Pulsed Field Ablation (PFA) System for the Treatment of Paroxysmal Atrial Fibrillation (PAF) by Irreversible Electroporation (IRE). "inspIRE"

Protocol Number:	BWI_2019_08
Sponsor:	Biosense Webster, Inc., a division of Johnson & Johnson with registered office at 31 Technology Drive, Suite 200 Irvine, CA 92618
Operating Company:	Johnson & Johnson Medical NV/SA with registered office at Leonardo Da Vincilaan 15, 1831 Diegem, Belgium, represented by Nathalie Macours.
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History of Changes:

Version— Date	Description
V 1.0 — 13 MAR 2020	Original Document

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 IRE system (Circular IRE Catheter and IRE Generator) may be different.

1. Table of Contents

2. List of Figures and Tables

3. List of Acronyms and Abbreviations

Acronym/ Abbreviation	Expanded Term
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
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
GCP	Good Clinical Practices

Acronym/ Abbreviation	Expanded Term
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
ICH	International Conference on Harmonization
IFU	Instruction for Use
ILR	Implantable Loop Recorder
IRE	Irreversible Electroporation
ITT	Intention to Treat
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
mITT	Modified Intent to Treat
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

Acronym/ Abbreviation	Expanded Term
QC	Quality Control
QoL	Quality of Life
RA	Right Atrium
RF	Radiofrequency
RFCA	Radiofrequency Catheter Ablation
RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDV	Source Data Verification
SOC	Standard Of Care
SP	Safety Population
SVC	Superior Vena Cava
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TS	Transseptal
TTE	Transthoracic Echocardiography
UADE	Unanticipated Adverse Device Effect
UM	User Manual
USADE	Unanticipated Serious Adverse Device Effect

4. Key Roles and Responsible Parties

SPONSOR:

Cardiovascular & Specialty Solutions (CSS)
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The Sponsor will finance the study, and a clinical trial agreement (CTA) will manage the relationship between the sponsor, the investigator and the institution. Including but not limited to description and aknowledgment of responsibilities, terms of collaboration, indemnification, requirements for payment, publication and intellectual property terms and guidelines for dispute resolution.

CONTACTS:

[redacted]

[redacted]

[redacted]

Whereas, the Clinical Study is sponsored by Biosense Webster Inc., Johnson and Johnson Medical NV/SA with registered offices at Leonardo Da Vincilaan 15, 1831 Diegem, Belgium, has been duly appointed by the Sponsor to conduct the Clinical Study on its behalf.

The sponsor maintains an updated list of Principal Investigators (PIs), the coordinating investigator (if appointed), address details of each investigational site, emergency contact details for the PI's at each site, roles and responsibilities and qualifications of each respective investigator, institutions,

corelabs (if applicable) and Contract Research Organizations (if applicable). The definitive list shall be integrated into the study report.

The current protocol has been developed based on regulations applicable in Europe, for countries outside Europe, a country specific version of this study protocol may be developed, further defining regional regulations, if applicable.

5. Protocol Summary

Full Title	Pulsed Field Ablation (PFA) System for the Treatment of Paroxysmal Atrial Fibrillation (PAF) by Irreversible Electroporation (IRE).
Short Title	inspIRE
Protocol Number	BWI_2019_08
Eudamed number	*<Available as from submission>*
Sponsor	Biosense Webster, Inc.
Indication	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 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 Circular IRE Catheter and the Multi-Channel IRE Generator. Multi-Channel IRE Generator [redacted] Circular IRE Catheter [redacted]

	[redacted]
Premarket or Post market	Premarket
Study Design	Prospective, single arm, multi-center, pre-market clinical evaluation of the IRE system (Circular IRE Catheter and IRE Generator) to demonstrate safety and long-term effectiveness when compared to a performance goal based on a historical control. The study shall include two sequential waves: Wave I of the study will enroll up to 40 subjects, who will undergo the index procedure and additional neurological, PV and esophageal assessments. Wave II of the study will enroll roll-ins, and up to 330 subjects in the main phase. Wave II subjects will undergo the index procedure and same follow-up schedule as Wave I subjects, excluding the additional neurological, and post procedural PV (unless symptomatic) and esophageal assessments. Bayesian adaptive design will be used for sample size selection in Wave II of the study.
Sample Size	As Wave I of the study is a safety characterization phase, a sample size of 40 subjects is intended to delineate safety and provide preliminary estimates for safety and acute effectiveness of the IRE system. Two sample size selection interim analyses will be performed in Wave II. Predictive probabilities of success will be used to determine whether the enrollment will be stopped or continued at each sample size selection interim analysis. The study may enroll up to a maximum of 330 subjects in the main phase.
Study Population	Patients scheduled to have a clinically-indicated ablation procedure for the management of their drug refractory PAF will be screened for enrollment per the study's inclusion and exclusion criteria.
Geographic areas to be included	Up to 30 sites mainly in Europe and possible other regions.

