		***6.4.2** Pre-Procedure/Baseline Assessments, Anticoagulation therapy:* *1) "**Uninterrupted anticoagulation management is mandatory for each study subject. For subjects on warfarin therapy, subjects shall be maintained on Warfarin for at least 3 weeks prior to treatment with an INR ≥ 2 (to be confirmed maximum 48h hours pre-procedure). Any INR <2 within 3 weeks prior to ablation will lead to exclusion of the patient or postponement of the study procedure. The results must be available prior to start of procedure**" was updated to "**Anticoagulation therapy (NOAC or low molecular weight heparin) MUST be in place at least 24 hours prior to ablation procedure**"* *2) "Imaging for detection of left atrial thrombus or other structural contraindications to an ablation procedure **is mandatory the day before or the day of the ablation procedure**" was updated to "Imaging for detection of left atrial thrombus or other structural contraindications to an ablation*

		*procedure **is mandatory within 48 hours prior to ablation procedure**", which was aligned with exclusion criteria and other parts of protocol.* *3) "The imaging method to be used for atrial thrombus detection is **TEE, Intracardiac Echocardiography (ICE), Cardiac CT or MRI**" was updated to "The imaging method to be used for atrial thrombus detection is **TEE, Intracardiac Echocardiography (ICE), Cardiac CT**", which was aligned with exclusion criteria.*
		***6.5.2** Study Ablation Procedure Sequence & Guidelines:* *1) "Administration of heparin bolus **prior or post to** transseptal puncture" was updated to "Administration of heparin bolus **prior to** transseptal puncture"* *2) "**ICE catheter is strongly recommended** to view the LA/PV anatomy and identify the contact between Circular IRE Catheter and the tissue before applications" was updated to "**ICE catheter is REQUIRED** to 1) screen for left atrial thrombus prior to transseptal puncture; 2) view the LA/PV anatomy and identify the contact between IRE Catheter and the tissue before applying ablation. Subjects shall be excluded from the study if left atrial thrombus was detected by ICE. Please refer to Exclusion criteria Item 6".*
	DMC/CEC description was added	*Description on DMC and CEC in Study Synopsis is added as follows: "The established Data Monitoring Committee (DMC) is to review the data and put forward recommendations according to the approved study specific procedure. The Clinical Events Committee (CEC) is to adjudicate the primary adverse events and operate following the regulations of the Committee."*
		13.2.1 Primary Adverse Event, Description on determination is added as follows: "The Clinical Events Committee (CEC) is to adjudicate the primary adverse events and operate following the regulations of the Committee."
	New China GCP requirment	*Section 13.5 Reporting procedures and contact information: "or device deficiency that may lead to SAE" is deleted and the procedure and time limit for SAE reporting is updated as per the the new version of "Medical Device Good Clinical Practices" (No. 28 Order) issued on May 1, 2022.*
		"(No.25 Order)" is deleted in section 10 and section 11.3.1.
		Section 13.2.6 table 6 and table 7, per the the new version of "Medical Device Good Clinical Practices" (No. 28 Order) issued on May 1, 2022, the definition of AE outcomes and definition of causal relationship are modified.
	Other minor updates	*Chinese characters for "12 months" in Study Synopsis and section **6.1.4.1** were corrected from "12 个" to "12 个月"*
		*Chinese characters for "6 months prior to" was modified from "前六个月" to "前 6 个月" with same meaning in section **6.4.2.***
		***6.5.5** Repeat Ablation Procedures:* *Chinerse translation for "**More than**" in "More than 1 repeat procedure for AF/AT/AFL of unknown origin+ during the blanking period is considered a failure mode for primary effectiveness" was corrected from **"至少 1 次(at least 1)"** to "**超过 1 次(more than 1)**", which was aligned with the definition of primary effectiveness endpoint*
		In Table 4 in section 13.2.1: Primary adverse events and description/criteria: Chinese translation for "new" in sentence of "Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality" was modified from "新" to "新发" , which kept same meaning but more professional.

		13.2.5 Revise the IRB to EC to ensure consistent name.
V2.1	***Dec 9, 2022***	***Updated contents***
	Roll-in cases were updated	*1. To ensure adequate roll-in cases for each investigor, maximum of roll-in cases was updated to 24 subjects, at most 2 roll-in cases per each investigator.* *2. Evaluable subjects were unchanged.* *After this amendment, the total sample size was increased to maximum of 147 subjects, including 123 evaluable non-roll-in subjects and max of 24 roll-in subjects.*
	Exclusion criteria	*Added "atrial flutter of unkown origin" to exclusion criteria #3 to be aligned with the requirement of "Ablation outside the PV" from session 6.5.2, detailed as below:* *"3.* Patients known to require ablation outside the PV region (atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, ventricular tachycardia and Wolff-Parkinson-White)*" was revised to "3.* Patients known to require ablation outside the PV region (atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, atrial flutter of unknown origin, ventricular tachycardia and Wolff-Parkinson-White).*"*
	Exclusion criteria	*Revised based on local practice suggested by China investigators in study initiation meeting.* *"*History of a documented lacunar infarction within the past 12 months*" was revised to "*History of a documented symptomatic lacunar infarction within the past 12 months*"*
	Primary endpoint	*According to protocol, DC or pharmacological cardioversion was allowed during blanking period. Cardioversion with Intravenous amiodarone during blanking period was not considered as a failure.* *To be more specified, "g)* Amiodarone is prescribed post index ablation procedure*" was revised to "g) Oral a*miodarone is prescribed post index ablation procedure*"*
	Study Ablation Procedure Sequence & Guidelines	*Add one caution before ablation to session 6.5.2. Study Ablation Procedure Sequence & Guidelines due to latest IFU amendment:* *"*Prior to delivering PFA energy, ensure adequate preparations are in place to commence emergency ventricular pacing, administer CPR, or apply other measures consistent with standard of care should the need arise.*"*
V2.2	***Apr 20, 2023***	***Updated contents***
	Inclusion criteria	*Based on the China AF guideline*, evidence update** and China clinical practice, the "Age 18 -75 years" was revied to "Age 18 - 80 years".* **The description in China AF guideline 2021: "the short-term (1 year) success rate and complication rate were comparable between AF patients >75 years indicated for CA ablation and younger AF patients."* *** evidence update:* *a) Abdin A, Yalin K, Lyan E,et al. Safety and efficacy of eryoballoon ablation for the treatment of atrial fibrillation in elderly patients. Clin Res Cardiol, 2019, 108 (2):167-174. DOI: 10. 1007/s00392-018-1336-x.* *b) 张良锋,周根青,吴晓宇,等.高龄老年心房颤动患者行导管射频消融的安全性和有效性研究. 中国心脏起搏与心电生理杂志,2020,34(6):549-554. DO1: 10. 13333/j. cmki. cjcpe. 2020. 06.008.*
	Study population	*Study population description was also updated due to inclusion criteria chage as below.* *"Patients aged 18-75 with symptomatic drug refractory PAF and indicated*

		for catheter ablation" in study synopsis section, section 2.2 and section 4.3 was revised to "Patients aged 18 – 80 years with symptomatic drug refractory PAF and indicated for catheter ablation"
	Intraprocedure ACT requirement	*Based on the China AF guideline 2021 update* and China clinical practice, the intraprocedure ACT requirement was revised from "⩾350 sec" to "⩾ 300 sec" and ACT test frequency was revised from "every 15-30 minutes" to "every12-18 minutes". An ACT⩾350 sec was recommended. The detailed changes were listed as below:* *1. "Optimally target an ACT 350-400 seconds prior to ablation and throughout the procedure" in section 6.3.1 was revised to "An ACT⩾ 350 seconds prior to ablation and throughout the procedure is recommended, and An ACT⩾300 seconds is required."* *2. "An ACT below 350s requires additional bolus of heparin until a minimal targeted ACT of 350s is reached. It is REQUIRED to check ACT levels on regular basis during the procedure to ensure an ACT target of ⩾350 seconds" in section 6.3.1 was revised to "An ACT below 300s requires additional bolus of heparin until a minimal targeted ACT of 300s is reached. It is REQUIRED to check ACT levels on regular basis during the procedure to ensure an ACT target of ⩾ 300 seconds"* *3. "REQUIRED: Confirmation of ACT ⩾ 350 sec. PRIOR to ablation with the Circular IRE Catheter" in section 6.5.2 was revised to "REQUIRED: Confirmation of ACT ⩾ 300 sec. PRIOR to ablation with the Circular IRE Catheter. An ACT⩾ 350 sec is recommended."* *4. "ACT MUST be targeted to be maintained ⩾ 350 sec throughout the ablation" in section 6.5.2 was revised to "ACT MUST be targeted to be maintained ⩾ 300 sec throughout the ablation."* *5. "ACT must be checked every 15-30 minutes while the Circular IRE Catheter is in the LA" in section 6.5.2 was revised to "ACT must be checked every 12-18 minutes during ablation procedure"* *6. "If ACT is below 350, heparin should be administered (except for any safety reasons) without pausing ablation procedure" in section 6.5.2 was revised to "If ACT is below 300, heparin should be administered (except for any safety reasons) without pausing ablation procedure."* **China AF guideline 2021 update: The intraprocedural ACT recommendation was 300 to 350 sec (I-B)*
	Other minor updates	*1. Adding missing item "physical exam" in section 6.4.2 to be aligned with study schedule in section 6.2* *2. "Standard 12 lead ECG" in this protocol was revised to "standard 12 or 15 leads ECG" to be aligned with hospital routine practice.* *3. "About 37% of the total number of non-roll-in subjects" in section 7.2.3 was revised to "about 33% of the total number of non-roll-in subjects" due to typing error.*

The Biosense Webster IRE system (Circular IRE Catheter (D-1412-01-SI) and Multi-Channel IRE Generator(D-1417-01-I)) is for investigational device use only and is not commercially available anywhere in the world. "Circular IRE Catheter and IRE Generator" are internal Biosense Webster project names and is not intended for any other external use. The final commercial or trade name of the PFA system (Circular IRE Catheter and IRE Generator) may be different.

Table of Contents

List of Abbreviations

Abbreviation	Description on abbreviation
AAD	Antiarrhythmic Drug
ACC/AHA	American College of Cardiology/American Heart Association
ACE	Asymptomatic Cerebral Emboli
ACT	Activated Clotting Time
AE	Adverse Event
AEF	Atrio Esophageal Fistula
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on Quality of Life
AFL	Atrial Flutter
AT	Atrial Tachycardia
CA	Competent Authority
CABG	Coronary Artery Bypass Graft
CEC	Clinical Events Committee
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine Phosphokinase
CRF	Case Report Form
CRO	Clinical Research Organization
CS	Coronary Sinus
CSR	Clinical Study Report
CT	Computed Tomography
CTI	Cavotricuspid Isthmus
CVA	Cerebrovascular Accident or Stroke
DM	Diabetes Mellitus
DMC	Data Monitoring Committee
EB	Ethics Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EHRA AF	European Heart Rhythm Association Atrial Fibrillation
EMEA	Europe, Middle East and Africa
EP	Electrophysiology
ESC	European Society of Cardiology
FAM	Fast Anatomical Mapping
FDA	Food and Drug Administration

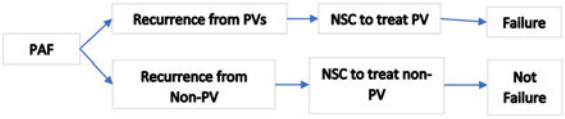
Fr	French
FU	Follow-Up
MD-GCP	Medical Device Good Clinical Practices
GERD	Gastroesophageal Reflux Disease
GSMC	Global Safety Monitoring Committee
HM	Holter Monitoring
HRS/EHRA/ECAS	Heart Rhythm Society / European Heart Rhythm Association / European Cardiac Arrhythmia Society
ICE	Intracardiac Echocardiography
ICF	Informed Consent Form
IFU	Instruction for Use
ILR	Implantable Loop Recorder
IRE	Irreversible Electroporation
LA	Left Atrium
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MEDDEV	Medical Device Directive Guidance
MDD	Medical Device Directive
MDR	Medical Device Regulation
MI	Myocardial Infarction
MMSE	Mini Mental State Examination
MRA	Magnetic Resonance Angiogram
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Scale
NAE	Neurological Assessment Evaluable
NIHSS	National Institute of Health Stroke Scale
NYHA	New York Heart Association
PAF	Paroxysmal Atrial Fibrillation
PFA	Pulsed Field Ablation
PFE	Pulsed Field Energy
PI	Principal Investigator
PN	Phrenic Nerve
PNP	Phrenic Nerve Paralysis
PP	Per Protocol
PPI	Proton Pump Inhibitors
PSU	Power Supply Unit
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation

QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
RA	Right Atrium
RF	Radiofrequency
RFCA	Radiofrequency Catheter Ablation
RV	Right Ventricle
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOC	Standard Of Care
SS	Safety Analysis Set
SVC	Superior Vena Cava
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TS	Transseptal
TTE	Transthoracic Echocardiography
UM	User Manual

Study Synopsis

Full study title	A prospective, multicenter, single arm with performance goal study to evaluate safety and effectiveness of Multi-electrode Circular IRE Catheter and Multi-Channel IRE Generator in paroxysmal AF
Study title in short	AFIRE study
Sponsor	Biosense Webster, Inc., a division of Johnson & Johnson Med Dev
Indications	Paroxysmal Atrial Fibrillation
Description of investigational Devices	IRE Ablation System The Biosense Webster IRE Ablation System consists of the • Multi-Channel IRE Generator (D-1417-01-I) • Multi-electrode Circular IRE Catheter (D-1412-01-SI) • related components and accessories The principal components of the IRE Ablation System to be evaluated in this investigation are the Multi-electrode Circular IRE Catheter and the Multi-Channel IRE Generator. Multi-Channel IRE Generator The Multi-Channel IRE Generator (hereinafter collectively referred to as "IRE Generator") CCI [redacted] Multi-electrode Circular IRE Catheter The Multi-electrode Circular IRE Catheter (D-1412-01-SI) (hereinafter collectively referred to as "Circular IRE Catheter") CCI [redacted] The catheter utilizes Pulsed Field Ablation (PFA) energy, which is a non-thermal ablative modality where ultra-rapid (< 1 second) electrical fields are applied to target tissues and has been designed to facilitate electrophysiological ablation of arrhythmias within the atria of the heart. The catheter is deployed in the left atrium (LA) after passing the right atrium (RA) via an 8.5 Fr guiding sheath. Its key function is to administer PFA energy to obtain Pulmonary Vein Isolation (PVI). The circular design facilitates the irreversible electroporation of targeted cardiomyocytes and thereby electrically isolating targeted PVs from the LA in patients with Paroxysmal Atrial Fibrillation (PAF).
Premarket or Post market	Premarket
Study design	This study is a prospective, multicenter, single-arm design with a performance

	goal. All subjects will be evaluated at discharge, 7 days, 1, 3, 6 and 12 months following the index procedure. One early success interim analysis is planned for this study.
Sample size	A maximum of 147 subjects (123 evaluable non-roll-in subjects + max of 24 roll-in subjects) will be enrolled.
Study population	Patients aged 18 – 80 years with symptomatic drug refractory PAF and indicated for catheter ablation
Study duration	**Duration: From 2022 to 2024**
Description on study procedures	Study evaluation time points include: 1. Screening 2. Study Procedure 3. Discharge 4. Follow-up at 7 days (telephone, virtual interview, or clinic visit) 5. Follow-up at 1 month (telephone, virtual interview or clinic visit) 6. Follow-up at 3 months (clinic visit) 7. Follow-up at 6 months (clinic visit) 8. Follow-up at 12 months (clinic visit)
Study objective	The primary objective of this study is to evaluate the long term off-AAD effectiveness of BWI IRE system in treatment of patients with symptomatic drug refractory PAF. Safety data will be evaluated as a secondary objective.
Primary endpoint	● **Long term effectiveness**: Freedomb ≥30 seconds from documented asymptomatic and symptomatic AF, AT, and AFL of unknown origin^{+} based on electrocardiographic data (ECG or 24h Holter) during the effectiveness evaluation period (91-365 days post index procedure). Additionally, if a subject meets any one of the following criteria, then the subject will be considered an effectiveness failure: a) Failure to achieve acute procedural success. Acute procedural success is defined as confirmation of entrance block in clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) after adenosine and/or isoproterenol challenge. b) Greater (>) than 1 repeat ablations for AF, AT, and AFL of unknown origin in the blanking period or any repeat ablation or surgical treatment for AF, AT, and AFL of unknown origin during the effectiveness evaluation period. c) Non-study catheter failure, including: i. Use of a non-study catheter (NSC) to treat pulmonary vein targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be canulated) and/or to ablate left atrial non-PV AF targets during the index procedure  ii. Use of a non-study catheter to treat pulmonary vein targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be canulated) during repeat procedure in the blanking period.

	 d) Direct current or pharmacological cardioversion for AF, AT, and AFL of unknown origin during the effectiveness evaluation period. e) Continuous AF, AT, and AFL of unknown origin on a standard 12-lead ECG during the effectiveness evaluation period. f) A Class I and/or Class III AAD is prescribed for AF, AT, and AFL of unknown origin during effectiveness evaluation period, or end date of Class I and/or Class III AAD past day 90 post procedure. g) Oral amiodarone is prescribed post index ablation procedure. [+]AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-Lead electrocardiogram (ECG) or entrainment maneuvers in an EP study
Secondary endpoints	● **Procedure and device safety**: The incidence of Primary Adverse Events (AEs) (within seven (7) days of the ablation procedure which uses investigational devices per protocol, including the initial and repeat procedures). PAEs include the following Adverse Events (Aes): Atrio-Esophageal Fistula*, Cardiac Tamponade[**,***]/ perforation[**], PNP (permanent)[+], Pulmonary Vein Stenosis[++], Device or procedure related death[+++], Stroke/ CVA[†,††], Major Vascular Access Complication Bleeding, Thromboembolism, Myocardial Infarction, TIA, Pericarditis, Pulmonary Edema (Respiratory insufficiency), Heart Block, Vagal Nerve Injury/ Gastroparesis [*] *Atrio-esophageal fistula occurring up to 90 days post AF ablation process procedure will be considered a PAE.* [**] *Cardiac Tamponade/Perforation occurring up to 30 days post AF ablation process procedure will be considered a PAE* [***] *Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.* [+] *Absent phrenic nerve function as assessed by a sniff test. Refer to Table 4 for permanent phrenic nerve paralysis definition.* [++] *Pulmonary Vein Stenosis occurring anytime during the 12-month follow up period will be considered a PAE.* [+++] *Device or procedure-related death anytime during or after the ablation procedure* [†] *Non-focal global encephalopathy requires unequivocal evidence based upon neuroimaging studies to be reported as a stroke* [††] *Modified Rankin score assessments should be made by certified individuals.* ● Occurrence of Serious Adverse Events (SAEs) within 7 days (early-onset), 8-30 days (peri-procedural) and >30 days (late onset) of initial ablation procedure ● **Acute Procedural Success** defined as confirmation of entrance block in all clinically relevant targeted PVs after adenosine/ isoproterenol challenge. Touching up with focal catheter will be considered as acute procedural failure. ● **Acute reconnection** identified by adenosine/isoproterenol challenge. Among all clinically relevant targeted PVs and by subject ● Rate of repeat ablation within the 12M FU period, including timing (blanking period or after blanking) and rate of PV reconnection

	● Procedural data, including but not limited to ➢ Total procedure time ➢ Mapping time ➢ PFA application time ➢ Number of PFA applications by PV and by subject ➢ Total fluoroscopy time ➢ Study catheter dwell time ➢ Ablation settings used ➢ Use of paralytics and anesthesia
Inclusion criteria	1. Diagnosed with Symptomatic PAF (Physician's note indicating recurrent self-terminating AF). At least one (1) electrocardiographically documented AF episode within twelve (12) months prior to enrollment. Electrocardiographic documentation may include, but is not limited to, electrocardiogram (ECG), Holter monitor, or other electrocardiographical devices accepted by investigators. 2. Failed at least one (1) Class I or Class III AAD as evidenced by recurrent symptomatic AF, contraindication or intolerable to both Class I and Class III AAD. 3. Age 18 - 80 years. 4. Able and willing to comply with all pre-procedure, post-procedure, and follow-up testing and visit requirements. 5. Willing and capable of providing consent.
Exclusion criteria	1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause (e.g., untreated documented obstructive sleep apnea and acute alcohol toxicity). 2. Previous LA ablation or surgery 3. Patients known to require ablation outside the PV region (atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, atrial flutter of unknown origin, ventricular tachycardia and Wolff-Parkinson-White). 4. Previously diagnosed with persistent AF (> 7 days in duration) 5. Severe dilatation of the LA (documented LAD >50mm antero-posterior diameter by Transthoracic Echocardiography (TTE) within 6 month prior to enrollment) 6. Documented left atrium (LA) thrombus within 48 hours prior to the index procedure by TEE or CT (in case of intolerance to TEE), or by ICE prior to transeptal puncture during procedure. 7. Documented severely compromised LVEF (LVEF <40%) by imaging within 6 months prior to enrollment 8. Uncontrolled heart failure or New York Heart Association (NYHA) Class III or IV 9. History of blood clotting, bleeding abnormalities or contraindication to anticoagulation (heparin, warfarin, or dabigatran) 10. History of a documented thromboembolic event (including TIA) within the past 12 months, or history of a documented left atrial appendage (LAA) thrombus 11. History of a documented symptomatic lacunar infarction within the past 12 months 12. Previous PCI/MI within the past 2 months 13. Coronary Artery Bypass Grafting (CABG) surgery within past 6 months

	14. Valvular surgery, cardiac surgery (e.g., ventriculotomy, atriotomy) or valvular cardiac (surgical or percutaneous) procedure. 15. Unstable angina pectoris within the past 6 months 16. Anticipated cardiac transplantation, cardiac surgery or other major surgery within the next 12 months. 17. Significant pulmonary disease (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces severe chronic symptoms 18. Known significant PV anomaly that in the opinion of the investigator would preclude enrollment in this study 19. Has known pulmonary vein stenosis 20. Pre-existing hemi diaphragmatic paralysis 21. Acute illness, active systemic infection or sepsis 22. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation. 23. Severe mitral regurgitation (Regurgitant volume 60 mL/beat, Regurgitant fraction 50%, and/or Effective regurgitant orifice area 0.40cm^2) 24. Presence of implanted pacemaker or Implantable Cardioverter-Defibrillator (ICD) or other implanted metal cardiac device that may interfere with the IRE energy field. 25. Presence of a condition that precludes vascular access (such as IVC filter) 26. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this study 27. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being 28. Current enrollment in an investigational study evaluating another device or drug. 29. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of childbearing age and plan on becoming pregnant during the course of the clinical investigation. 30. Life expectancy less than 12 months 31. History of massive haemorrhage within the past 6 months. 32. Blood test anomaly: HGB≤90 g/L or PLT <100*10^9 /L. 33. Liver function anomaly: Cirrhosis or bilirubin > 2 times the upper limit of the normal value or transaminase anomaly: AST/ALT/ALP > 3 times the upper limit of the normal value. 34. Renal function anomaly: Dialysis, kidney transplant, Cr > 2.26 mg/d or > 200 μmol/L, CCR < 30 mL/ (min*1.73 m^2). 35. Presenting contra-indications for the devices used in the study, as indicated in the respective Instructions for Use (IFU)
Statistical analysis	**Sample size calculation**: The sample size is determined by the primary effectiveness endpoint comparing to pre-specified performance goal (PG). CCI [redacted]

	CCI **Statistical analysis of study endpoints**: CCI Secondary Endpoint: The safety endpoints will be evaluated on all subjects for those who have the catheter inserted or treated with the BWI IRE system. The number of events, the number and percentage of subjects experiencing any PAE, AE and serious AE will be summarized by using the terms of MedDRA.
Interim analysis	CCI
DMC/CEC required	DMC and CEC will be established for this study. The established Data Monitoring Committee (DMC) is to review the data and put forward recommendations according to the approved study specific procedure. The Clinical Events Committee (CEC) is to adjudicate the primary adverse events and operate following the regulations of the Committee.

Schedule of assessments

Assessments	Pre-procedure	Procedure	Pre-Discharge	Follow-up					
				7 Day	1 Month	3 Month	6 Month	12 Month	(UNS)
Visit	Screening/ Baseline	D0	D/C	D7 (D7-10)	D30 (D23-37)	D90 (D76-104)	D180 (D150-210)	D365 (D335-395)	
Clinic visit	●		●	(●)[1]	(●)[1]	●	●	●	●
Patient Informed Consent[2]	●								
Inc&Excl Criteria	●								
Demographics	●								
Physical Exam	●		●		(●)[1]	●	●	●	●
Medical History[3]	●								
Pregnancy test[4]	●								
LA and LVEF assessment[5]	●								
LA thrombus detection[6]	●	●							
Ablation Assessments		●							
Device Deficiencies		●							
TTE[7]			●						
Concomitant medication[8]	●	●	●	●	●	●	●	●	●
(Repeat ablation)[9]				(●)	(●)	(●)	(●)	(●)	(●)
AF/AT/AFL recurrence			●	●	●	●	●	●	●
12 or 15 leads ECG	(●)[10]		●			●	●	●	(●)[10]
24-hour Holter						●	●	●	
Adverse Events[11]	●	●	●	●	●	●	●	●	●
Completion/ discontinuation form[12]		(●)	(●)	(●)	(●)	(●)	(●)	●	

1 Telephone/virtual or clinic visit.

2 Procedure must be done within 90 days of consent.

3 Medical history should include but not be limited to vital signs, arrhythmia, AAD therapy failure, NYHA, CHA2DS2-VASc score, thromboembolic events and other heart diseases.

4 In all women of childbearing age and potential (within 2 years after menopause). To be completed within 72-hours prior to ablation procedure.

5 Imaging should be done within 6 months prior to enrollment.

6 Performed within 48 hours of the ablation procedure to rule out the presence of atrial thrombus using one of the following modalities TEE, ICE, CT (TEE intolerance).

7 All subjects will undergo TTE prior to discharge to evaluate pericardial effusion.

8 Concomitant medication: only cardiac (i.e. anti-arrhythmia drugs, PPI, anticoagulation regimen) & index procedure related (i.e. adenosine, pain medication) & AE treatment.

9 Repeat ablation: any ablation procedure performed after the index procedure; data will be recorded at follow-up as well as at any unscheduled visits.

10 Standard of care 12 or 15 leads ECG will be collected if available.

11 Aes must be collected from the time the subject signs the informed consent onward.

12 12-month visit/ last completed visit or last data collection.

1. Sponsor Information

(I). Name of sponsor

Biosense Webster, Inc. (BWI)

(II). Address of sponsor

31 Technology Drive, Suite 200 Irvine, CA 92618

(III). Contact information of sponsor

+1 800-729-9010

(IV). Name, address, contact information

Johnson & Johnson Medical (Shanghai) Ltd. (JJMS)

Location C, 1/2/3 F, #439 Fu Te Xi Yi Road, Pilot Free Trade Zone, Shanghai, P.R.China

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2. Clinical Trial Objective and Contents

2.1. Clinical trial objective

The primary objective of this study is to evaluate the long term off-AAD effectiveness of BWI IRE system in treatment of patients with symptomatic drug refractory PAF. Safety data will be evaluated as a secondary objective.

2.2. Clinical trial contents

This study is a prospective, multicenter, single-arm design with a performance goal. All subjects will be evaluated at discharge, 7 days, 1, 3, 6 and 12 months following the index procedure. One early success interim analysis is planned for this study. Study population are patients aged 18 – 80 years with symptomatic drug refractory PAF and indicated for catheter ablation.

A total of 123 non-roll-in subjects will be enrolled. Given at most 2 roll-in cases are planned for each investigator, a maximum of 147 subjects (including 123 non-roll-in and maximum of 24 roll-in subjects) will be enrolled in this study. All patients are treated with BWI IRE system and then followed for 12 months.

The primary endpoint is long term effectiveness without AAD use in effectiveness evaluation period, defined as freedom ≥30 seconds from documented asymptomatic and symptomatic AF, AT, and AFL of unknown origin based on electrocardiographic data (ECG or 24h Holter) during the effectiveness evaluation period (91-365 days post index procedure), with additional failure modes in section 6.1.5

Safety endpoint is defined as the incidence of Primary Adverse Events (Aes) (within seven (7) days of the ablation procedure which uses investigational devices per protocol, including the initial and repeat procedures). PAEs include the following Adverse Events (Aes): Atrio-Esophageal Fistula, Cardiac Tamponade/ perforation, PNP (permanent), Pulmonary Vein Stenosis, Device or procedure related death, Stroke/ CVA, Major Vascular Access Complication Bleeding, Thromboembolism, Myocardial Infarction, TIA, Pericarditis, Pulmonary Edema (Respiratory insufficiency), Heart Block, Vagal Nerve Injury/ Gastroparesis. More details can be found in section 6.1.6

3. Background Information of the Clinical Trial

3.1. Disease introduction

3.1.1. Explanation of the disease

Atrial Fibrillation (AF) is the most common sustained arrhythmia in humans. It affects anywhere from 0.4% to 1% of the general population, and increases in prevalence with age to approximately 8% in patients over 80 years of age.[1, 2] The primary clinical benefit of AF ablation is improvement in Quality of Life (QoL) resulting from the elimination of arrhythmia-related symptoms such as palpitations, fatigue, or effort intolerance.[3] In recognition of this, the elimination of symptomatic atrial arrhythmias was recommended by the 2017 HRS/EHRA/ECAS Consensus on Catheter and Surgical Ablation of Atrial Fibrillation.[3] The opinion of the ESC as expressed in their 2019 AF Management Guidelines is that "Catheter ablation of symptomatic Paroxysmal Atrial Fibrillation (PAF) is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on Antiarrhythmic Drug (AAD) therapy and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced center."[2, 4, 5]

3.1.2. Selection of diagnosis and treatment method

The 2017 HRS/EHRA/ECAS consensus statement states that electrical isolation of the Pulmonary Veins (PVs) from the Left Atrium (LA) is the "cornerstone for most AF ablation procedures" and that "complete electrical isolation of all PVs

should be the goal."[3] Point-by-point ablation with radiofrequency (RF) catheters has provided positive results for treating many types of supraventricular arrhythmias,[6, 7] including PAF.[6-12] However, the procedure is technically complex and has a long learning curve. RF ablation success is highly dependent on operator skill and is associated with a high degree of PV reconnection.[13-15] Additionally, RF ablation carries a major complication rate of roughly 4.5%.[16]

In order to reduce technical complexity and potentially decrease major complications, circular ablation catheters were developed. Use of a Circular IRE Catheter allows for a different energy source for ablation and selective tissue destruction utilizing PFA energy[17-25] to create lesions and isolate PVs.

While RF and cryo-ablation techniques are based on thermal energy transfer to induce local tissue necrosis, Irreversible Electroporation (IRE) is a non-thermal cell death following pulsed field ablation technology which might be used to treat atrial arrhythmias.[23] It is suggested that non-thermal IRE is the trigger of apoptotic processes at the cellular level because the major damages occur after electroporation, within minutes/hours after the pulse application.[26-28] Short pulses with high voltages cause unrecoverable permeabilization of cell membranes, triggering apoptosis rather than necrosis, and as such might be safer for structures adjacent to the myocardium.[25]

It has been known that uniphasic electric pulses cause muscle contractions, using biphasic pulses, should prevent muscle contractions during IRE. It is believed that using a biphasic waveform will mitigate muscle contractions during IRE and therefore gives the possibility to perform procedures without administration of paralytic agents.

High correlation has been observed in animal models between targeted areas and tissue death with well distinguishable transition zones between treated and untreated tissue.[17]

IRE is considered nonthermal if the optimal balance has been reached to induce nonnecrotic selective cellular death. The technique has the capability to spare adjacent heat sensitive structures or tissues which would be of benefit in the reduction of possible complications know with RF and cryo energy. Although using the same electrical parameter, IRE energy delivery may be affected by other parameters like active electrode area impacting the tissue-electrode impedance. Therefore, literature describes the need of balancing Pulsed Field Ablation (PFA) application parameters (in example voltage, pulse width and interpulse distance) with physical parameters (in example electrode area, reference proximity) to achieve optimal efficacy and possible benefits of this approach versus RF energy delivery techniques.[24]

IRE of the myocardium is studied on animals resulting in clear lesions in the cardiac tissue, with no charring or temperature changes. Lesion size correlations are described in literature with pulse duration, number of pulses, higher voltage and lower interpulse distance. Interestingly the majority of the animal studies report sparing of the extracellular structures. [29-35]

Influence on adjacent structures has been previously studied. Of the well described complications in RF ablation techniques, the tissue specificity of IRE has been considered as a major advantage.[36] Recoverable proof of IRE effect on phrenic nerves has been described, suggesting that permanent damage can be avoided with IRE.[37-40] As rare but dangerous complication of RF ablation, namely development of lethal Atrio-Esophageal Fistula (AEF), might be minimized with IRE as it's suggestive that the risk with IRE would only be limited to the muscular layer of the esophagus. [41]

Biosense Webster developed the novel proprietary technology system, including Multi-Channel Circular IRE Catheter and Multi-Channel IRE Generator. With standardized bipolar, biphasic, non-thermal IRE energy delivery and circular catheter design, BWI IRE system might be confirmed to provide expected long term efficacy and safety performance in this study.

3.2. Previous Experience with Biosense Webster IRE Ablation System

Pre-clinical studies were conducted to assess the safety and effectiveness of the IRE ablation system. One clinical study is ongoing in Europe.