<table>
<tr><td>Anticipated Study Timeline</td><td>Total duration:
Approximately 17 months of enrollment:
Wave I: 4 months in a maximum of 7 sites
Wave II: 13 months in a maximum of 30 sites
+ 12 months Follow-Up (FU)</td></tr>
<tr><td>Procedure(s) description</td><td>Subjects will arrive to the electrophysiology (EP) laboratory for their ablation procedure and will undergo preparation for the procedure per the hospital's standard protocol (discretion of investigator).

The AF Ablation procedure will follow below sequence:
1. Anatomical mapping of the LA
2. PVI using the study catheter
3. Confirmation of PV isolation (entrance block) with adenosine/isoproterenol challenge
4. If necessary, treatment of acute reconnections with additional applications of PFA energy
5. Confirmation of entrance block of all targeted PVs

In this study protocol, IRE ablation modality is to be used as the primary mode for PVI. If PVI cannot be achieved with PFA, the IRE system should be disconnected prior to use of a commercial Radiofrequency (RF) system, to complete the procedure.

The Circular IRE Catheter should not be used for lesions outside the PV region</td></tr>
<tr><td>Primary Objective</td><td>The primary objective of this clinical investigation is to demonstrate safety and long-term effectiveness of the IRE system (Circular IRE Catheter and IRE Generator) when used for isolation of the atrial PVs in treatment of subjects with PAF.</td></tr>
<tr><td>Primary Endpoints</td><td>Only Wave II subject data will be used for the purpose of primary hypothesis testing. Wave I and roll-in subject data will be separately analyzed (not part of the primary hypothesis testing).

Acute Safety
The primary safety endpoint is the incidence of Primary Adverse Events (PAEs) (within seven (7) days of the initial mapping and ablation procedure). PAEs include the following Adverse Events (AEs):
<table><tr><td>Atrio-Esophageal Fistula*</td><td>Phrenic Nerve Paralysis (permanent)</td></tr><tr><td>Cardiac Tamponade/perforation</td><td>Pulmonary Vein Stenosis*</td></tr><tr><td>Device or procedure related death*</td><td>Stroke/CVA</td></tr><tr><td>Major Vascular Access Complication/Bleeding</td><td>Thromboembolism</td></tr><tr><td>Myocardial Infarction</td><td>Transient Ischemic Attack (TIA)</td></tr><tr><td>Pericarditis</td><td></td></tr></table>* Device or procedure related death, pulmonary vein stenosis and atrio-esophageal fistula that occur greater than one week (7 days) post-procedure are considered and analyzed as PAEs.</td></tr>
</table>

	Long term effectiveness Freedom from documented (symptomatic and asymptomatic) atrial arrhythmia (Atrial Fibrillation (AF), Atrial Tachycardia (AT) or Atrial Flutter (AFL)) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365). Acute procedural failure (i.e., failure to confirm entrance block, with or without touch-up, in all PVs except those that are silent and/or cannot be cannulated post-procedure) will be considered a long-term effectiveness failure.
Secondary Endpoints	– Acute Procedural Success defined as confirmation of entrance block in all clinically relevant targeted PVs after adenosine/ isoproterenol challenge. Use of a non-study catheter to achieve PVI is considered an acute procedural success failure. – Freedom from documented symptomatic atrial arrhythmia (AF, AT or AFL) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365). – Quality of Life (QoL): the change of QoL assessed by comparing the Atrial Fibrillation Effect on Quality-of-Life (AFEQT™) scores before and after the ablation procedure.
Additional Endpoints	**Safety** – Occurrence of individual PAEs from the primary composite – Occurrence of Serious Adverse Device Effects (SADEs) – 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 – Occurrence of non-SAEs – Occurrence of clinically symptomatic severe PV stenosis as documented by CT/MRA **Effectiveness** – Ablation by a non-study catheter for PVI (touch-up) among all clinically relevant targeted PVs and by subject – Acute reconnection identified by adenosine/isoproterenol challenge. among all clinically relevant targeted PVs and by subject – % repeat ablation within the 12M FU period o Timing (blanking period or after blanking) o % PV reconnection – Freedom from documented symptomatic and asymptomatic atrial fibrillation (AF) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365). – Freedom from documented (symptomatic and asymptomatic) atrial arrhythmia (AF, AT or AFL) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365) with the following criteria also deemed failure:

	○ Taking a new class I/III Antiarrhythmic Drug (AAD) for AF or a previously failed class I/III AAD at a greater than the highest ineffective historical dose for AF during the effectiveness evaluation period ○ Greater than 2 repeat ablations for AF/AT or AFL in the blanking period or any repeat ablation for AF/AT or AFL during the effectiveness evaluation period **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 **Neurological Assessment (Wave I)** - Occurrence of new post-ablation asymptomatic and symptomatic cerebral emboli as determined by Magnetic Resonance Imaging (MRI) evaluations - Occurrence of new or worsening neurological deficits post-ablation and at follow-up, compared to baseline - Occurrence, anatomical location and size of asymptomatic and symptomatic cerebral emboli observed pre-and post-ablation as determined by MRI evaluations. - Summary of Mini Mental State Examination (MMSE), National Institute of Health Stroke Scale (NIHSS) and Modified Rankin Scale (mRS) at baseline, post-ablation and during follow-up (if lesions were identified in prior evaluation) **CT/MRA (Wave I)** - Occurrence of severe PV stenosis at 3 months post-ablation as determined by Computed Tomography (CT)/ Magnetic Resonance Angiogram (MRA) evaluations. **Endoscopy (Wave I)** - Occurrence of post-ablation esophageal lesions as determined by post-procedure endoscopy
Inclusion Criteria	1. Diagnosed with Symptomatic PAF. 2. Selected for AF ablation procedure by PVI. 3. Failed at least one AAD (class I to IV) as evidenced by recurrent symptomatic AF, or intolerable or contraindicated to the AAD. 4. Age 18 -75 years 5. Willing and capable of providing consent 6. Able and willing to comply with all pre-, post-, and follow-up testing and requirements
Exclusion Criteria	1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause. 2. Previous LA ablation or surgery

	3. Patients known to require ablation outside the PV region (e.g. CTI region, atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, ventricular tachycardia and Wolff-Parkinson-White). 4. Previously diagnosed with persistent AF (> 7 days in duration) 5. Severe dilatation of the LA (LAD >50mm antero-posterior diameter in case of Transthoracic Echocardiography (TTE)) 6. Presence of LA thrombus 7. Severely compromised LVEF (LVEF <40%) 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 6 months 11. Previous PCI/MI within the past 2 months 12. Coronary Artery Bypass Grafting (CABG) in conjunction with valvular surgery, cardiac surgery (e.g. ventriculotomy, atriotomy) or valvular cardiac (surgical or percutaneous) procedure. 13. Unstable angina pectoris within the past 6 months 14. Anticipated cardiac transplantation, cardiac surgery or other major surgery within the next 12 months. 15. 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 16. Known significant PV anomaly that in the opinion of the investigator would preclude enrollment in this study 17. Has known pulmonary vein stenosis 18. Acute illness, active systemic infection or sepsis 19. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation. 20. Severe mitral regurgitation 21. Presence of implanted pacemaker or Implantable Cardioverter-Defibrillator (ICD) or other implanted metal cardiac device that may interfere with the IRE energy field. 22. Presence of a condition that precludes vascular access (such as IVC filter) 23. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this study 24. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being 25. Current enrollment in an investigational study evaluating another device or drug. 26. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of child bearing age and plan on becoming pregnant during the course of the clinical investigation. 27. Life expectancy less than 12 months

	28. Presenting contra-indications for the devices used in the study, as indicated in the respective Instructions For Use (IFU) Additional exclusion criteria for Wave I subjects: 29. Contraindication for MRI such as use of contrast agents due to advanced renal disease, claustrophobia etc. (at PI discretion) 30. Presence of iron-containing metal fragments in the body 31. Unresolved pre-existing neurological deficit. 32. Uncontrolled significant GastroEsophageal Reflux Disease (GERD)
Safety Assessments	The safety endpoint is the incidence of early onset Primary Adverse Events (PAEs) (within seven (7) days of the initial ablation procedure). Additional safety assessments on neurological lesions, esophageal lesions and PV stenosis will be performed for the Wave I subjects.
Statistical Analysis	The main phase of the study (Wave II) will use a Bayesian adaptive design to determine the sample size. The timing of sample size selection interim analyses will be described in the Statistical Analysis Plan (SAP). A maximum of 330 subjects may be enrolled in the main study phase. An additional interim analysis will be performed for claiming early trial success when 30 subjects reach full 12-month of follow-up and all subjects in three months of follow-up. If the criteria for early success are met, filing for CE Mark will be performed while 12-month follow-up is ongoing in the remaining subjects. **<u>Final Primary safety analysis</u>** The final analysis for the primary safety endpoint will use a beta-binomial model with a non-informative uniform prior. The endpoint will be considered a success if the posterior probability of the safety rate being less than 14% is greater than 0.975. H_0: $\Pr(P_s < 0.14) \leq 0.975$ H_a: $\Pr(P_s < 0.14) > 0.975$ **<u>Final Primary effectiveness analysis</u>** The final analysis for the primary effectiveness endpoint will use a beta-binomial model with a non-informative uniform prior. The endpoint will be considered a success if the posterior probability of the primary effectiveness success rate being greater than 50% is greater than 0.9775. H_0: $\Pr(P_E > 0.50) \leq 0.9775$ H_a: $\Pr(P_E > 0.50) > 0.9775$

Interim Analysis	Detailed information on analysis performed within the study will be described in the statistical Analysis plan. Sample size selection analysis and an interim analysis for claiming early trial success will be performed.
Determination if DSMB/DMC/CEC required	DMC and CEC will be established for this study - DMC will assess subjects' data for safety on regular intervals for Wave I and Wave II and make recommendations on study adaptations. - CEC will adjudicate primary safety endpoint events for Wave I and Wave II.
Time and Events Schedule	**See table 1 below**