3.2.1. Animal Testing: Porcine Beating Heart Model (GLP Survival Study)

An in-vivo animal study titled "Safety Evaluation of the Circular IRE Catheter and IRE Generator in a Chronic Porcine Beating Heart Model" Testing performed under this protocol was GLP compliant and conformed to the guidelines for nonclinical laboratory studies as described in the Code of Federal Regulations, 21 Part 58.

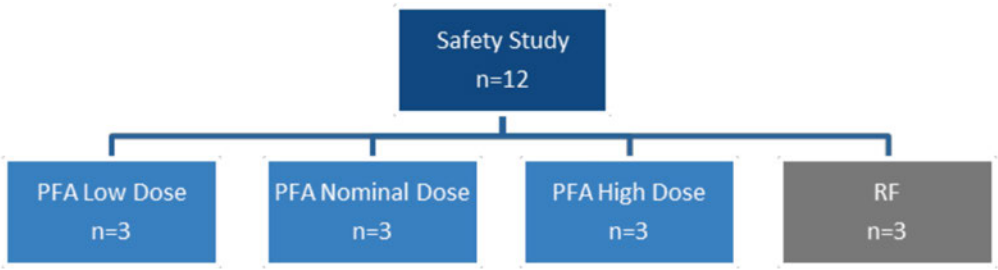
Purpose

The purpose of this study was to demonstrate the overall safety of the Biosense Webster IRE Ablation System, which includes the IRE Generator and Circular IRE Catheter, when ablating at clinically relevant anatomical locations like the pulmonary veins and left posterior wall, in a simulated clinical use scenario in combination with a CARTOTM 3 System, nGEN irrigation pump, catheter interface cables, and a pacing system in a chronic beating heart model. Various doses (differing in the number of applications) of PFA were delivered to characterize performance and safety relative to a radiofrequency (RF) control, THERMOCOOL SMARTTOUCH® SF Catheter with SMARTABLATE®

Generator. As part of this study, BWI captured and analyzed ECG data to determine whether arrythmia (if any) is correlated with timing of pulse delivery with respect to the cardiac cycle. Additionally, overall performance of the BWI IRE Ablation System will be evaluated using a 7-point Likert Scale

Scope

The study consisted of four arms, 3 PFA and 1 RF. All PFA animals were treated with the same energy setting with different numbers of PFA applications (doses) at each catheter location, without moving the catheter: Low Dose (1 application/catheter location), Nominal Dose (3 applications/catheter location), and High Dose (6 applications/catheter location). In each of these PFA arms, the designated dose (low, nominal or high) is delivered at four locations per pulmonary vein (i.e., 3 x 4 pattern) and the same dose is employed in every animal in each of the three PFA arms. Additionally, an RF arm served as a comparative control. A total of 12 animals (plus 2 backups) were included in the study. Note that in this discussion, and throughout the study report, the terms ablation and application are used synonymously to represent a user initiated PFA energy delivery event while the term dose or dosage are used to represent the number of applications delivered before the catheter is moved.



Safety of the Test devices were evaluated using the following assessments:

- Occurrence of thrombus and/or char on the catheter tip, following energy delivery
- Occurrence of clinically significant steam pop (leading to significant pericardial effusion and/or cardiac tamponade)
- Occurrence of mural thrombus in the treated heart chambers
- Occurrence of pulmonary vein (PV) stenosis
- Occurrence of collateral damage to organs surrounding organs (lungs, esophagus, phrenic nerve, pericardium)
- Occurrence of intracardiac tissue damage due to mechanical injury from the device

- Occurrence of thrombo-emboli (micro-emboli) in upstream/downstream tissues

Efficacy of the Test devices were evaluated using the following assessments:

- Ability to demonstrate 100% acute effectiveness of ablation in the left atrium
- Ability to demonstrate 80% chronic effectiveness of ablation at the PVs

Performance of the Test devices were evaluated using the following assessments:

- Survey answers and qualitative results in the form of written comments will be recorded and analyzed. The results will be considered passing if average of all the responses per question meet 5 and above on the Likert's scale of 1-7

In addition to these safety and effectiveness endpoints, the study also included:

- Detailed gross and histological assessment
- An arrhythmogenicity evaluation was performed which annotated each application of energy to identify where in the cardiac cycle energy was delivered

Result Summary

Testing was performed on twelve (12) male Yorkshire pigs. All animals in the arms 1-3 were treated using PFA with the IRE Generator and Circular IRE Catheter. Doses used were Low (arm 1), Nominal (arm 2), and High (arm 3). As a control, animals in Group 4 received a clinically relevant RF dose using the SMARTABLATE Generator and THERMOCOOL SMARTTOUCH SF Catheter and served as the control group. After concluding Day 30±5 follow-up procedures, animals were humanely euthanized under anesthesia, and gross necropsies were performed.

Energy was applied to targeted tissue areas wall thickness and their anatomic relevance to an atrial fibrillation treatment procedure. These included areas in the left atrium (LA) such as the right superior pulmonary vein (RSPV) and right inferior pulmonary vein (RIPV), atrial roof/posterior wall, left atrial appendage, and mitral valve annulus, and in the right atrium (RA) the lateral wall.

Safety:

Throughout the procedure, no signs of respiratory distress, pain or other abnormal behaviors were observed in any of the study animals. Additionally, no mural

thrombus, coagulum or charring, cardiac effusion and/or tamponade were noted for the duration of the study nor was evidence of steam pop detected in any of the enrolled animals. All animals survived until their scheduled termination time points.

In all PFA arms, ablation energy was applied directly to the phrenic nerve. In the RF arm, RF was applied more conservatively adjacent to the phrenic so as not to risk the chronic survival of the animal. Subsequent phrenic nerve capture after pacing was successful in all animals in all arms, demonstrating no loss of phrenic function. Pulmonary vein stenosis assessment was based on fluoroscopic measurements. No clinically relevant reduction in PV diameter was noted for any animal following Day 1 ablations and Day 30±5 follow-up (remap) procedures. Upon gross pathological inspection, it was noted that ablations were created in intended anatomical regions with no significant collateral injury.

All animals in all arms (test and control) showed a similar safety profile for the specified protocol endpoints.

All safety acceptance criteria for the study were met.

Efficacy:

Three physicians performed the ablation treatment on each of 1 animal per arm.

Confirmation of elimination of PV potential using a Pentaray® diagnostic mapping catheter, following initial ablation procedure was confirmed in all animals, meeting the expectation of 100% acute effectiveness of ablation in the left atrium.

For chronic evaluations on Day 30±5, all PFA treated animals presented 100% chronic PV isolation, although some areas of low voltage can be seen more prominently in the “Low” arm compared to the Nominal and High. In the RF arm, 83.3% chronic PV isolation was achieved.

All effectiveness acceptance criteria for the study were met.

Performance:

The overall performance of the Circular IRE Catheter and IRE Generator was evaluated using a 7-point Likert Scale by three (3) physicians. The average of all the responses per question met a 5 and above on the Likert’s scale, meeting the acceptance criteria. All performance acceptance criteria for the study were met.

Gross Pathology and Histology Analysis:

Gross Pathology

There were no gross signs of collateral injury to any of the adjacent anatomic structures, including aorta, lungs, esophagus, pericardium, and/or phrenic nerve adjacent to the ablation lesions.

Histology

All histology findings were within expectations. Both PFA and RF treated tissues produced expected degree of post-ablation tissue modulation and repair, but the RF treatment group differed remarkably when the severity of the lesions was compared.

Conclusion

The Circular IRE Catheter with the IRE Generator meets all acceptance criteria as listed in protocol P/TR-0034530.

This study confirms the overall effectiveness and safety of the Circular IRE Catheter when used with the IRE Generator and the CARTOTM 3 System, when simulating a clinical pulmonary vein isolation (PVI) procedure in a porcine beating heart model.

3.2.2. Summary of OUS Clinical Study

BWI has initiated a prospective, single-arm, multi-center, pre-market clinical evaluation of the IRE Ablation System in Europe (InspIRE, NCT04524364) to demonstrate the safety and long-term effectiveness in the treatment of paroxysmal atrial fibrillation when compared to a performance goal. Enrollment commenced on August 26, 2020, and the study will enroll up to 180-330 subjects with sample size adaptation based on accruing data. The study is currently ongoing.

The study has 2 sequential phases. Wave 1, the safety characterization phase of the study enrolled 40 subjects. Wave 2, the pivotal phase of the study is currently enrolling.

Acute procedural success, defined as confirmation of entrance block in all clinically relevant targeted pulmonary veins after adenosine/ isoproterenol challenge without use of a non-study catheter to achieve PVI, was achieved in all subjects treated with the study catheter in Wave 1 of the study.

No primary adverse events including atrio-esophageal fistula, phrenic nerve paralysis, cardiac tamponade/perforation, pulmonary vein stenosis, device or procedure-related death, or stroke/CVA have been reported in the Wave 1 phase of the study.

3.3. Product registration and the reason for clinical trial registration in China

The investigational devices have not been registered in any other coutries. The reason for AFIRE study is to provide long term effectiveness outcome without AAD use in effectiveness evaluation period and safety performance in Chinese population and local practice, which will be used to support BWI IRE system registration in China.

4. CCI

4.1. CCI

4.1.1. CCI

CCI

4.2. CCI

4.2.1. CCI

CCI

CCI

[redacted]

CCI

[redacted]

Figure 1: CCI [redacted]

4.2.2. CCI [redacted]

CCI

[redacted]

CCI

[redacted]

CCI

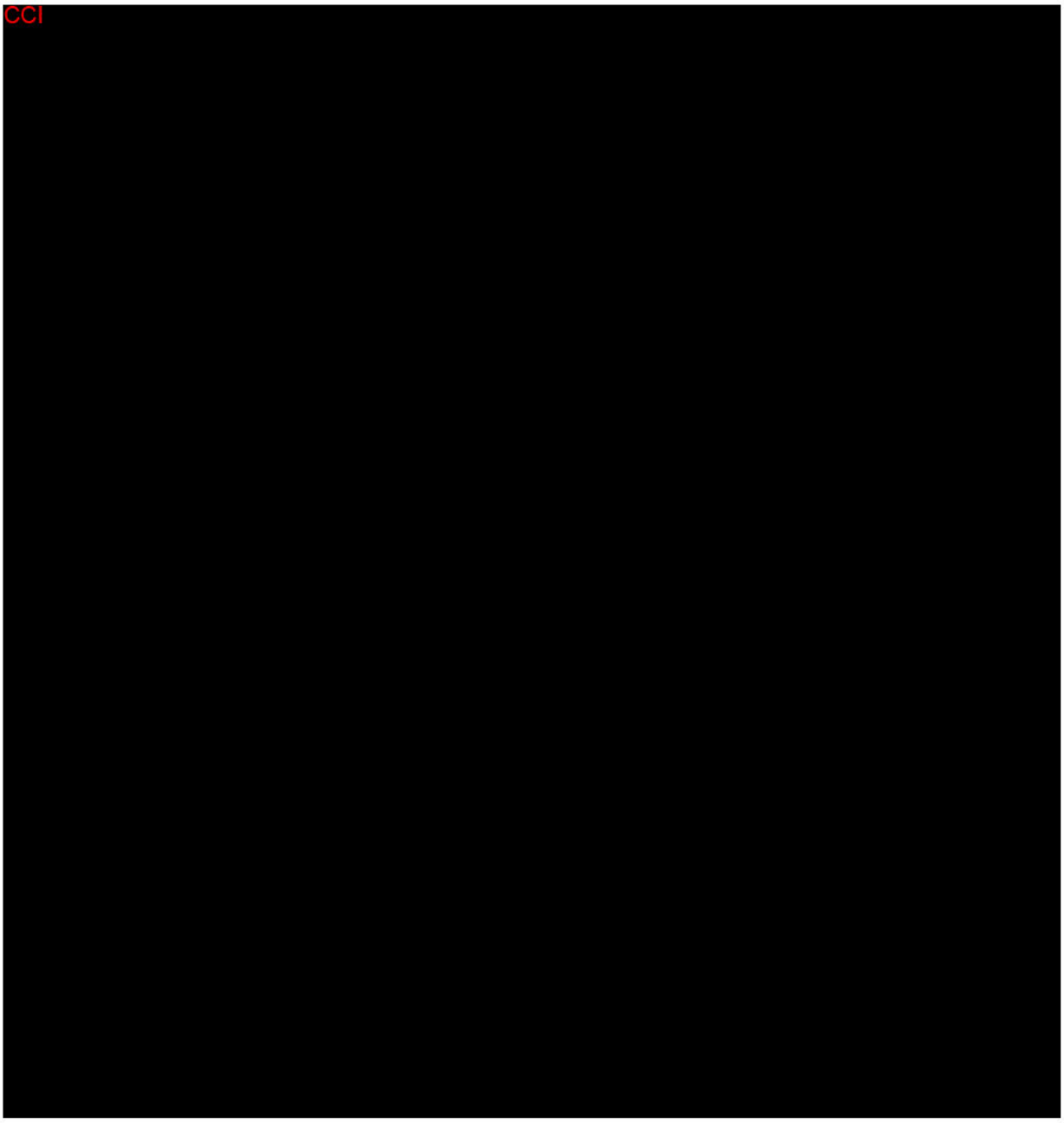


Figure 2: CCI

4.2.3. System Components

CCI

CCI

[redacted]

4.2.4. CCI

CCI

[redacted]

Table 1. CCI

CCI

[redacted]

CCI

[redacted]

4.3. Study population

Patients aged 18 – 80 years with symptomatic drug refractory PAF and indicated for catheter ablation.

5. Indications, Contraindications and Precautions of the Product (From IFU approved by country of origin)

Please refer to IFUs of Multi-Channel IRE Generator（D-1417-01-I）and Circular IRE Catheter（D-1412-01-SI）

6. Overall Design

6.1. Study design

6.1.1. Study objective

The primary objective of this study is to evaluate the long term off-AAD effectiveness of BWI IRE system in treatment of patients with symptomatic drug refractory PAF. Safety data will be evaluated as a secondary objective.

6.1.2. Selection of study method and justification

This study is a prospective, multicenter, single-arm design with a performance goal. Its rationale is as follows:

Prospective: The prospective study is insusceptible to bias, with no need of recall, in which the incidence can be calculated, and the definition of symptom and condition can maintain consistency.

Multicenter: With patients from multiple sites more representative than that from a single site, the result bias caused by systematic errors of a single site may be reduced.

Single arm with a performance goal: The Sponsor has carefully considered the most appropriate study design for the assessment of the IRE Ablation system. The 2017 HRS/EHRA/ ECAS/APHRS/SOLAECE Expert Consensus[3] Statement on Catheter and Surgical Ablation of Atrial Fibrillation addressed the appropriateness and concerns of randomized control (non-inferiority) studies–- "…the possibility of a downward "creep" in acceptable effectiveness (if each device is numerically inferior but statistically equivalent to the prior comparator device). In the future, we expect that devices designed to treat patients with symptomatic PAF might alternatively be evaluated in nonrandomized trials, comparing prespecified performance goals or objective performance criteria (OPC), if uniformly established and applied." Similar concerns may be extended to the evaluation of safety given the rapid pace of technology development in this arena. This is balanced by the establishment of the treatment of PAF by catheter ablation as a safe procedure with pulmonary vein isolation (PVI) as the cornerstone of treatment. Data published from many recent prospective multi-center clinical trials[43-46] for ablation devices demonstrate that the safety and effectiveness rates for similar primary endpoints are comparable across the varied technologies in a well-defined PAF patient population, further supporting acute PVI as a reliable treatment in reducing long term recurrence of PAF. Accordingly, this study is designed to be multicenter and single arm with comparison to rigorously determined performance goals for effectiveness. The planned performance goal for long term effectiveness is 50%, based on the minimum chronic acceptable success rate for paroxysmal AF at 12-month follow-up as recommended in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement3 on Catheter and Surgical Ablation of AF.

Meanwhile, in the trial, the appropriate sample size as needed will be estimated according to the scientific hypothesis of comparison between the trial group and the performance goal, and the permissible Type I and Type II errors, ensuring the statistical significance of the results.

6.1.3. Measures for reducing and avoiding bias

Prospective design will be adopted for this study, so as to avoid bias that may be caused by retrospective study.

Strict inclusion and exclusion criteria will be implemented to avoid selection bias. Meanwhile, in the study, the data of objective indicators will be collected. The study related data will be recorded in the original medical records as much as possible, and checked in the monitoring process. The training for the investigators should be enhanced, so as to assure the scientific attitude of investigators.

Investigators should communicate more with subjects to improve their

compliance. This will help to reduce the informational bias.

Clinical outcomes will be measured in a standardized manners using standard 12 or 15 leads ECG and 24h Holter, which are standardized and objective clinical assessment tools for identify the recurrence of atrial arrthymia.