Table 1: Subject Treatment and Follow-up Schedule

Assessments	Pre-Procedure	Pre-Discharge	Follow-up					
			7 Day	1 Month	3 Month	6 Month	12 Month	UNS
Study Day			D7	D30	D90	D180	D365	
Visit window			D7-D9	D23-D37	D76-D104	D166-D194	D335-D379	
Clinic visit	●	●	(●)	●	●	●	●	●[18]
Phone call			●					
Patient Informed Consent[1]	●							
Demographics	●							
Medical History[2]	●							
Pregnancy test[3]	●							
LA and LVEF assessment[4]	●							
Left atrial thrombus detection[5]	●							
Pericardial fluid assessment		●						
12 Lead ECG[6]	●	●		●	●	●	●	●[19]
Atrial Arrhythmia monitoring (Remote)[7]					●	●	●	●[19]
Atrial Arrhythmia monitoring (24 hour Holter)[8]					●	●	●	●[19]
Repeat ablations[9]			●	●	●	●	●	●[19]
Concomitant Medication[10]		●	●	●	●	●	●	●[19]
Device Deficiencies		●						
Adverse Events[11]	●	●	●	●	●	●	●	●[19]
AFEQT[20]	●				●	●	●	
Cardiac CT/MRA	●				●[12]			
Wave I subjects ONLY additional assessments								
Endoscopy		●[13]						
Cerebral MRI[14]	●[16]	●[17]		●[18]	●[18]	●[18]	●[18]	●[19]
Neurological Exam[15]	●[16]	●[17]		●[18]	●[18]	●[18]	●[18]	●[19]
NIH Stroke Scale[20]	●[16]	●[17]		●[18]	●[18]	●[18]	●[18]	●[19]
mRS	●[16]			●	●[18]	●[18]	●[18]	●[19]
MMSE[20]	●[16]			●	●[18]	●[18]	●[18]	●[19]

1. Procedure must be done within 60 days of consent.
2. Medical history-including but not limited to arrhythmia, AAD therapy failure, heart disease (NYHA), vital signs, CHA2DS2score and thromboembolic events.
3. In all women of childbearing age and potential. To be completed within 72-hours prior to ablation procedure.
4. Imaging within 6 months prior to procedure to assess the LA and LVEF, in case 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.
5. Performed the day before procedure or day of ablation procedure to rule out the presence of atrial thrombus using one of the following modalities TEE, ICE, CT, MRI.
6. If Standard of care assessment (For pre-procedure, can be performed before ICF signature)
7. Arrhythmia monitoring via remote monitoring once per week as from 3-month follow-up visit to the end of 5-month follow-up and monthly as of 6-month follow-up visit and whenever subject feels symptoms.
8. Arrhythmia monitoring via 24H Holter, site to contact subject and verify if any symptoms experienced during the Holter monitoring.
9. Information on any repeat ablation after the index procedure will be collected
10. Concomitant medication: only cardiac (i.e. anti-arrhythmia drugs, anticoagulation regimen) & index procedure related (i.e. adenosine, pain medication)

11. AEs must be collected from the time the subject signs the informed consent onward.
12. To be completed within 6 months prior to ablation procedure, For Wave I subjects: CT-MRA to be repeated at 3M FU. For Wave I and Wave II subjects, CT-MRA to be repeated post procedure in case subject presents with PV stenosis symptoms.
13. Endoscopy preferable prior to discharge and no later than 72-hours after procedure. For procedures on Friday a window of a maximum of 96 hours is justified.
14. If observations are noted on the post-procedure MRI, the subject must have follow-up MRI at the next follow-up visit(s) until observations are resolved.
15. A certified/qualified physician expert must perform neurologic exams at pre-and post-ablation and possibly at other follow-up visits, pending previous findings of micro-emboli/neurologic deficits.
16. To be completed within 72-hours pre-procedure. For procedures on Monday a window of a maximum of 96 hours is justified.
17. To be completed within 72-hours post-procedure. For procedures on Friday a window of a maximum of 96 hours is justified.
18. Full neurological follow up to be undertaken if neurologic symptoms and/or cerebral ischemic lesions identified in a prior evaluation.
19. If subject returns for a potential study related cardiovascular or neurological visit outside of the protocol-defined visit schedule as deemed required per investigators discretion.
20. Patient questionnaires will only be used in countries with validated languages.

6. Background Information and Scientific Rationale

6.1 Background Information

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]

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 unipolar 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 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]

Circular catheters are merely referred to and used in animal and clinical trial settings for the purpose of Pulmonary Vein Isolation (PVI) by means of IRE ablation. [33, 34, 42] Biosense Webster developed the novel proprietary technology system, including Circular IRE Catheter and Multi-Channel IRE Generator which might confirm that standardization pulse delivery in optimal conditions will provide balance between efficacy and safety.

6.2 Previous Experience with the Circular IRE Catheter

6.2.1 Circular IRE Catheter In-Vivo Porcine Beating Heart Model

Refer to IB for detailed description of the testing performed.

A single-arm study was used to evaluate overall safety of the Circular IRE Catheter with pulsed field ablation, when simulating a clinical electrophysiology (EP) pulmonary vein isolation in a canine beating heart model to demonstrate safety and efficacy, Animals were kept alive for 7 days post ablation procedure before being humanely euthanized, to assess chronic safety and effectiveness related to pulmonary vein isolation procedure and for tissue harvest.

The study evaluated the Circular IRE Catheter and its ability to work in conjunction with the Multi-Channel IRE Generator and the CARTO®3 V7 and accessories,
The following equipment was used during testing:

- Circular IRE Catheter
- IRE Generator
- 8.5F compatible sheath
- CARTO®3 V7 software compatible with Circular IRE Catheter
- Catheter Interface Cable

- Standard Pacing and recording system
- nGEN™ irrigation pump

The safety endpoints included:

- Occurrence of thrombus
- Occurrence of steam pop leading to pericardial effusion and or tamponade
- Occurrence of mural thrombus
- Pulmonary vein stenosis
- Occurrence of collateral damage
- Occurrence of intracardiac tissue damage due to mechanical injury
- Occurrence of peripheral thrombo-emboli

The efficacy endpoints included:

- Acute isolation of pulmonary veins
- Acute isolation of right atrial targets
- Durable lesion formation after 7 days

Gross pathology and histopathology examination were performed, and cardiac tissue was found to be normal. There was no evidence of thrombus, dissection, perforation, or other cardiac injury in LA of all animals where the Circular IRE Catheter was manipulated in the PVs.

Based on the results of safety and performance of Circular IRE Catheter in conjunction with Multi-Channel IRE Generator and ancillary equipment, all characteristics passed the acceptance criteria.

6.3 Rationale for Design of the Clinical Investigation

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 both safety and 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 Statement[3] on Catheter and Surgical Ablation of AF. Data from large multicenter pre and post-market clinical trials of AF ablation devices which were published between 2014 to 2019 were reviewed as a first step to deriving the performance goal for the safety endpoint. A meta-analysis approach was taken to estimate the average composite endpoint rate. The following trials were reviewed: Fire & Ice[43], Heartlight[44], TOCCASTAR[45], ZERO-AF[47], and SMART-AF[46]. These trials are representative of different catheter designs and energy sources. Since the definition of the safety composite varies across the studies reviewed, individual complication rates were reviewed and utilized to derive composite rates from each trial that are more closely aligned with the proposed primary safety composite endpoint definition. The meta-analysis yielded a composite primary safety endpoint rate of 7% (95% UCB: 8%). A margin of indifference of 6 percentage points was utilized to set the PG of 14%.

6.4 Potential Risk and Benefit

The overall risks posed by use of the Circular IRE Catheter, with the Multi-Channel IRE Generator are expected to be comparable to those anticipated during routine use of radio frequency (RF) catheter ablation systems and use of AAD therapy according to current AF management guidelines. Appropriate measures have been outlined in this protocol to minimize the risk to subjects, while still providing the possible benefits (including but not limited to safety/effectiveness) of the treatment options to be studied.

Pulse-field ablation used to create irreversible electroporation has been used in the treatment of oncology for the past decade, although treatment of patients with Atrial Fibrillation with this technology began only recently. Nonetheless, when compared to the usual standards of practice and published literature few, if any, the occurrence of thermal injuries which can be caused by RF ablation, are minimized with pulse field ablation. A summary of risks associated with catheter ablation, including analysis of and plans to minimize these risks, is provided below.

6.4.1 Known Potential Risks

Pericarditis: With any circular-based ablation, pericarditis can occur due to mechanical or thermal irritation of the myocardium. This tends to be underreported as it is usually transient and resolves without intervention.[3]

Phrenic Nerve Palsy (PNP): Injury to the Phrenic Nerve (PN) is not expected with the PFA energy provided, however, irritation of the phrenic nerve that resolves acutely has been noted in the literature.[37] Prior to ablation in the region of the RSPV, investigators are encouraged to perform precautionary measures such as evaluation of proximity to the phrenic nerve and pacing maneuvers.[3]

Atrio-Esophageal Fistula (AEF): AEF is a rare but catastrophic complication of AF ablation that can occur due to the anatomical proximity of the esophagus to the posterior wall of the LA and that is associated with a high mortality rate.[48] In patients, the application of traditional RF energy along the posterior LA can result in thermal injury to the esophagus and the formation of an AEF.[3] As PFA energy is non-thermal, AEF is not an expected outcome and has not been reported in the literature.[41, 43] However, it is unknown if extreme overapplication of energy could result in AEF.

Many investigators attempt to mitigate esophageal damage by monitoring endoluminal temperature during the ablation procedure. Additionally, it is possible that proper use of PFA

technology itself mitigates the risk for this injury.

Pulmonary vein stenosis: The risk of pulmonary Adverse Events (AEs) (e.g. PV stenosis, thrombus and hypertension) associated with a PFA procedure is unknown. PV stenosis has not been reported following pulsed field applications.[42, 49] However, in RF procedures, the risk of PV stenosis is small (<4%) and can be prevented by delivering energy outside of the pulmonary vein ostium.[3]

Thrombus formation: The Circular IRE Catheter is irrigated. If the catheter was not being continuously irrigated, a thrombus could form. Embolization of thrombus could produce to produce stroke, Myocardial Infarction (MI), or other ischemic injury. To prevent this injury, the irrigation should be maintained throughout the procedure.

Cardiac perforation/ Pericardial effusion/ cardiac tamponade: Cardiac perforation may result from catheter manipulation or application of RF current (risk is <1%). Cardiac perforation may result in pericardial effusion or cardiac tamponade which requires percutaneous pericardial drainage or surgical repair.[3] To prevent effusion and tamponade, the Circular IRE Catheter should be used as instructed, including ensuring that the catheter is not turned counterclockwise while inside of the patient.