6.1.4. Selection of subjects

6.1.4.1. Inclusion criteria

1. Diagnosed with Symptomatic PAF (Physician's note indicating recurrent self-terminating AF). At least one (1) electrocardiographically documented AF episode within twelve (12) months prior to enrollment. Electrocardiographic documentation may include, but is not limited to, electrocardiogram (ECG), Holter monitor, or telemetry strip.
2. Failed at least one (1) Class I or Class III AAD as evidenced by recurrent symptomatic AF, contraindicated or intolerable to both Class I and Class III AAD.
3. Age 18 - 80 years.
4. Able and willing to comply with all pre-procedure, post-procedure, and follow-up testing and visit requirements.
5. Willing and capable of providing consent.

6.1.4.2. Exclusion criteria

1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause (e.g., untreated documented obstructive sleep apnea and acute alcohol toxicity).
2. Previous LA ablation or surgery
3. Patients known to require ablation outside the PV region (atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, atrial flutter of unknown origin, ventricular tachycardia and Wolff-Parkinson-White).
4. Previously diagnosed with persistent AF (> 7 days in duration)
5. Severe dilatation of the LA (documented LAD >50mm antero-posterior diameter by Transthoracic Echocardiography (TTE) within 6 month prior to enrollment)
6. Documented left atrium (LA) thrombus within 48 hours prior to the index procedure by TEE or CT (in case of intolerance to TEE) , or by ICE prior

to transeptal puncture during procedure

7. Documented severely compromised LVEF (LVEF <40%) by imaging within 6 months prior to enrollment
8. Uncontrolled heart failure or New York Heart Association (NYHA) Class III or IV
9. History of blood clotting, bleeding abnormalities or contraindication to anticoagulation (heparin, warfarin, or dabigatran)
10. History of a documented thromboembolic event (including TIA) within the past 12 months, or history of a documented left atrial appendage (LAA) thrombus
11. History of a documented symptomatic lacunar infarction within the past 12 months
12. Previous PCI/MI within the past 2 months
13. Coronary Artery Bypass Grafting (CABG) surgery within past 6 months
14. Valvular surgery, cardiac surgery (e.g. ventriculotomy, atriotomy) or valvular cardiac (surgical or percutaneous) procedure.
15. Unstable angina pectoris within the past 6 months
16. Anticipated cardiac transplantation, cardiac surgery or other major surgery within the next 12 months.
17. Significant pulmonary disease (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces severe chronic symptoms
18. Known significant PV anomaly that in the opinion of the investigator would preclude enrollment in this study
19. Has known pulmonary vein stenosis
20. Pre-existing hemi diaphragmatic paralysis
21. Acute illness, active systemic infection or sepsis
22. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation.
23. Severe mitral regurgitation (Regurgitant volume 60 mL/beat, Regurgitant fraction 50%, and/or Effective regurgitant orifice area 0.40cm2)

24. Presence of implanted pacemaker or Implantable Cardioverter-Defibrillator (ICD) or other implanted metal cardiac device that may interfere with the IRE energy field.
25. Presence of a condition that precludes vascular access (such as IVC filter)
26. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this study
27. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being
28. Current enrollment in an investigational study evaluating another device or drug.
29. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of childbearing age and plan on becoming pregnant during the course of the clinical investigation.
30. Life expectancy less than 12 months.
31. History of massive haemorrhage within the past 6 months.
32. Blood test anomaly: HGB≤90 g/L or PLT <100*10^9 /L.
33. Liver function anomaly: Cirrhosis or bilirubin > 2 times the upper limit of the normal value or transaminase anomaly: AST/ALT/ALP > 3 times the upper limit of the normal value.
34. Renal function anomaly: Dialysis, kidney transplant, Cr > 2.26 mg/d or > 200 μmol/L, CCR < 30 mL/ (min*1.73 m^2).
35. Presenting contra-indications for the devices used in the study, as indicated in the respective Instructions for Use (IFU)

6.1.4.3. Reasons for early termination of subjects

Possible reasons for early termination may include, but are not limited to the following:

1. Withdrawal of informed consent form (ICF): The subject decides to withdraw from the study. This decision must be“" independent decision“" and should be documented in the subject study file;
2. Investigato”s discretion: The investigator may choose to the withdraw a subject from the study if there are safety concerns;
3. Adverse events (aEs): AE or SAE may lead to subject discontinuation from the study. If the investigator decides to discontinue a subject from

the study, this subject must be followed up until the AE is resolved or until the stable clinical endpoint is reached;

4. Death (if applicable);
5. Loss to follow-up: All subjects should return to participate in all scheduled clinical follow-ups, providing the appropriate contact information in order to complete the specified (telephone) follow-up. Every attempt will be made to have all subjects complete the follow-up visit schedule. A subject will not be considered lost to follow-up until the last study visit. If a subject can't return for mandatory clinical visits, 3 telephone calls should be made to attempt to contact the subject to return to clinics and/or obtain safety information. Each attempt to contact should be recorded in the source document. If the subject does not response to 3 telephone calls, the investigator must send a registered mail or the EMS which can record the mode of sending and receiving to the subject. If the subject makes no response to the registered mail or EMS which can record the mode of sending and receiving and makes no further contact, this subject should be considered to have missed the scheduled visit.
6. Termination by the sponsor.

Procedure for subject's termination in the study:

If the subject is terminated from the study before end of visit in the study, the reasons for discontinuation should be documented in the source document and kept in the study files and submitted via CRF/eCRF.

Subjects with premature discontinuation from the study will be included in the analysis set according to the definition of analysis set in the protocol; however, new subjects may not be enrolled to replace these subjects.

Criteria for sponsor's termination of the trial are as follows:

The sponsor reserves the right to temporarily suspend/terminate or prematurely discontinue the studies either at a single site, multiple sites or all sites. Reasons may include, but are not limited to safety issue, ethical issue, administrative issue, inaccurate or incomplete data record, non-compliance or unsatisfactory enrollment with respect to quality or quantity.

Procedure for sponsor's termination of the study:

If the study is prematurely terminated or suspended, the sponsor will inform all institutions of the termination or suspension and the reason(s) for the termination or suspension, in accordance with applicable regulatory requirement(s). The

investigators and EC should also be informed and provided with reason(s) for the termination or suspension by the institutions, as specified by the applicable regulatory requirement(s). The suspended study should not be resumed without the consent of the EC.

6.1.4.4. Enrollment time

Subjects will be considered successfully enrolled into the study after completion of the following process:

- Completion of the informed consent process and signing the ICF.
- Discretion by the investigator that the subject meets all inclusion criteria (including intra-procedure inclusion criteria) and does not meet any exclusion criteria.

No operation procedures related to the study (except for SOC) should be conducted prior to signing the ICF.

6.1.4.5. Expected overall duration of clinical trial and justification

The expected overall duration is about 31 months, including the time of EC, signing the contract, subject'' enrollment and follow-up, data management and statistical analysis, and writing the clinical summary report.

6.1.4.6. Expected duration of participation of each subject

The duration of each subject's participation in the study is about 12 months according to the follow-up schedule specified in the protocol.

6.1.4.7. Number of subjects required for the clinical trial

A total of 123 non-roll-in subjects will be enrolled. Given at most 2 roll-in cases are planned per each investigator, a maximum number of 147 subjects (including both non-roll-in and roll-in subjects) will be enrolled.

See Section 7.2 "Calculation of Sample Size" for the basis for selecting such sample size.

6.1.4.8. Subject Enrollment Disposition

- Enrolled Subjects: Patients who sign the ICF and meet all eligibility criteria.
- Excluded Subjects: Subjects who are enrolled but never undergo insertion of the study catheter. Excluded subjects will be subjected to safety event reporting between ICF signature and date of exclusion. Enrolled Subjects found to be ineligible prior to insertion of the catheter are also considered as excluded.

- Evaluable Subjects: All enrolled subjects who have the study catheter inserted.
- Discontinued Subjects: Evaluable subjects but do not undergo ablation (i.e., no energy is delivered with the study catheter).
    - Discontinued subjects will remain in follow-up for 3-months post catheter insertion.
    - If an SAE is reported for a discontinued subject, the subject will be followed until event resolution (with or without sequelae), stabilization, or until the event is adequately explained.
- Lost to Follow-up Subjects: Evaluable subjects of which contact is lost after most recent visit (despite 3 documented attempts to contact the subject).
- Withdrawn / Early Termination Subjects: Subjects who withdraw consent for study participation or are withdrawn by the investigator, are terminated from the study prior to completion of all follow-up visits.
- Completed Subjects: Enrolled subjects who have not been excluded, discontinued, withdrawn, terminated early, or lost-to-follow-up from the study prior to the final study visit.

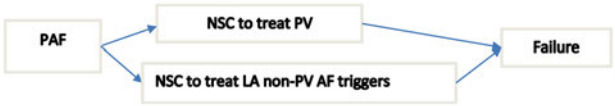
6.1.5. Effectiveness evaluation method

6.1.5.1. Description on effectiveness parameters

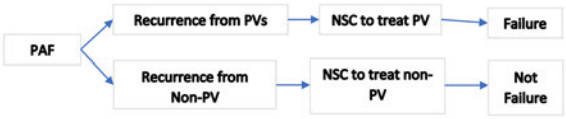
1) Primary effectiveness endpoint:

- Long term effectiveness: Freedom ≥30 seconds from documented asymptomatic and symptomatic AF, AT, and AFL of unknown origin^{+} based on electrocardiographic data (ECG or 24h Holter) during the effectiveness evaluation period (91-365 days post index procedure). Additionally, if a subject meets any one of the following criteria, then the subject will be considered an effectiveness failure:
    a) Failure to achieve acute procedural success. Acute procedural success is defined as confirmation of entrance block in clinically relevant PVs (all PVs except those that are silent and/or cannot be cannulated) after adenosine and/or isoproterenol challenge.
    b) Greater (>) than 1 repeat ablations for AF, AT, and AFL of unknown origin in the blanking period or any repeat ablation or surgical treatment for AF, AT, and AFL of unknown origin during the effectiveness evaluation period.
    c) Non-study catheter failure, including:

- Use of a non-study catheter (NSC) to treat pulmonary vein targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be canulated) and/or to ablate left atrial non-PV AF targets during the index procedure



- Use of a non-study catheter to treat pulmonary vein targets to achieve isolation of clinically relevant PVs (all PVs except those that are silent and/or cannot be canulated) during repeat procedure in the blanking period



d) Direct current or pharmacological cardioversion for AF, AT, and AFL of unknown origin during the effectiveness evaluation period.

e) Continuous AF, AT, and AFL of unknown origin on a standard 12 or 15-lead ECG during the effectiveness evaluation period.

f) A Class I and/or Class III AAD is prescribed for AF, AT, and AFL of unknown origin during effectiveness evaluation period, or end date of Class I and/or Class III AAD past day 90 post procedure.

g) Oral amiodarone is prescribed post index ablation procedure

[+]AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12 or 15-Lead electrocardiogram (ECG) or entrainment maneuvers in an EP study

2) Secondary effectiveness endpoint:

- Acute Procedural Success defined as confirmation of entrance block in all clinically relevant targeted PVs after adenosine/ isoproterenol challenge. Touching up with focal catheter will be considered as acute procedural failure.
- Acute reconnection identified by adenosine/isoproterenol challenge. Among all clinically relevant targeted PVs and by subject
- Rate of PV ablation by a non-study catheter (touch-up) among all

clinically relevant targeted PVs and by subject

- Rate of repeated ablation within the 12M FU period, including timing (blanking period or after blanking) and rate of PV reconnection

6.1.5.2. Selection of method and time to evaluate, record and analyze the effectiveness parameters

1) Long term effectiveness will be evaluated and recorded during effectiveness evaluation period (day 91 to day 365 post index procedure) by ECG and 24h Holter at 3 months, 6 months and 12 months follow-up points. Recurrence during blanking period (day 1 to day 90 post index procedure) is not considered as long term effectiveness failure.
2) Acute effectiveness will be evaluated and recorded at the end of procedure by the method of adenosine/isoproterenol challenge.
3) All the repeated ablations will be evaluated and recorded during the study.

For the analysis of the above endpoints, see Section 7.

6.1.6. Safety evaluation method

6.1.6.1. Description on safety parameters

Safety endpoints include

1) Procedure and device safety: The incidence of Primary Adverse Events (Aes) (within seven (7) days of the ablation procedure which uses investigational devices per protocol, including the initial and repeat procedures). PAEs include the following Adverse Events (Aes): Atrio-Esophageal Fistula*, Cardiac Tamponade**,***/ perforation**, PNP (permanent)+, Pulmonary Vein Stenosis++, Device or procedure related death+++, Stroke/ CVA†,††, Major Vascular Access Complication Bleeding, Thromboembolism, Myocardial Infarction, TIA, Pericarditis, Pulmonary Edema (Respiratory insufficiency), Heart Block, Vagal Nerve Injury/ Gastroparesis

** Atrio-esophageal fistula occurring up to 90 days post AF ablation process procedure will be considered a PAE.*

***Cardiac Tamponade/Perforation occurring up to 30 days post AF ablation process procedure will be considered a PAE*

**** Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.*

+ Absent phrenic nerve function as assessed by a sniff test. Refer to Table 4 for permanent phrenic nerve paralysis definition.

++ Pulmonary Vein Stenosis occurring anytime during the 12-month follow

up period will be considered a PAE.

+++ Device or procedure-related death anytime during or after the ablation procedure

† Non-focal global encephalopathy requires unequivocal evidence based upon neuroimaging studies to be reported as a stroke

†† Modified Rankin score assessments should be made by certified individuals.

2) Occurrence of Serious Adverse Events (SAEs) within 7 days (early-onset), 8-30 days (peri-procedural) and >30 days (late onset) of initial ablation procedure

3) **AEs and serious adverse events (SAEs).** Aes will be summarized, including the number of Aes and the number and percentage of subjects experiencing any Aes, the number of all SAEs and all related SAEs and number and percentage of subjects experiencing any SAEs.

6.1.6.2. Selection of method and time to evaluate, record and analyze the safety parameters

Records will be collected in the e-CRF at the discharge, Day, 1 Month, 3 Month, 6 Month and 12 Month follow-up visits respectively based on the investigator's notes, medical records and examination results. Aes will be collected after ICF signature. For the analysis of safety endpoints, see Section 7.

6.2. Study Schedule

Schedule of Assessments

Table 2. The schedule of assessment of the study

Assessments	Pre-procedure	Procedure	Pre-Discharge	Follow-up					
				7 Day	1 Month	3 Month	6 Month	12 Month	(UNS)
Visit	Screening/ Baseline	D0	D/C	D7 D7-10	D30 D23-37	D90 D76-104	D180 D150-210	D365 D335-395	
Clinic visit	●		●	(●)[1]	(●)[1]	●	●	●	●
Patient Informed Consent [2]	●								
Inc&Excl Criteria	●								
Demographics	●								
Physical Exam	●		●		(●)[1]	●	●	●	●
Medical History [3]	●								
Pregnancy test [4]	●								
LA and LVEF assessment[5]	●								
LA thrombus detection [6]	●	●							

Assessments	Pre-procedure	Procedure	Pre-Discharge	Follow-up					
				7 Day	1 Month	3 Month	6 Month	12 Month	(UNS)
Ablation Assessments		●							
Device Deficiencies		●							
TTE[7]			●						
Concomitant medication[8]	●	●	●	●	●	●	●	●	●
(Repeat ablation)[9]				(●)	(●)	(●)	(●)	(●)	(●)
AF/AT/AFL recurrence			●	●	●	●	●	●	●
12 or 15 leads ECG	(●)[10]		●			●	●	●	(●)[10]
24-hour Holter						●	●	●	
Adverse Events[11]	●	●	●	●	●	●	●	●	●
Completion/ discontinuation form[12]		(●)	(●)	(●)	(●)	(●)	(●)	●	

1 Telephone/virtual or clinic visit.
2 Procedure must be done within 90 days of consent.
3 Medical history should include but not be limited to vital signs, arrhythmia, AAD therapy failure, NYHA, CHA2DS2-VASc score, thromboembolic events and other heart diseases.
4 In all women of childbearing age and potential (within 2 years after menopause). To be completed within 72-hours prior to ablation procedure.
5 Imaging should be done within 6 months prior to enrollment
6 Performed within 48 hours of the ablation procedure to rule out the presence of atrial thrombus using one of the following modalities TEE, ICE, CT (TEE intolerance).
7 All subjects will undergo TTE prior to discharge to evaluate pericardial effusion
8 Concomitant medication: only cardiac (i.e. anti-arrhythmia drugs, PPI, anticoagulation regimen) & index procedure related (i.e. adenosine, pain medication) & AE treatment
9 Repeat ablation: any ablation procedure performed after the index procedure; data will be recorded at follow-up as well as at any unscheduled visits.
10 Standard of care 12 or 15 leads ECG will be collected if available.
11 Aes must be collected from the time the subject signs the informed consent onward.
12 12-month visit/ last completed visit or last data collection

6.3. Medication/device operation specification

6.3.1. Medication use

PRIOR to the procedure

- Anticoagulation therapy (NOAC or low molecular weight heparin) MUST be in place at least 24 hours prior to ablation procedure. AAD therapy and administration of Proton Pump Inhibitors (PPI) should be managed as per the institution's standard of care.