Cerebral ischemic lesions: According to HRS guidelines, 2017, Asymptomatic Cerebral Emboli (ACE) incidence is varying from 2%-15% as a complication to AF ablation.[3] As pulsed field ablation is a new energy modality for treating Atrial Fibrillation, there is limited data on the potential for incidence of cerebral ischemic lesions. An ACE is defined as an occlusion of a blood vessel in the brain due to an embolus that does not result in any acute clinical symptoms and is therefore 'silent'. Emboli can result from a thrombus, gas, air, tissue or fat. Source of micro-emboli include thrombi, which can develop on sheaths, materials, air introduction through sheath or during catheter exchange. Additionally, the hazard of microbubble formation in pulse field ablation, leads to an unknown level of risk of ACE.[51]

Heart block: The application of PFA energy close to the AV node or HIS bundle could damage or destroy the normal AV conduction system, producing complete heart block and requiring implantation of a permanent pacemaker.

Vascular access / bleeding complication: Vascular access complication, femoral arteriovenous fistula, hematoma, and pseudoaneurysm are commonly reported in procedures requiring femoral access. Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels occur in rare circumstances (risk <1%). These types of injuries may cause hemorrhage, hematoma or ischemic injury to an extremity or major organ. Hemorrhage could occur as a result of anticoagulation (risk <0.5%), which may require transfusion.[3]

Radiation exposure: Radiation exposure during the fluoroscopic imaging of the catheters may result in an increase in the lifetime risk of developing a fatal malignancy (0.1%) or a genetic defect in offspring (0.002%).[51-53]

Infection: The percutaneous procedure carries risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%).[54, 55] This risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.[3]

Allergic Reaction: A patient could develop an allergic reaction and/or inflammation due to the local anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure (risk <1%).[53, 56-60] The If an allergic reaction occurs, typical standard of care precautions should be taken.

Ventricular Tachycardia: Ventricular Fibrillation or other arrythmia: The literature suggests that in some instances PFA energy could induce ventricular tachycardia, ventricular fibrillation (ventricular rate usually >300 bpm), or another arrythmia.[61-64] Care should be taken to carefully monitor the patient's ECG recordings throughout the procedure.

Muscular Nerve Injury: Pulse field ablations have been associated with muscular contraction in the literature.[65, 66] These contractions can cause acute or post procedural patient discomfort. Patient comfort should be maintained through local pain management standards of care.

Hypervolemia/Fluid Overload: The Circular IRE Catheter is an irrigated catheter. Excessive use of irrigation could cause hemodynamic imbalance. To prevent hypervolemia, ensure that the catheter is used per its instructions for use.

Risk due to Arcing: The hazard of arcing[67] of energy creates a risk for patient injuries including Cardiac Arrest, burns, papillary muscle rupture, valve rupture, or cardiac perforation. To prevent such harms, the physician should use the catheter and generator per their intended directions for use.

Pulmonary injury: Pulmonary injuries, such as pneumothorax, may be caused by thermal injury during traditional RF injury.[68] As pulsed field ablation is a non-thermal modality, this injury is not expected to occur. However, to keep the risk of pulmonary injuries low, energy should delivery should be halted after ECG signals have been sufficiently attenuated.[3]

Additional contraindications: Additional contraindications for pulse field ablation include: myxoma, prosthetic valves, history of myocardial infarction, implantable device such as a pacemaker, defibrillator, or other implanted metal cardiac device, and pregnancy.

6.4.2 Minimization of Risk

The criteria for subject selection, methods, personnel, facilities, and training that are specified in this study are intended to minimize the risk to subjects undergoing this procedure.

Patient selection: Subjects will be screened carefully prior to enrollment in the study to ensure compliance with the inclusion and exclusion criteria. The exclusion criteria have been developed to exclude subjects with a medical history or condition that increases their risk of AEs (refer to section 9.2 for the Exclusion Criteria).[22]

Pre-procedure imaging: Subjects must have a pre-procedure Transesophageal Echocardiogram (TEE) or other imaging technique to screen for the presence of LA thrombus, which is intended to decrease the potential for thromboembolic complications.

Within procedure safeguards: Investigators highly skilled in intracardiac mapping and AF ablation with ablation catheters will be selected for participation in the study. AF ablation procedures will be performed in EP laboratories with the assistance of skilled nurses and technicians. Ablating investigators will undergo training, prior to enrolling subjects (refer to

section 18.1.1).

The risk of PNP will be minimized by encouraging monitoring the PN with pacing maneuvers before the ablation. No new ablations should be delivered on or near the PN if evidence of PN impairment is observed and the catheter should be repositioned.

The risk of PV stenosis will be minimized by not positioning the circular catheter within the tubular portion of the target PV.

The risk of ACE will be minimized by implementing an anti-coagulation regimen prior to catheter introduction into the LA and during procedure to avoid thrombi/emboli during procedure. Investigators will be instructed to remove air bubbles prior to insertion and to minimize catheter exchange during procedure to mitigate the of risk air introduction.