DURING the procedure

- Administer a heparin bolus prior to transseptal puncture.
- An ACT⩾350 seconds prior to ablation and throughout the procedure is recommended, and An ACT⩾300 seconds is required.
- An ACT below 300s requires additional bolus of heparin until a minimal targeted ACT of 300s is reached. It is REQUIRED to check ACT levels every 12-18 minutes during the ablation procedure to ensure an ACT target of ≥300 seconds.
- Flush all tubing and sheath continuously with heparinized saline.

FOLLOWING the procedure

- Anticoagulation therapy is REQUIRED for at least 2 months following ablation.
- Decisions regarding continuation of systemic anticoagulation beyond 2 months post ablation should be based on the subject's stroke risk profile. Per HRS guidance systemic anticoagulation is recommended be continued beyond two months post-procedure in subjects with a CHA2DS2-VASc score of ≥ 2 (unless deemed contraindicated based on clinical considerations).
- AAD management:
    - During this study, current AF management guidelines and the institution's standard of care practices are to be followed as closely as possible for AAD therapy.
    - A Class I and/or Class III AAD can be administered for AF during the blanking period and terminated before the end of the blanking period. If a Class I/III AAD is prescribed /administered after day 90 post procedure or oral amiodarone is prescribed/administered at any time post procedure, it MUST be accompanied by documentation of arrhythmia. If a Class I and/or Class III AAD is continued or started past Day 90, the subject will be considered a primary effectiveness failure. If oral amiodarone is prescribed and/or taken at any time post index ablation procedure, the subject will be considered a primary effectiveness failure.
- PPI administration following the procedure is at investigator discretion.
- Additional medications needed to treat clinical indications are at investigator discretion.

6.3.2. Device operation specification

Please refer to IFU of IRE Generator（D-1417-01-I） and Circular IRE Catheter（D-1412-01-SI）

6.4. Study procedure

6.4.1. Screening and Informed Consent

Candidates presenting to the institution with symptomatic PAF and considered for an ablation procedure should be screened by the investigator or designated member of the research team for study eligibility per the protocol inclusion and exclusion criteria. Sites will be instructed to screen all subjects who require a documented ablation procedure for symptomatic PAF without regard to sex or race.

The study investigator or designated member of the research team will obtain written informed consent from the subject. The patient informed consent procedure must be done within 90 days before the actual study procedure takes place. The background of the proposed study and the potential benefits and risks of the study should be explained to the subject. The subject or legal representative must sign the consent form prior to any study-specific exams or tests are provided to them that fall outside of the standard of care. The consent form used must have prior approval from the CAs and study site's EC. Failure to obtain informed consent renders the subject ineligible for participation in the study.

The investigator and/or designee must also clearly document the process of obtaining informed consent in the subject’s source documents. The voluntary process of informed consent confirms the subject’s willingness to participate in the study. It’s the investigator’s responsibility to ensure that the informed consent process is performed in accordance with Medical Device Good Clinical Practice (MD-GCP) and with applicable local and national regulations. If new information becomes available that can significantly affect a subject’s future health and/or medical care, this information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing by dating and signing an amended ICF.

Each subject screened for enrollment in the clinical investigation who signs the patient ICF will be enrolled into the study. No subject should undergo any clinical investigation specific tests or examinations that fall outside the standard of care without first signing the patient ICF for this clinical investigation.

6.4.2. Pre-Procedure/Baseline Assessments

Below pre-procedure assessments and data collection must be performed prior to

the ablation procedure.

- Patient Information and Consent (procedure must be done within 90 days of consent)
- Demographics (age, gender, etc).
- Medical history, including but not limited to arrhythmia, heart disease, thromboembolic events, lung/respiratory problems.
    - AF history (first evidence of AF, number of episodes, symptoms, etc).
    - NYHA Functional Class Scale.
    - CHA2DS2 VASc Score. CHA2DS2 VASc will be scored for all subjects.
    - Vital signs (length, weight, etc.)
    - Medication history: Medication history (cardiac medication, AAD medication, anticoagulation regimen and any other clinically significant medication history) shall be gathered by interview or from medical records following enrolment but prior to the ablation procedure and should be recorded in the eCRF.
    - Anticoagulation therapy: Anticoagulation therapy (NOAC or low molecular weight heparin) MUST be in place at least 24 hours prior to ablation procedure
- Physical exam
- Pregnancy test must be done on all women of childbearing age and potential within 72-hours prior to the procedure and documented in the subject's medical chart.
- Imaging (TTE or other acceptable equivalent cardiac imaging – i.e. CT/MRI) within 6 months prior to procedure to assess the LA and LVEF. Must be collected within 6 months prior to procedure, in case of the imaging assessment is older than 6 months LA/LVEF, dimensions shall be re-measured during the index procedure prior to insertion of the study catheter. In case of re-measurements before study catheter insertion fail to meet the LA and/or LVEF criteria, the subject will be considered as not meeting eligibility and will be excluded.
- Imaging for detection of left atrial thrombus or other structural contraindications to an ablation procedure is mandatory within 48 hours prior to ablation procedure. Presence of a thrombus will require

postponement of the ablation procedure or may even lead to exclusion of the subject from further study involvement. The imaging method to be used for atrial thrombus detection is TEE, Intracardiac Echocardiography (ICE), Cardiac CT.

- Electrocardiogram (12-Lead ECG). Data from 12-lead ECG recordings will be collected if performed standard of care.
- Adverse Events must be collected from the time the subject signs the informed consent onwards.
- Cardiac CT is required to be performed within 6 months prior to the ablation procedure to assess the structure and size of the PVs and the left atrial anatomy.

6.5. Study Ablation Procedure Guidelines

6.5.1. CCI

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Figure 3: CCI

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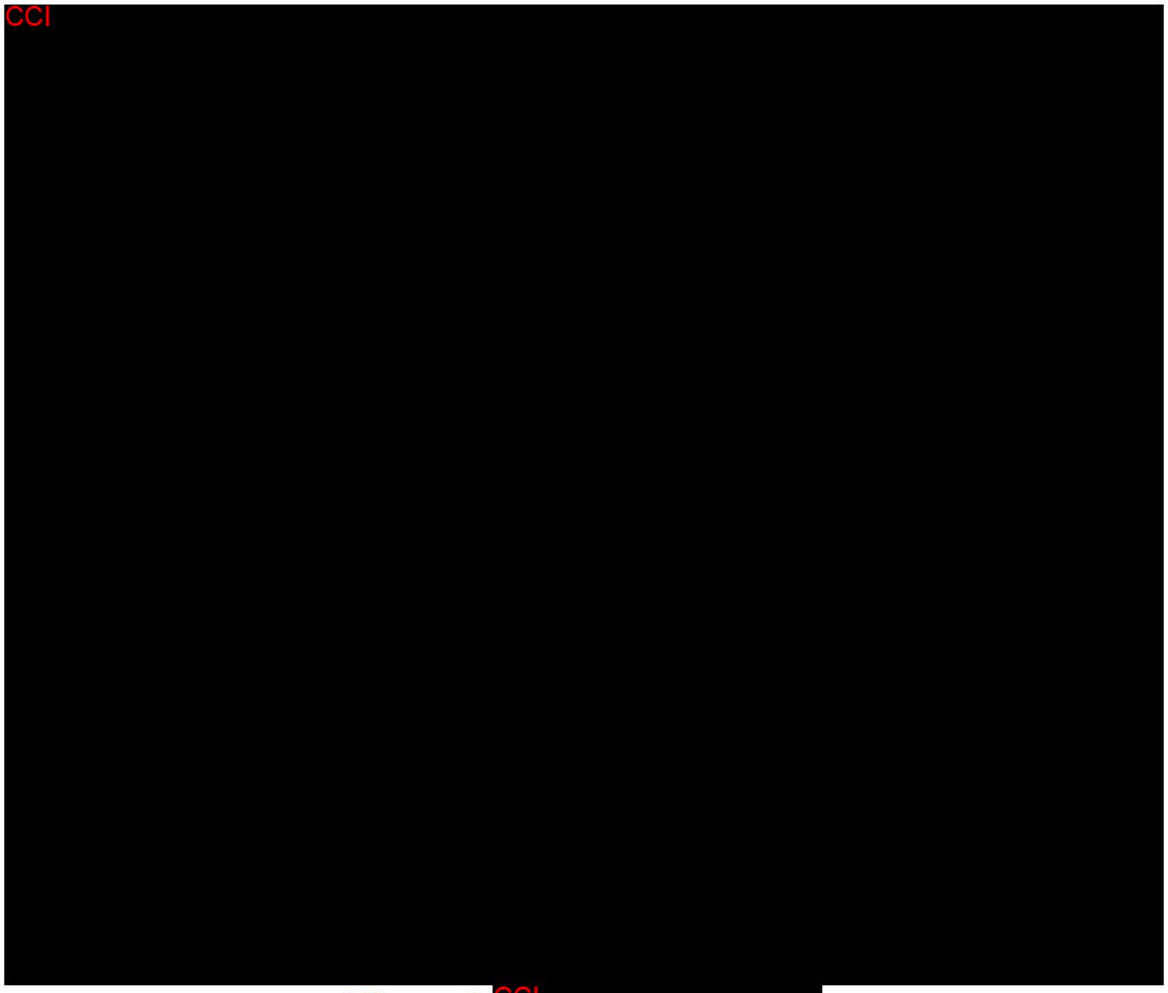

Figure 4: CCI

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6.5.2. CCI

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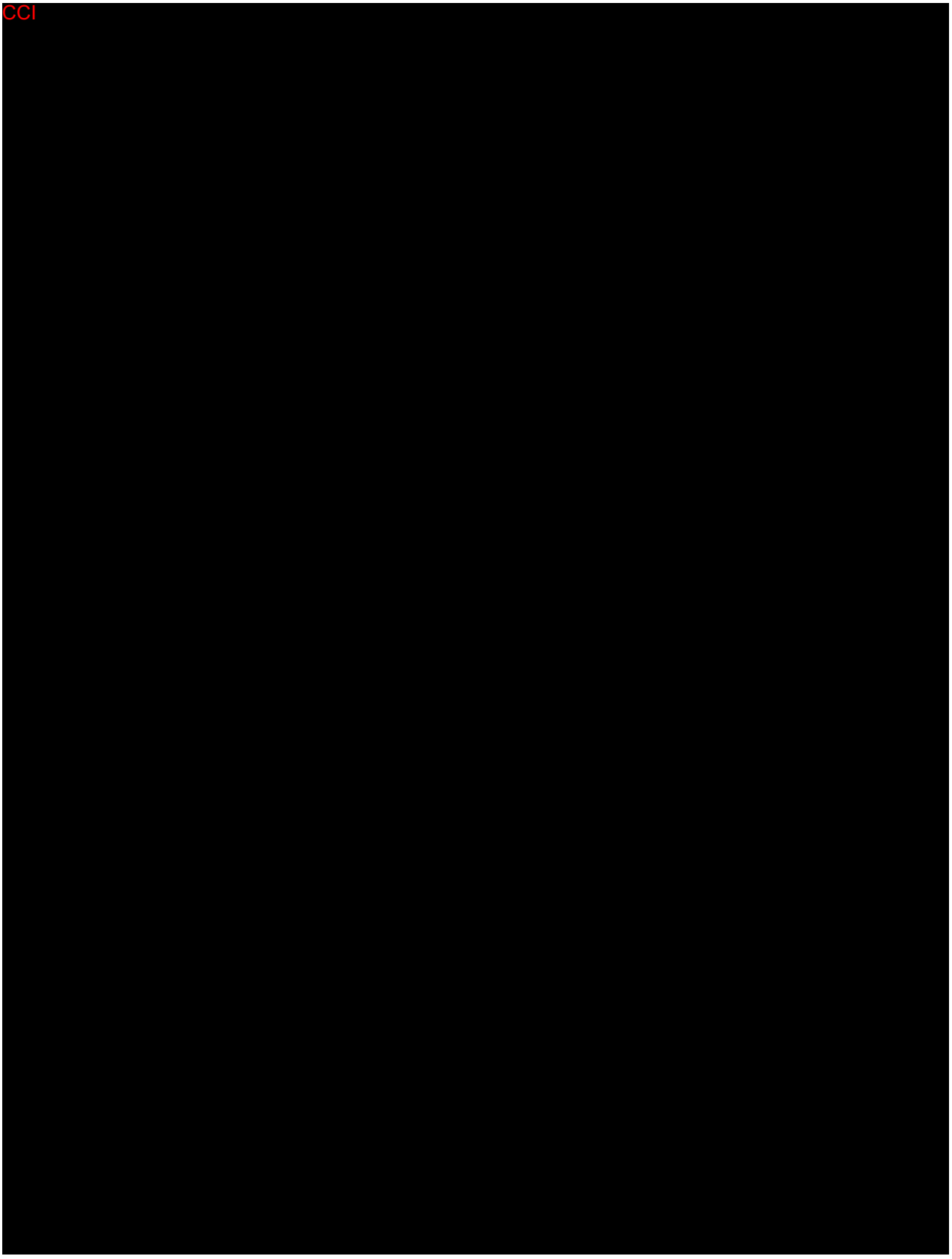

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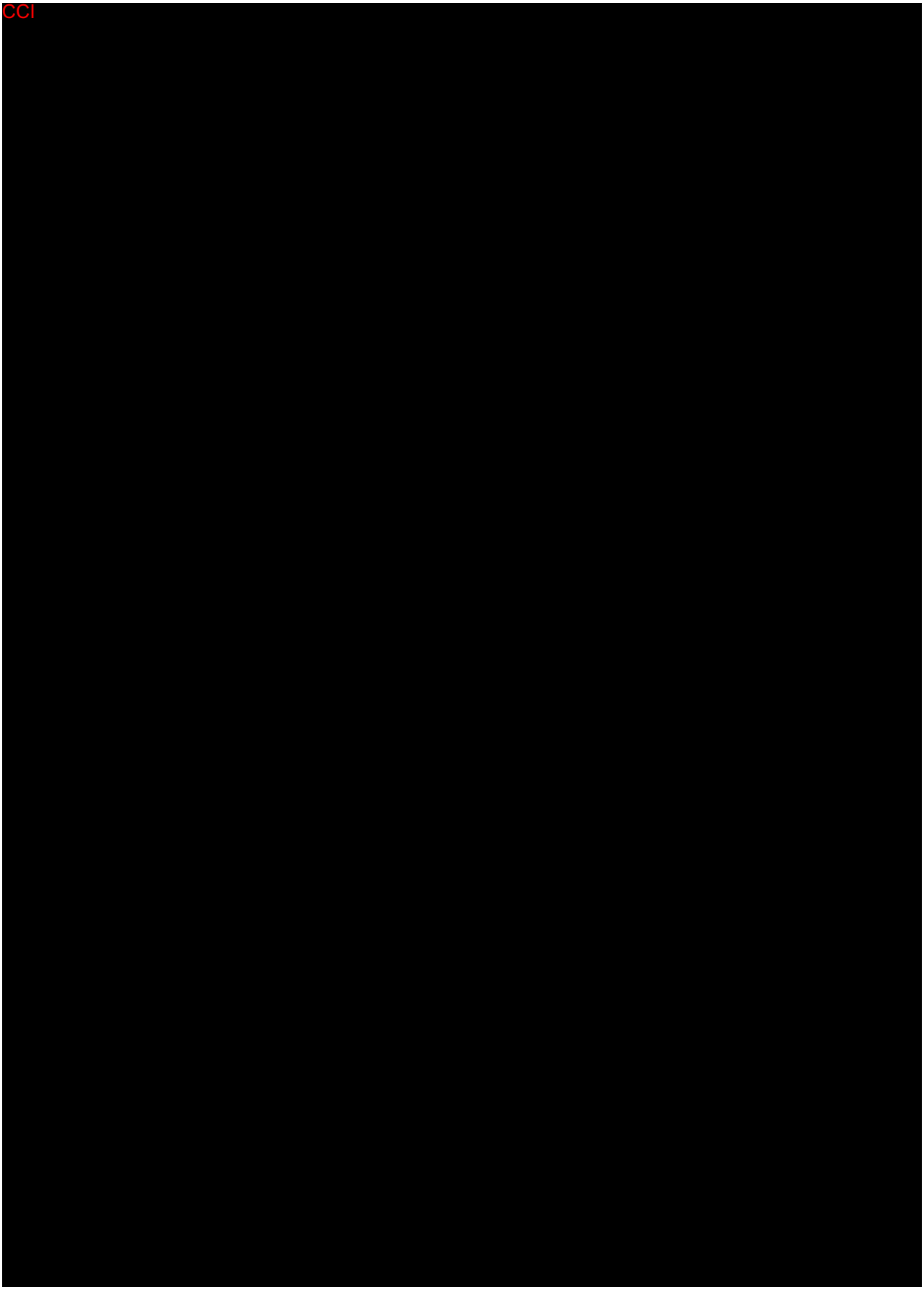

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6.5.3. Collection of Ablation Procedure Data for Post-Analysis (non-SOC)

At the completion of the study ablation procedure, two back-up copies of the CARTO®3 and generator system log files will be made. One copy should be kept at the site within the investigator site or patient binders, and one fully anonymized copy will be provided to/collected by the Sponsor.