The risk of pericarditis will be minimized by encouraging the use of the lowest level of appropriate energy.

The risk of cardiac perforation, perfusion, and tamponade events will be minimized by training physicians to not rotated the Circular IRE Catheter counterclockwise.

The risks of AEF, pulmonary injury, and other related thermal events will be minimized by the technology itself and encouraging the use of the lowest appropriate energy setting.

The risk of thrombi and hypervolemia will be minimized by encouraging the use of irrigation settings per the catheter's Instructions for Use.

The risk of induction of ventricular tachycardia and other arrythmias have been minimized by the design of the catheter, which uses biphasic energy with very short duration pulses.

The risk of heart block will be minimized by limited use of the IRE Circular Catheter in the left atria during the procedure per the catheter's instructions for use.

The risk of vascular access complications can be minimized by using clinical standards of care, and an IRE Circular catheter compatible sheath.

To mitigate the risk of radiation exposure, Physicians may use standard clinical practices to minimize or eliminate X-ray exposure during the procedure.

The risk of infection and allergic reactions can be minimized by using not using product where the packaging has been compromised, or already used, or reprocessed.

Pain and discomfort due to muscular contraction, can be mitigated through proper administration of pharmaceuticals for patient comfort.

The likelihood for arcing has been mitigated with the design of the generator. To further prevent the associated risks from arcing, do not operate the device in patients with metal cardiac implants.

Post-procedural management: In accordance with the 2016 ESC AF Management Guidelines[3], all subjects will be recommended to be maintained on systemic oral anticoagulation therapy for at least two months post-procedure, beginning within 6 hours post-procedure. After two-

months post-procedure, a decision regarding continuation of systemic anti-coagulation agents will be based on the patient risk for thromboembolism. Systemic oral anticoagulation will be recommended to be continued beyond two-months post-ablation in patients with CHA_2DS_2-VASc score ≥2.

Safety data during enrollment and follow-up will be closely monitored and evaluated per the specific safety management plan for the study. Also, refer to safety section (section 15) for more information on safety management.

DMC and CEC: Finally, a Data Monitoring Committee (DMC) will assess subjects' data for safety on regular intervals for Wave I and Wave II and make recommendations on study adaptations as described in the DMC Charter. A Clinical Events Committee (CEC) will be implemented to adjudicate primary safety endpoint events for Wave I and Wave II. The CEC will operate as described in the CEC Charter.

6.4.3 Known Potential Benefits

In patients with AF, elimination of or a reduction in symptoms is a major driving force for therapy. The primary clinical benefit of ablation of AF is an improvement in QoL resulting from the elimination of arrhythmia-related symptoms such as palpitations, fatigue, or effort intolerance.[66] The Circular IRE Catheter is intended to allow for the ablation of larger areas of tissue compared to traditional single tip catheters. Thus, the Circular IRE Catheter should possess the benefit of reduced procedure time and fewer catheter exchanges.

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]

Additionally, other PFA cardiac technologies, have shown in early reports that IRE creates durable lesions at effectiveness rates higher than that seen in radiofrequency trials.

Further reference can be made to the Risk-Benefit Analysis (RBA) for more information.

7. Objectives and Purpose

7.1 Objective

The primary objective of this clinical investigation is to demonstrate safety and long-term effectiveness of the IRE system (Circular IRE Catheter and IRE Generator) when used for isolation of the atrial PVs in treatment of subjects with PAF. Specifically:

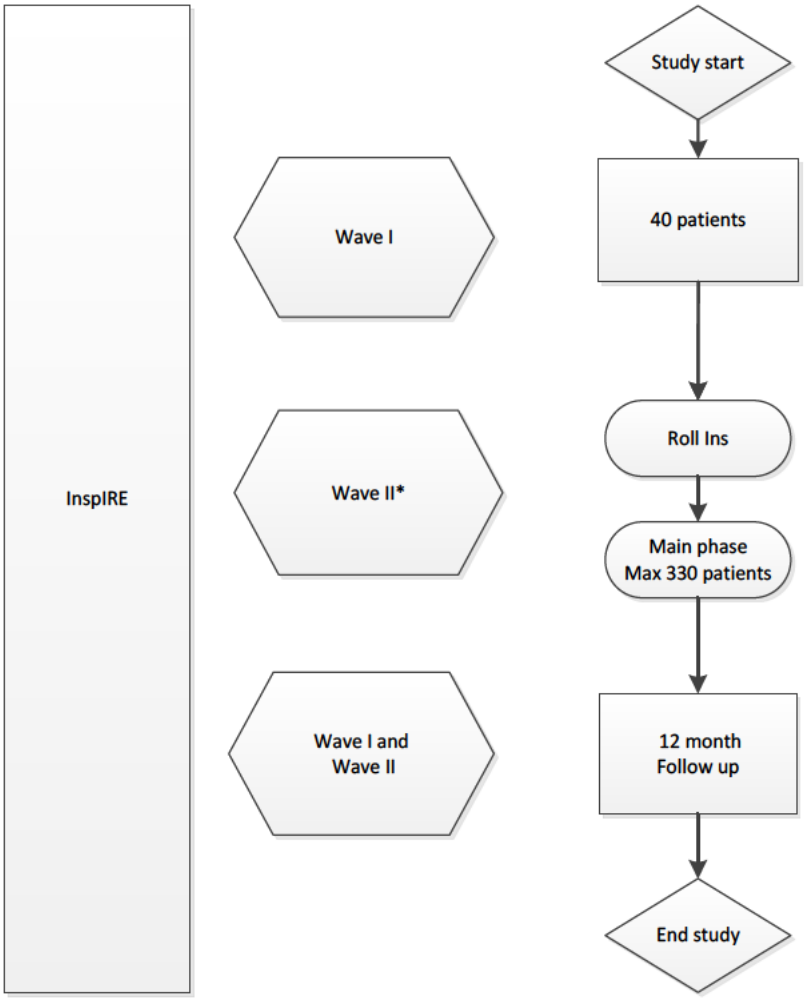
- To demonstrate safety based on early-onset Primary Adverse Events (PAEs) (within 7 days following the ablation procedure).
- To demonstrate long term effectiveness based on the freedom from documented (symptomatic and asymptomatic) atrial arrhythmia (AF, Atrial Tachycardia (AT) or Atrial Flutter (AFL)) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365).