6.5.4. Data Collection during Study Ablation Procedure

Procedural data collection will be done through anonymized (or de-identified) generator files, anonymized (or de-identified) CARTO®3 data files, procedural worksheets and subject medical files. Documentation of procedural data will be kept in the subject's CRF, anonymized (or de-identified) back-up generator files and back-up CARTO®3 datafiles for study analysis. The following information will be collected during the procedure, including but not limited to:

- Technical parameters are collected via CARTO® datafiles and generator files, including but not limited to:
    - Number of PFA applications

  - Ablation locations/ targets
  - Energy delivered
  - PFA application time
  - Ablation settings
  - Ablation lesion information will be collected in the CARTO®3 system and IRE Generator

- Other procedural parameters are collected via Electronic Data Capture (EDC), including but not limited to:
  - Use of a non-study catheter for PVI
  - Number of PFA applications per target PV
  - Number of RF applications required with a non-study catheter
  - PVI confirmed with Lasso® or PentaRay or Circular IRE Catheter
  - PV acute reconnection (early or dormant)
  - Procedure time (from first femoral puncture to last catheter out)
  - Mapping time (start mapping - end mapping)
  - Total fluoroscopy time
  - Total study catheter LA dwell time (from first study catheter insertion in LA until study catheter removal from LA)
  - ECG data
  - Total fluid delivered via study catheter
  - Total fluid delivered via intravenous line (if captured)
  - Fluid output (if captured)
  - Device deficiency information (if applicable)
  - Procedural medication (paralytics)
  - Anesthesia type

6.5.5. Repeat Ablation Procedures

Repeat procedures may be performed at the discretion of the investigator. Repeat procedures for AF/AT/AFL of unknown origin^{+} recurrences during the blanking period (90 days post index procedure) must be conducted with the investigational device for ablating PV reconnections. More than 1 repeat procedure for AF/AT/AFL of

unknown origin[+] during the blanking period is considered a failure mode for primary effectiveness. Procedures for CTI dependent flutter in the follow up period are not considered repeat procedures per protocol.

Repeat procedures performed after the blanking period may be managed per investigator discretion using a commercially available ablation catheter and generator. The follow-up schedule will remain based on the initial ablation procedure.

For the repeat procedures for AF/AT/AFL of unknown origin+, investigators must collect and provide information on location of reconnections of PVs and in case of atrial flutter recurrence, confirm if CTI dependent flutter or AFL of unknown origin.

[+]AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12 or 15 leads ECG or entrainment maneuvers in an EP study.

6.5.6. Post-Ablation Follow-up Schedule

The subject will be required to complete follow-up visits through 12 months post initial ablation procedure. Follow-up will be done at discharge, 7 day +3 days (phone call or clinic visit), 1 month ± 7 days (phone call or clinic visit), 3 month ±14 days, 6 month ± 30 days and 12 month ± 30 days (clinic visit). Follow-up visit schedule should be based on the date of the index study ablation procedure and will not reset if subject undergoes a repeat AF ablation procedure.

Prior to hospital discharge, the following assessments should be performed:

- Physical exam MUST be performed pre-discharge.
    - If physical exam demonstrates new abnormal neurological findings as compared to the one performed at baseline, a formal neurological consult and examination with appropriate imaging (i.e., DW-MRI) needs to be done to confirm or rule out any suspected diagnosis of stroke.
    - Diagnosis of stroke/CVA must be confirmed by at least one of the following:
        - Neurology or neurosurgical specialist
        - Neuroimaging procedure (MR or CT scan or cerebral angiography)
        - Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage)

  - Stroke: (diagnosis as above, preferably with positive neuroimaging study)
    - Minor-Modified Rankin sore<2 at 30 and 90 days
    - Major-Modified Rankin score>=2 at 30 and 90 days
    - MRS assessments should be made by certified individuals

- Medication regimen (Cardiac, anti-coagulation, PPIs and AE related)
- TTE should be performed to evaluate pericardial effusion
- AEs events
- AF/AT/AFL recurrence
- 12 or 15 leads ECG

At 7 day, 1-, 3-, 6-, 12-month follow-up, and at any unscheduled visits, the following assessments will be performed:

- Physical exam: exam should be performed at all clinical visits (except at 7 day follow-up)
- 12 or 15 leads ECG. Data from 12 or 15 leads ECG recordings will be collected at 3-, 6- and 12-month follow-up visits. ECG data will be collected at unscheduled visits if completed as standard of care.
- 24 Hour Holter: Holter monitor will be used at 3-, 6- and 12-month follow-up visits to monitor the subjects' heart rhythm for 24 hours continuously.
- Cardiac CT/MRA image: Any subjects who have symptoms suggestive of PV stenosis should undergo CT/MRA imaging.
- Adverse Events: AEs must be collected from the time the subject signs the informed consent onwards.
- AF/AT/AFL recurrences: for subjects with AFL recurrence identified though Holter monitoring, a 12 or 15 leads ECG MUST be collected.
- Medication: Cardiac and Anti-coagulation medication regimen, AE related
- Repeat ablation: any ablation procedure performed after the index procedure will be recorded at 3-, 6- and 12-month follow-up as well as at any unscheduled visits.
- Cardiac related hospitalization and cardioversions

- Subject completion/ discontinuation form (12-month)

Early Termination Visit

If early termination of the study is required due to safety concerns, each site will undergo a monitoring visit to conclude any outstanding issues, collect all outstanding CRF information, verify device accountability, and discuss any other items relevant to the conclusion of the study. Any enrolled subjects will continue to be followed per the study protocol requirements. In case of early termination due to safety concerns, reporting to EC and CA may be required per local regulations.

Unscheduled Visit

If a subject returns for a potential study related cardiovascular or neurological visit outside of the protocol-defined visit schedule provided in table 2, the visit will be considered "unscheduled" (UNS). An investigator may request an unscheduled visit in the presence of a new or worsened cardiovascular condition or neurological deficit. If the unscheduled visit is for a repeat ablation procedure, the protocol follow-up schedule is based on the index ablation procedure. For all unscheduled visits, an unscheduled visit eCRF must be completed and the subject must also return for their next scheduled study visit per clinical investigational plan.

6.6. Monitoring plan

This study is carried out according to the *Good Clinical Practice for Medical Device Trials* and relevant international laws and regulations, criteria, etc., such as the Declaration of Helsinki.

The sponsor bears the monitoring responsibility for the clinical trial and will select the qualified monitor to execute the monitoring responsibility.

The monitor should comply with the relevant laws and regulations and the standard operating procedure (SOP) established by the sponsor regarding the monitoring to monitor each phase of this study.

The monitor should contact and visit the investigators at a regular basis and perform on-site visit/monitoring for the study. The monitor should conduct a visit when the first subject is enrolled in each site and conduct a necessary visit at a regular basis during the study.

The monitoring includes the visit to study sites, verification of source data, communication with investigators and study sites, ensuring that this study is carried out strictly in compliance with the trial protocol and the requirements of such regulations as Good Clinical Practice.

The on-site monitoring includes verifying whether the source documents and source data are true, accurate, complete, and clear, and whether the source document of each subject is complete.

This study may be audited by the sponsor or inspected by the regulatory authority. If such audit/inspection is performed, the investigator and institution must agree the auditor to access to the records of subjects. The investigator agrees the sponsor or its appointed representative and regulatory authority to monitor all project-related study documents on site by signing on the signature page of this trial protocol.

7. Statistical Considerations

7.1. Statistical design, method and analysis procedure

This study is a single-arm, prospective, multi-center clinical study with the prespecified performance goals.

The primary effectiveness endpoint is the long term effectiveness and will be evaluated on all non-roll-in subjects for whom receive ablation power. Group sequential design using the O'Brien and Fleming (OBF) sequential testing procedure with one interim analysis will be performed when 50% of treated patients with full 12-month follow-up data to claim early trial success. If early success is not achieved, a final analysis will be performed using all subjects' full follow-up data. The endpoint will be considered successful if the one-sided lower confidence bound based on Normal Approximation method with Binomial Distribution for its rate is greater than the PG value of 50%.

The safety endpoints will be evaluated on all subjects for whom have the catheter inserted or ablated with the IRE system. The number of events, the number and percentage of subjects experiencing any PAE, AE and serious AE will be summarized by using the terms of MedDRA.

CCI [redacted]

CCI [redacted]

7.2. Calculation of sample size

7.2.1. CCI [redacted]

CCI [redacted]

7.2.2. Number of subjects with each disease in clinical trial and reason for determination

According to the inclusion and exclusion criteria of this study, subjects with drug refractory PAF and indicated for catheter ablation will be enrolled, and limits are not set for other diseases.

7.2.3. Minimum and maximum number of subjects in each study site and justification

A total of 123 non-roll-in patients will be enrolled. Each site will compete for enrollment, and the maximum number of non-roll-in subjects enrolled in a single site is no more than 40 (about 33% of the total number of non-roll-in subjects), to ensure enrollment of subjects from different sites and increase the representativeness in the target population.

7.2.4. Significance level and power of clinical trial

For the primary endpoint, the one-sided significance level of 0.025 is used.

The power of this clinical study is around 80%.

7.2.5. Expected drop-out rate

Expected drop-out rate is set as 10% in this study.

7.3. CCI [redacted]

CCI [redacted]

[redacted]

[redacted]

7.4. Criteria for terminating the trial based on the statistical reasons and justification

The interim analysis for study early termination is not planned, so this section is not applicable.

7.5. Statistical method of all data, together with the handling method of missing, unused and wrong data (including discontinuation and withdrawal) and unreasonable data

Analysis of demographic characteristics, baseline data and operation information

Demographics, baseline characteristics and procedural information will be

analyzed in the full analysis set (FAS) and the safety analysis set.

The descriptive statistics of continuous variables will include the number of subjects with valid data, number of missing, mean, standard deviation, quartiles, minimum and maximum. The descriptive statistics of categorical variables will include the frequency and percentage. The number of missing will not be included in the denominator for percentage calculation.

The data analysis plan will be documented in detail in the Statistical Analysis Plan.

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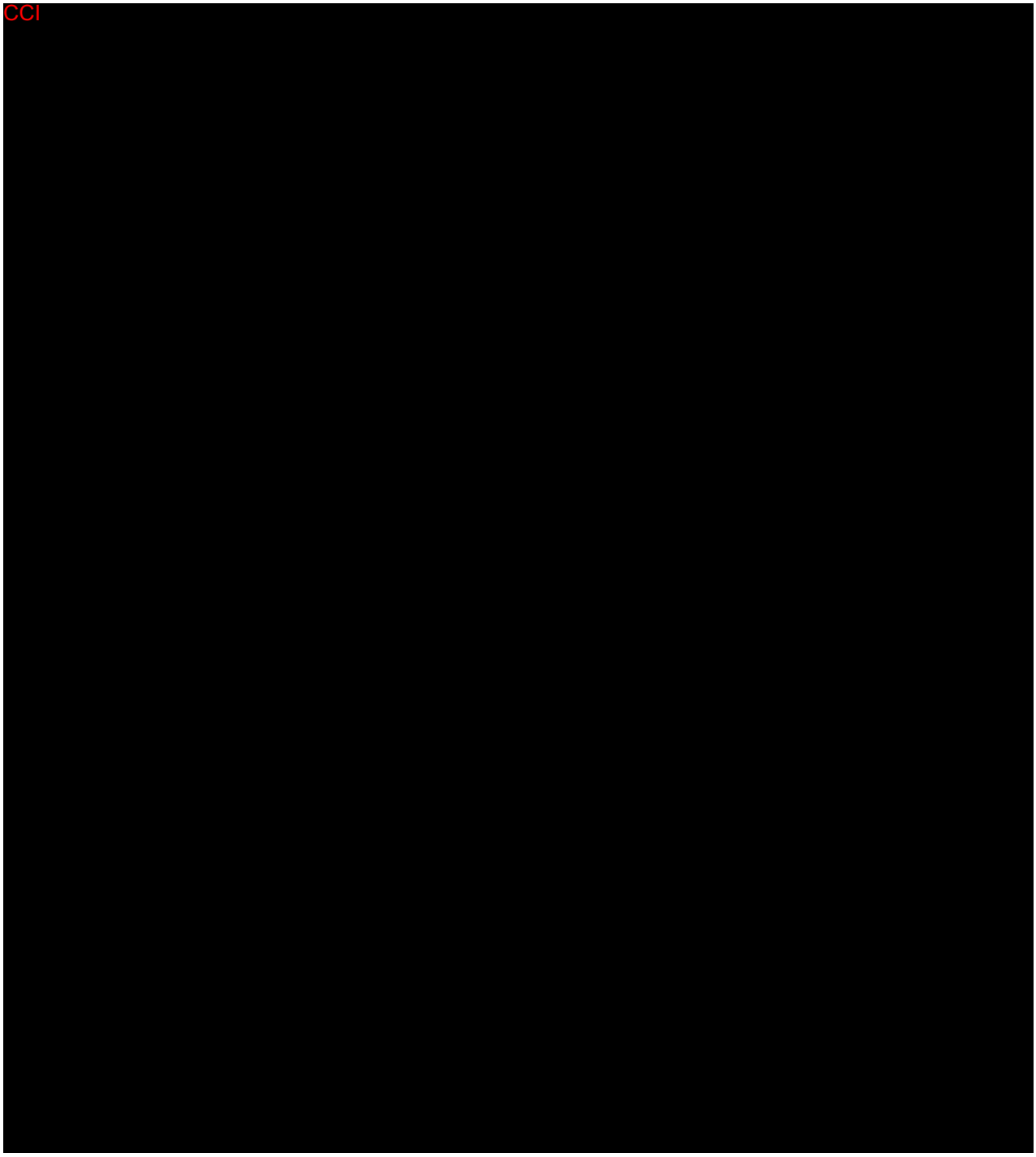

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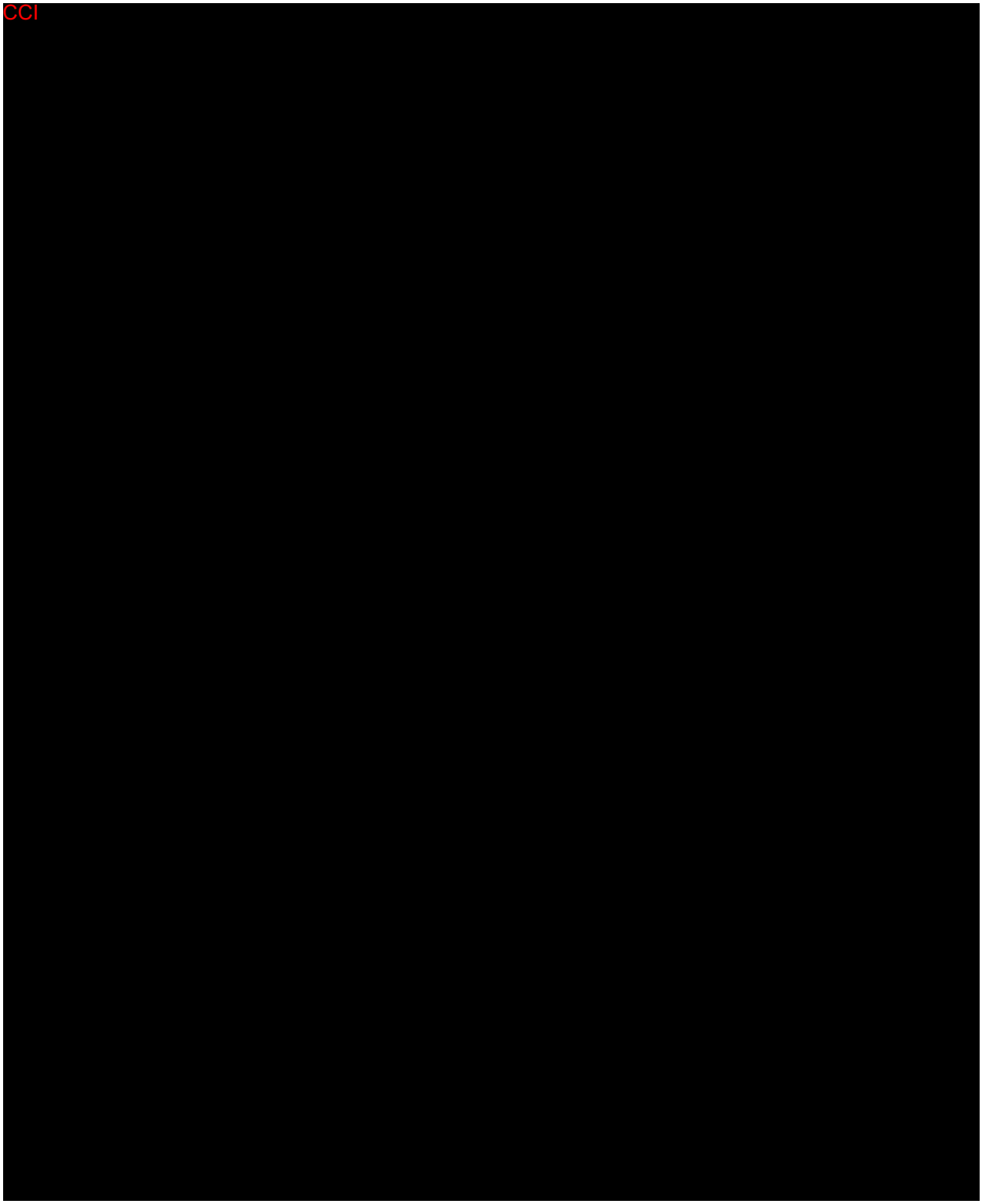

Analysis of secondary endpoints

All secondary endpoints will be analyzed on the FAS.

- Acute Procedural Success: the number and percentage of patients with acute procedural success will be calculated, and the two-sided 95% confidence

interval (CI) will be calculated by the exact (Clopper-Pearson) test method.

- Acute reconnection identified by adenosine/isoproterenol challenge among all clinically relevant targeted PVs and by subject: the number and percentage of PVs/patients with acute reconnection will be calculated, and the two-sided 95% CI will be calculated by the exact (Clopper-Pearson) test method.
- Rate of PV ablation by a non-study catheter (touch-up) among all clinically relevant targeted PVs and by subject: same statistical analysis method as acute reconnection.
- Rate of repeated ablation within the 12M FU period: same statistical analysis method as acute procedural success.

The secondary endpoints will not be used for statistical inference, but for descriptive purposes. Therefore, multiplicity will not be adjusted.

Analysis of safety endpoints

The safety endpoints will be analyzed in the safety set.

AEs will be summarized, including the number of AEs and the number and percentage of subjects experiencing any AEs. All PAE, SAEs and all procedure-/device-related AEs will analyzed in same way. The severity, relationship, AE treatment intervention, seriousness and outcome of all AEs will be described.

In addition, all AEs, PAE, serious and non-serious AEs will be summarized according to the system organ classification and preferred terms of MedDRA, and a list will be generated, including but not limited to subject identification number, age, AE term, start and end time (corresponding duration post procedure), severity, relationship, AE treatment intervention, seriousness, and outcome.

Handling of missing value

Subjects will be contacted by different means, such as by telephone, to avoid missing value.

For the primary endpoint, missing primary endpoint data of the subjects in the FAS will be excluded from the final primary effectiveness analysis as described in “Primary analysis of primary endpoint” of Section 7.5.

For those who had the investigational device inserted but not ablated, they would be replaced, and new subjects should be screened and enrolled to ensure total 110 evaluable non-roll-in subjects.

For baseline information, operational information, or secondary endpoints, all observed data will be used for analysis. Missing data imputation will not be

performed.

7.6. Protocol deviation

Protocol deviations will be classified into major protocol deviations and minor protocol deviations according to the provisions set in the Protocol Deviation Classification Table. All protocol deviations will be described by classification and degree.

7.7. Selection criteria for subjects included in the analysis and justification

All subjects that meet the inclusion criteria and does not meet the exclusion criteria are considered to meet the requirements for recruitment. The analysis sets in this study are defined as follows:

7.7.1. CCI

CCI

7.7.2. CCI

CCI

7.7.3. CCI

CCI

7.7.4. CCI

CCI

8. Data Management

The individual subject data collected during the trial will be recorded in the corresponding study database. Data will be reviewed by members of the data management team and the corresponding sponsor's study team. For any unexpected or missing data point, a query will be generated and sent to the study site for resolution.

After all subjects complete all follow-up evaluation, database will be locked, and

the data analysis will be performed.

9. Feasibility Analysis

9.1. Possibility analysis on success

The isolation of pulmonary veins (PVI) from the left atrium is the cornerstone for AF ablation procedures. The clinical data from different technologies and catheter designs have shown that PVI is safe and effective in treatment of paroxysmal AF. The BWI PFA system have been proven with features of non-thermal, irreversible, and cardiac tissue selection, which might be used to treat atrial arrhythmias. In pre-clinical studies, it showed that the predicate products were safe and could produce durable lesions.

Although there was limited clinical data about PFA technology in AF ablation, the features of non-thermal and cardiac tissue selection make this technology safer for structures adjacent to the myocardium. So, it is unlikely that the study will be terminated due to safety problems.

The investigational device is provided free of charge, which will not increase the burden of the subjects, so the difficulty in recruiting and screening subjects is acceptable.

9.2. Possibility analysis on failure

Long term effectiveness is unknown for PFA technology. There is limited clinical data for this technology in cardiac ablation area. there may be some undetected problems that may result in some unforeseen results in this study.

Patients will be followed 3 times in clinic and 2 time by phone and have ECG and 24h Holter at 3M/6M/12M follow-ups, which is not SOC and would be challenging in following up.

10. Quality Control of Clinical Trial

During the clinical study, the sponsor and investigator should execute their respective responsibilities according to the *Good Clinical Practice for Medical Device Trials* and applicable relevant Chinese and international regulations. They should also strictly follow the clinical trial protocol, to ensure the quality of clinical trial.

The sponsor should, according to the requirements of the clinical trial protocol, organize the training on the clinical trial protocol and the use and maintenance of investigational product for all investigators participating in the trial, to ensure consistency in the implementation of clinical trial protocol and the use of

investigational products.

During the implementation of study, the sponsor is responsible for monitoring each phase of clinical trial. The clinical monitor designated by the sponsor or designated representative should comply with the relevant SOP and clinical trial protocol that are established by the sponsor to monitor the clinical trial, to ensure the complete, accurate, true, and reliable data.

To ensure the quality of study, the sponsor may authorize the qualified QC or auditor to audit the clinical trial as needed. The investigator should allow the auditors to access to the original data and documents related to this study after receiving the notification.

When the medical products administration or other health administrative authority appoints the inspection personnel to carry out inspection, the study sites and investigators should cooperate and immediately notify the sponsor.

11. Ethical Issues and Informed Consent of Clinical Trial

11.1. Ethical considerations

The study should comply with Chinese laws and regulations, the Declaration of Helsinki and other international consensus, to protect the rights, safety, and health of subjects, including at least the following contents:

1) Ensure that the subjects are fully informed and agree to participate in the study voluntarily;
2) Respect and protect the privacy of subjects, and keep the records that may identify subjects confidential;
3) The production of the investigational medical device should meet relevant requirements of the applicable medical device quality management system; the use of the investigational medical device should meet the requirements of their IFUs, the protocol and relevant operation guidance;
4) Select the qualified study sites and investigators;
5) A subject has the right to withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or the institution;
6) The study protocol and amendment, the ICF and amendment and other study-related applicable documents should be approved by the EC before implementation.

11.2. Approval of trial protocol

Before the trial protocol is submitted to China Food and Drug Administration (if necessary), the EC and other authorities for approval, the internal review and approval should be completed according to the company's SOP.

The clinical trial protocol can be implemented only after the written approval from the EC is obtained.

11.3. Informed consent process

11.3.1. Informed consent process

The written consent of all candidate subjects or their legal authorized representatives must be obtained prior to performing any study operations/procedures (except for SOC operation procedures). Once the investigator determines that the subjects are suitable for participating in this study, the investigator must explain the study background and procedures, possible benefits and risks, etc. to the subjects or their legal authorized representatives. Only the subject who signs the ICF (Informed Consent Form) of the latest version that is approved by the EC (Ethics Committee (EC)) prior to participating in the study is eligible to participate in this study. The subject who does not sign the written ICF is not eligible to participate in this study.

Each subject (or legally authorized representative) must sign and date the ICF of the latest version that is approved by the EC (and other documents as per local regulations) prior to performance of any study-related activity or procedure, that is not standard of care and the study has been fully explained.

The voluntary process of obtaining written informed consent confirms the subject’s willingness to participate in the study. The Investigator and/or designee must clearly document the process of obtaining informed consent in the subject clinical record. The investigator has responsibilities to ensure the process of obtaining the informed consent is implemented according to It is the Investigator’s responsibility to ensure that the informed consent process is performed in accordance with the *Good Clinical Practice for Medical Device Trials* and relevant regulations, such as Declaration of Helsinki.

12. Device Management

In this study, the sponsor will provide all investigational devices. The package is clearly marked with "For Clinical Trial Only". All devices must be stored according to the conditions specified by the product label and IFU. The principal investigator is responsible for ensuring that the device is properly stored at the site.

The principal investigator or the person designated personnel by the principal

investigator must be responsible for all investigational devices throughout the clinical study and at the end of the study. During the study, the investigational devices must be kept in a locked or safe place. Inventory records of all devices received, used, or returned must be maintained during the clinical trial. The principal investigator must allow the monitor to enter the safe place where the investigational devices are kept in order to check the inventory. At the end of the clinical trial, all unused investigational devices must be returned to Johnson & Johnson Medical (Shanghai) Ltd., and an appropriate investigational device return form must be provided.

12.1. Packaging and labeling of investigational devices

All investigational devices provided by the sponsor in this study are prepared, packaged and labeled by qualified staff or designated personnel of the sponsor in accordance with the company's SOP, Good Manufacturing Practice for Medical Devices (GMP) and relevant local laws/regulations.

The label of each device meets the requirements of guidelines issued by regulatory authorities, GMP, local laws and regulations and company's SOP, and indicates that the investigational product is only for clinical trial.

12.2. Shipment of investigational devices

The sponsor or designated personnel of the sponsor will supply the devices to the study sites according to the device storage conditions in the device IFU.

12.3. Management of investigational devices

The sponsor will be responsible for providing qualified investigational products to the study sites. Each study site should designate related person to be responsible for the management of investigational devices. When the study sites receive the investigational products, they should check the investigational products and ensure that the packages of the investigational products are complete, the quantity is correct, and the transportation conditions meet the requirements.

During the study, the designated person is responsible for recording and counting the usage of the investigational products.

Records related to the receiving, distribution, use, recovery and disposal of investigational products should be kept in accordance with the requirements of Medical Device Good Clinical Practice (MD-GCP).

The investigators should ensure to use the investigational medical device only for the subjects of this clinical trial.

The principal investigator must allow the monitor to enter the safe place where

the investigational devices are kept during the clinical trial in order to check the inventory. At the end of the clinical trial, the unused investigational devices must be returned together with the relevant investigational device return form.

12.4. Return and destruction of investigational devices

All unopened and unused (e.g., expired), opened but unused, damaged, mislabeled or malfunctioning investigational devices should be sent back to the address designated by the sponsor. The corresponding form should be completed, and the devices should be properly returned to the address specified by the sponsor. The appropriate form(s) must be completed, and the device must be returned by courier to an address specified by the sponsor.

13. AEs and Device Complaints reporting

13.1. AEs recording

An adverse event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) occurring during a clinical study, whether or not related to the study device or ablation procedure.

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

- Any medical condition that is present at the time of screening. Such conditions should be added to the medical history if not previously reported. However, if the study subject's condition deteriorates at any time during the study, it should be recorded as an AE.
- Minor pericarditis attributable to the ablation procedure defined as pleuritic chest discomfort with or without pericardial rub and ECG changes.
- A trace/ trivial pericardial effusion that is asymptomatic, requires no medical intervention, and does not extend hospitalization will not be considered an adverse event.
- Postoperative incision pain, fever, incisional scar formation and abnormal lab test values are expected to occur and should not be recorded as AEs unless the investigator considers incision pain, fever, incisional scar formation and abnormal lab test values exceed the normal expected range for postoperative response or are related to the investigational device.

The following clinical events will not be considered an adverse event for this clinical study but will be captured in the database separately:

- Recurrence of pre-existing AF/AT/AFL of unknown origin+
- AF/AT/AFL of unknown origin requiring direct current cardioversion or pharmacological cardioversion (and accompanying hospitalization) during the blanking period. However, new onset of left atrial flutter occurring post ablation is an AE. For subjects with AFL recurrence identified through Holter monitoring; a 12 or 15 leads ECG MUST be collected.
- Re-ablation for AF or pre-existing AT/AFL of unknown origin+ (including accompanying hospitalization) itself is not an AE. However, any complication associated with the repeat ablation procedures is considered an AE and shall be reported within the applicable timelines.

From signing the ICF by the subject, the investigator should determine whether an AE occurs and determine its relationship to the investigational device or procedure at each evaluation for the subjects recruited for the clinical study.

Other AEs, investigational device malfunctions and other product issues must be recorded in the medical record and entered in the e-CRF.

13.2. Classification

Any of the following events, and any death or hospitalization while on study, is to be reported to the sponsor immediately when investigator is awarness. The sponsor may request additional information after the initial notification

13.2.1. Primary Adverse Event

A primary AE is one of the following events occurring within seven (7) days following an AF ablation procedure with the Circular IRE Catheter when used with IRE generator per protocol. Table 4 provides the PAEs and their descriptions.

A Clinical Events Committee (CEC) will be implemented to adjudicate the primary adverse events. The CEC will operate as described in the CEC Charter.

All reported Primary AEs will be monitored until they are adequately resolved or explained. The Clinical Events Committee (CEC) is to adjudicate the primary adverse events and operate following the regulations of the Committee.

Table 4: Primary adverse events and description/criteria

Primary AE	Description/ Criteria
Death (device or procedure related)	Subject death directly related to the device or procedure and occurs at any time during or after the procedure.
Atrio-Esophageal Fistula*	Is defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophagus 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 or MRI scan is the most common method of documentation of an atrio-esophageal fistula.
Cardiac Tamponade**,***/Perforation**	The development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure. A significant pericardial effusion is one which results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1 cm or more pericardial effusion as documented by echocardiography. Cardiac tamponade should also be classified as "early" or "late" depending on whether it is diagnosed during or following initial discharge from the hospital.
Myocardial Infarction	The presence of any one of the following criteria: • Detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB) which persists for more than 1 h • Development of new pathological Q waves on an ECG, and • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Stroke/ Cerebrovascular Accident	Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. Duration of a focal or global neurological deficit ≥24 h; or <24 h, if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)† Confirmation of the diagnosis by at least one of the following: • Neurology or neurosurgical specialist • Neuroimaging procedure (MR or CT scan or cerebral angiography) • Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) Stroke: (diagnosis as above, preferably with positive neuroimaging study) • Minor—Modified Rankin score <2 at 30 and 90 days†† • Major—Modified Rankin score ≥2 at 30 and 90 days
Thromboembolism	Formation of a clot (thrombus) inside a blood vessel causing obstruction to blood flow. The thrombus can migrate (embolus) and obstruct distal vascular sites. Diagnostic tests to help detect thromboembolisms may include but are not limited to angiography (pulmonary or distal), ventilation-perfusion (V/Q) scans, venography, Doppler ultrasonography, spiral CT, and echocardiography. For the purposes of this study, silent

	(asymptomatic) cerebral embolism will not be considered a PAE.
Transient Ischemic Attack	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24h. Neuroimaging without tissue injury.
Phrenic Nerve Injury / Diaphragmatic Paralysis	Absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis is considered to be permanent when not resolved at the final follow-up.
Heart Block	Impairment of AV conduction requiring intervention (e.g., temporary or permanent pacemaker) due to iatrogenic cause (e.g., inappropriate RF application, traumatic maneuvering of catheter or other intracardiac devices).
Pulmonary Vein Stenosis+	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. PV stenosis (> 70% PV narrowing) regardless of the presence or absence of symptoms and PV stenosis with ≥ 50% PV narrowing when accompanied with relevant and related symptoms that cannot be explained by other etiologies will be considered a primary adverse event.
Pulmonary Edema (Respiratory Insufficiency)	Respiratory insufficiency resulting in pulmonary complications necessitating intubation or other significant intervention (including diuretics administered specifically for treating pulmonary edema or ICU hospitalization requiring oxygen administration but not intubation). Exclusion criteria include: • Pneumonia – infiltrate, fever and leukocytosis • Acute Respiratory Distress Syndrome
Vagal Nerve Injury/ Gastroparesis	Injury to the vagal nerve that results in esophageal dysmotility or gastroparesis. Vagal nerve injury is considered to be a major complication if it prolongs hospitalization++++, requires hospitalization, or results in ongoing symptoms for more than 30 days following an ablation procedure.
Pericarditis	Should be considered a major complication following ablation if it results in effusion which leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization++++ by more than 48 h, requires hospitalization++++, or persists for more than 30 days following the ablation procedure.
Major Vascular Access Complication / Bleeding	Major Bleeding: A major complication of AF ablation if it requires and/or treated with transfusion or results in a 20% or greater fall in HCT. Major Vascular Access Complication: Defined as hematoma, an AV fistula, or a pseudoaneurysm which requires intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.

* Atrio-esophageal fistula that occurs greater than one week (7 days) post-procedure and up to 90 days post-procedure is considered and analyzed as a PAE.

** Cardiac Tamponade/Perforation occurring within 30 days of the AF ablation process will be considered Primary AEs

*** Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.

+ Pulmonary Vein Stenosis will be considered as a PAE if it occurs anytime during the 12- month follow up period.

† Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.

†† Modified Rankin score assessments should be made by certified individuals. ++++"Hospitalization" means the event necessitated an admission to a health care facility e.g., with at least an overnight stay. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

13.2.2. Serious AEs

A SAE is any AE that results in a death or a serious deterioration in the health of the subject during the clinical trial, including a life-threatening illness or injury, a permanent impairment of a body structure or a body function, in-patient hospitalization or prolongation of existing hospitalization*, medical or surgical intervention to prevent permanent impairment of a body structure or a body function; or results in fetal distress, foetal death or congenital abnormality, congenital anomaly, etc.

If it is a disease that exists before the scheduled hospitalization and/or medical intervention, or the operation required by the protocol but no serious deterioration in health, it will not be regarded as an SAE.

"Hospitalization" means the event necessitated an admission to a health care facility e.g., with at least an overnight stay. Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

*Planned hospitalization for a condition present prior to the participant's enrollment in the study will not meet the definition of an SAE but should nevertheless be included in routine study reporting.

13.2.3. Non-Serious AEs

A non-serious AE is any event that results in minimal transient impairment of a body function or damage to a body structure and does not require any intervention listed under the criteria for "Serious Adverse Event." Non-serious adverse events require routine reporting via EDC.

13.2.4. Anticipated AEs

An anticipated AE is one that has been reported in previous studies of cardiac ablation and can be anticipated in this current study as per the risk analysis. Appendix II provides a comprehensive list of anticipated AEs. If listed then report event as anticipated.

13.2.5. Unanticipated Serious Adverse Device Effects

A (serious) adverse device effect (SADE) is any (serious) adverse effect on subjects' health, safety, rights, welfare, and life-threatening problems including death, which is caused by, or associated with the study device. Accordingly, relationship to device or study is a crucial assessment by investigators. An unanticipated adverse device effect (UADE) or unanticipated serious adverse device effect (USADE) is any ADE or SADE that has not been previously identified in nature, severity, or degree of incidence in the study plan or risk analysis report. An investigator shall submit to the reviewing EC a report of any unanticipated adverse device effect occurring during an investigation per EC requirements.

13.2.6. Intensity or Severity, Outcome and Causality

Intensity (or severity) of AEs is defined as follows as table 5:

Table 5. Definition of intensity (or severity) of AEs

Mild	Awareness of sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no sequelae.
Moderate	Interferes, but does not hinder, the subject's usual activity and may require treatment.
Severe	Symptom(s) causing severe discomfort and significant impact on the subject's usual activity and requires treatment or intervention.

AE outcomes are assessed according to the following classifications as table 6:

Table 6. Definition of AE outcomes

Recovered/ Resolved	Subject recovered withoutsequelae..
Recovered/Resolved	Subject recovered with sequelae.
Not recovered/ resolved, onging	AE is ongoing without improvement or worsening in overall condition
Recovering/Resolving	Subject's condition is improving but residual effects remain.
Not recovered/ resolved , worsening	AE is ongoing with worsening in overall condition.
Fatal	Subject died as a result of the adverse event, whether or not the AE is related to the device or procedure. Note: deaths from any cause occurring on this study are to follow expedited reporting.
Others	Others：like AE outcome is unknown (e.g., subject lost to follow-up)

The causal relationship should be rated as table 7:

Table 7. Definition of causal relationship

Caused by	Relation	Definition of Relation
Device	Definitely (Causal relationship)	The event is associated with the investigational device beyond reasonable doubt
	Possible	The relationship with the use of investigational device

		seems relevant and/or the event cannot reasonably be explained by another cause, but additional information my be obtained. Or the relationship with the use of investigational device is weak but cannot be ruled out completely
	Unlikely	The occurrence of AE is more possibly related to other factors, or the temporal sequence did not reasonably show the relationship between product application and the event
	Not related	Relationship to the investigational device can be excluded.
Study procedure	Definitely (Causal relationship)	The event is associated with the procedure beyond reasonable doubt.[1]
	Possible	The relationship with the study procedure seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained. Or the relationship with the study procedure is weak but cannot be ruled out completely
	Unlikely	The occurrence of AE is more possibly related to other factors, or the temporal sequence did not reasonably show the relationship between study procedure and the event
	Not related	Relationship to the study procedure can be excluded.

[1] If event is deemed related to procedure, site should indicate whether related to index or repeat if applicable.

13.3. Device complaints

Device complaint refers to any defects of the marketed products regarding identification, quality, durability, reliability, safety, effectiveness or product performance that are reported in a written, electronic or oral manner. If there are any complaints about Johnson & Johnson's products, the study site must inform the monitor and follow up and report them according to the procedures specified by the sponsor. After receiving the complaint information from the study site, the monitor will follow up and report it according to the manner and time limit specified by the sponsor, and coordinate with the study site on the return of relevant investigational products.

13.4. Device deficiencies

The device deficiency is defined as unreasonable risk occurred under normal use of medical device during the clinical trial, which may do harm to human health and life safety, such as label error, quality problem and fault.

13.5. Reporting procedures and contact information

The investigator should ensure to provide the sufficient treatment for any AEs of any subjects, including the laboratory test values with clinical significance and related to this study.

The investigator should report the AE to the sponsor through e-CRF within 2

weeks after learning of the AE. The investigator should record the nature, severity, treatment and outcome of AE, and determine whether it is related to the investigational device, medication or surgery specified in the trial protocol.

The investigator should follow up all AEs until the event is resolved (with or without sequelae), or if the event causes the permanent damage, it should be followed up until the event is stable and the clinical outcome is determined. When the event is not resolved or stable at the end of study, the medical monitor in this clinical study will decide whether it is necessary to collect the further follow-up information.

The investigator must report any SAE to the administrative department for medical device clinical trials of the study site, the sponsor and the EC within 24 hours after learning of such SAE or device deficiency, and should provide further information if requested by the sponsor.

The investigator should record all device deficiencies and complaints occurred during the clinical trial, and contact the sponsor's monitor or corresponding contact person in time. Detailed reporting process and contact person are shown in the Safety Events Management Plan. According to the requirements of the sponsor, the defective investigational devices should be returned to the sponsor as much as possible.

For the SAE, the sponsor should, according to the regulatory requirements, report to other clinical trial institutions participated in the clinical trial, Ethics Committee and principal investigators, the drug administration department where the sponsor is located, the drug administration department where the clinical trial institution is located and health administration department, within 7 days of being informed of a death or life-threatening serious adverse event (SAE) associated with a clinical trial medical device, and within 15 days after being informed of non-death or non-life threatening serious adverse events associated with a clinical trial medical device or other serious security risk information, and shall take risk control measures.

14. Provisions for Deviation from Clinical Trial Protocol and the Amendment to Clinical Trial Protocol

The protocol deviation is defined as the circumstances that fail to comply with the requirements of clinical trial protocol intentionally or unintentionally.

The sponsor's investigator should record and report all protocol deviations in a timely manner.

If protocol amendment is required, the sponsor or designated person should

submit the change data of trial protocol to the investigator, EC, etc. according to the relevant laws and regulations. All major amendments must be approved by the EC and regulatory authority (if needed) prior to implementing any changes to study procedures.

15. Direct Access to Source Data and Documents

The source data is defined as all information in the original record and its approved copy with regard to the clinical findings, observations and other activities in the clinical trial, which can be used for reproduction and evaluation of clinical trial. The source documents are documents in which the source data are recorded, including printed or electronic documents.

The information in the subject's medical records and other study related documents (source documents) must be maintained and retained by the investigator. The investigator should allow the monitors and auditors/inspectors to look up, including but not limited to the following information:

- Medical/physical condition of the study subject that meets the inclusion criteria in the trial protocol prior to participating this study;
- Medical records in which informed consent process is recorded;
- Operational description on use and implantation of the investigational product;
- All examination results and follow-ups;
- Examined printed output file or report (for example, X-ray film) that is dated and signed;
- Description on AEs and follow-ups of AEs (description on events, severity, date of occurrence, duration, correlation with the investigational device, study procedures, outcome and treatment of AEs, concomitant medications when AE occur);
- Description on device deficiencies
- Study subject's status at the end of the study or withdrawal from the study.

16. Finance and Insurance

See the relevant study contract and insurance document.

17. Contents of Clinical Trial Report

According to the regulatory requirements, the clinical trial report should include the following contents:

The clinical trial report should be consistent with the clinical trial protocol, mainly including:

(I). General information;
(II). Summary;
(III). Introduction;
(IV). Clinical trial objective;
(V). Clinical trial method;
(VI). Clinical trial contents;
(VII). General clinical information;
(VIII). Investigational medical device and control medical device or control diagnostic and therapeutic method;
(IX). Statistical analysis methods and evaluation methods adopted;
(X). Clinical evaluation criteria;
(XI). Organizational structure of clinical trial;
(XII). Ethical description;
(XIII). Clinical trial results;
(XIV). AEs found in the clinical trial and their handling;
(XV). Analysis and discussion of clinical trial results, especially the indications, scope of application, contraindications and precautions;
(XVI). Clinical trial conclusion;
(XVII). Existing problems and improvement suggestions;
(XVIII). List of investigators;
(XIX). Other conditions that need to be described;

18. Confidentiality Principle

The personal data of the subject participating in the trial is confidential; however, the EC, sponsor and health administrative authority and their authorized representatives may review the personal data of the subjects participating in the trial according to the established procedure.

The personal data of subjects should be kept confidential during the entire period of clinical study, and it should be ensured that the source data can be tracked through information. Therefore, a unique subject identification number (study site number and subject number) is used to identify all data of each subject reported. If the data is kept strictly confidential and it is ensured that the privacy of the subject has been protected, the data related to this study is available for the third party (for example, under the inspection of regulatory authority).

19. Agreement on Publication of Trial Results

If needed, an article for multi-center clinical trial will be prepared and published

in the prestigious scientific journal at the end of the study. No major results of any individual study site in this study are allowed to be published before the multi-center trial results are prepared and published. In case of exceptions, such as analysis of pre-defined and non-pre-defined other endpoints, or such secondary analyses and other proposed investigations, prior approval of the sponsor is required. To timely extract the statement and publish, the second publication will be entrusted to the corresponding principal authors. The final analysis and review of all multi-center trial data are required to be approved by the sponsor.

20. Responsibilities of Parties Involved

20.1. Responsibilities of sponsor

The sponsor is responsible for the initiation, application, organization and monitoring of a clinical trial and is responsible for the quality of the clinical trial. This includes: select qualified study sites and their investigators; organize the preparation and revision of study related documents before or during the trial; provide necessary training for the investigators to carry out this clinical trial. Ensure that investigators follow the clinical trial protocol; provide qualified investigational products and other study related articles required for implementation of this trial according to the regulatory requirements; collect and report AEs, SAEs and device deficiencies according to regulations; coordinate and organize the clinical trial reporting and final registration application at the end of the study.

20.2. Responsibilities of study sites and investigators

The study sites should evaluate the relevant resources according to the features of investigational medical device prior to the clinical trial, so as to decide whether to carry out this clinical trial. The administrative department for medical device clinical trials of the study site should cooperate with the sponsor to submit the clinical study application to the EC and submit relevant documents according to regulations. The study sites should properly keep the records and basic documents of clinical trial according to relevant laws & regulations and the time limit agreed with the sponsor.

The investigator should ensure that relevant staff participating in the trial has enough resources and receive study-related training, and keep the training related documents, and should carry out the study according to the clinical trial protocol.

The study sites and investigators should ensure that the data, documents and records generated in the clinical trial are true, accurate, clear and safe, should accept and cooperate with the monitoring and audit of the sponsor, the supervision of the EC, as well as the inspection of the health administrative authority, and

provide all required records related to the trial. The investigators should ensure to complete all records and reports at the end of clinical trial. The investigators should also ensure that the received investigational medical devices are properly handled and recorded according to the requirements.

20.3. Responsibilities of other interested parties

See the study-related contract.

INVESTIGATOR'S STATEMENT:

I agree:

1. To carry out this clinical trial in strict compliance with Declaration of Helsinki, current laws and regulations of China, and the requirements of the trial protocol.
2. To accurately record all data required into the CRF and complete the clinical trial report on time.
3. The investigational medical device will be used only for this clinical trial; the receipt and use of the investigational medical device will be recorded completely and accurately and the records will be retained throughout the clinical trial.
4. To allow monitors and auditors authorized or designated by the sponsor as well as regulatory authorities to conduct monitoring, audit and inspection on the clinical trial.
5. To strictly perform the articles of clinical trial contract/agreement signed among parties.

I have already read the clinical trial protocol entirely, including the above statement, and I fully agree all the above contents.

Comments of sponsor Signature (stamp) MMDDYYYY

Comments of investigator Signature MMDDYYYY

Comments of the medical device study site Signature (stamp) MMDDYYYY

Appendix I: References

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Appendix II: ANTICIPATED ADVERSE EVENTS

(Acute) renal failure	Infection, systemic
(Aspiration) pneumonia	Inflammation
(Skin) laceration	Isolated ST segment elevation
(Vascular) bleeding	Liver toxicity
Acute Respiratory Distress Syndrome (ARDS)	Local Hematoma/ecchymosis
Air embolism	Localized skin reaction
Allergic reaction to contrast media Allergic skin reaction	Mitral Insufficiency
Allergic skin reaction	Myocardial infarction with or without ST elevation
Altered Mental Status Confusion; Altered Level of Consciousness;	Nausea
Anaphylactic shock	Neurological disorders (poor coordination)
Anemia	Neurological disorders (tremor)
Anesthesia complications/reactions	Neuropraxia/Muscle contraction
Anoxic or hypoxic encephalopathy	Palpitations
Aortic Puncture	Papillary Muscle tear/injury
Apnea - sedation induced	Pericardial effusion resulting in tamponade
Arrhythmia (new or worsening of pre-existing arrhythmia)	Pericardial effusion without tamponade
Asthmatic attack	Pericarditis
Asymptomatic Cerebral Emboli	Periesophageal vagal nerve injury
Atelectasis	Peripheral nerve injury
Atrial fibrillation	Phlebitis
Atrial Septal Defect (acquired)	Phrenic nerve damage/injury
Atrio-Esophageal fistula	Pleural effusion
Auditory Disorder	Pneumothorax
AV fistula	Post- and perioperative pain
Back Pain	Post Procedural Hematuria
Bone disorder	Pseudoaneurysm
Bronchial fistula, Broncho-pericardium fistula	Pulmonary edema
Cardiac arrest	Pulmonary embolism
Cardiac pacemaker insertion or replacement	Pulmonary hypertension
Cardiac perforation	Pulmonary toxicity, like acute pulmonary syndrome
Cardiac Valve Rupture/Damage	Pulmonary vein dissection
Cardiogenic Shock	Pulmonary vein stenosis
Cerebro-Vascular accident (CVA)/Stroke	Renal Artery Stenosis
Chest pain/discomfort	Respiratory arrest
Complete or incomplete heart block	Respiratory depression
Conduction block	Respiratory failure

Coronary Artery Stenosis	Respiratory infection
Coronary artery thrombosis	Retinal Artery Embolism
Death	Retroperitoneal bleeding
Deep venous thrombosis	Rhabdomyolysis, including produced by body positio n or propofol
Diaphragmatic paralysis	Sedation induced CO2 retention with lethargy and cholecystitis
Dislodgement/Malfunction of pacemaker/defibrilator leads	Seizure
Disseminated Intravascular Coagulation	Sepsis
Dizziness, presyncope, vertigo	Sinus bradycardia
Dysphagia	Sinus tachycardia
Dyspnea	Skin burn or necrosis
Endocarditis	Skin discoloration
Epigastric Distress	Skin edema
Epistaxis	Skin or soft tissue (radiation) injury/tear
Esophageal injury / perforation	Subclavian artery puncture
Expressive aphasia	Temperature elevation / Fever
Fatigue	Thrombocytopenia
Gastric hypomotility	Thromboembolism
Gastroesophageal reflux	Thrombosis
Gastrointestinal disorders	Thyroid disorders
Gastrointestinal diverticulosis	Toxic reaction
Gastroparesis	Transient extremity numbness
Headache	Transient Ischemic attack (TIA)
Heart failure (acute or chronic)	Urinary Retention Postoperative
Heart injury	Urinary tract injury or infection related to the urinary catheter
Heart valve insufficiency	Valvular damage/insufficiency
Hemoptysis	Vascular (access) dissection (including coronary arteries)
Hemorrhage	Vascular occlusion
Hemothorax	Vasovagal reactions
High/increased creatine phosphokinase (CPK)	Ventricular Fibrillation
Hypertension	Vessel damage/trauma
Hypervolemia	Vessel perforation
Hypotension	Vessel spasm (including coronary arteries)
Hypovolemia	Visual disturbance
Hypoxia	Worsening of pre-existing pulmonary disease
Increased phosphokinase level	Wound healing disturbance