7.2 Purpose

The primary purpose of this study is to prove that the use of the IRE Ablation System, incorporating both the Circular IRE Catheter and the IRE Generator, for the isolation of the PVs in treatment of subjects with PAF is safe and effective. The results of this provide evidence to support CE-mark registration of these devices

Wave I will serve as characterization of safety and provide preliminary estimates for safety and acute effectiveness of the system under study.

8. Study Design and Endpoints



* Acute data from Wave I will be used for both, preliminary acute safety and acute performance, of the IRE system before proceeding with Wave II.

8.1 Description of the Study Design

The design of the study will be carried out as an interventional, prospective, multicenter, single-arm clinical study. The study will enroll subjects with drug refractory, symptomatic PAF who are candidates for catheter ablation. All study subjects will be followed though 12 months post-ablation.

For the purpose of characterization of safety and to provide preliminary estimates for safety and acute effectiveness of the IRE system, Wave I of the study will enroll up to 40 subjects, who will undergo the index procedure and additional neurological, PV and esophageal assessments. For the purpose of safety and long-term effectiveness Wave II of the study will enroll up to 330 main study phase subjects plus roll-ins. Acute data from Wave I will be assessed for both, preliminary acute safety and acute performance, of the IRE system before proceeding with Wave II. Wave II enrollment can be initiated when all Wave I subjects have

reached 7 days follow up unless the Sponsor deems otherwise per sections 25 (Study Suspension or Termination) and 6.4.2 (Minimization of Risk).

An adaptive Bayesian design to will be used to determine the sample size. Two sample size selection interim analyses will be performed based on the primary effectiveness endpoint. Study success as defined by the main study endpoints will be analyzed for the respective Wave II analysis populations further described in the statistical section of this protocol (section 20). An additional interim analysis will be performed for claiming early trial success when 30 subjects reach full 12-month of follow-up and all subjects reach three months of follow-up.

In Wave II, the first 1-3 subjects for each ablating physician will be considered roll-in subjects to verify consistent workflow for study device components and to minimize any learning curve effects. Operators whom performed procedures in Wave I may be exempted from roll-ins for Wave II per training charter. The roll-in phase will include a maximum of 180 subjects.

Subjects will be evaluated prior to the procedure, prior to discharge, and post procedure at 7 days (Day 7-9), 1 month (Day 23-37), 3 months (Day 76-104), 6 months (Day 166-194), and 12 months (Day 335-379).

8.1.1 Wave I Subjects

A prospective evaluation of 40 subjects will be included in Wave I of the study. Wave I subjects will, in addition to the general study follow-up schedule, undergo additional neurological, PV and esophageal assessments. The subjects of Wave I will meet all inclusion and exclusion criteria, including the additional exclusion criteria specific to Wave I.

Additional assessments for Wave I subjects include:

1. Cerebral MRI, National Institute of Health Stroke Scale (NIHSS), Modified Rankin Scale (mRS), Mini Mental State Examination (MMSE) and general neurological assessments for evaluation of neurological incidences. Note: Patient questionnaires will only be used in countries with validated languages
2. Cardiac Computed Tomography (CT) or Magnetic Resonance Angiogram (MRA) at 3 months AND in case of symptoms, for evaluation of PV stenosis.
3. Endoscopy post-procedure for evaluation of esophageal lesions.

8.1.2 Wave II: Roll-In Subjects

New devices often require operators to scale a learning curve. The inclusion of a roll-in phase in the study will allow learning for the operators, and an evaluation of safety and effectiveness of the device that is not diminished by the early learning curve. In addition to a requirement for IRE ablation System training for ablating physicians, further experience within the context of this clinical investigational plan will serve to generate a clearer perspective of the effectiveness of the IRE ablation System in treating PAF subjects. Therefore, as of Wave II, up to the first 3 subjects (operator dependent based on criteria defined per training charter) treated by an ablating physician with the study catheter will be prospectively assigned as roll-in subjects to minimize the learning curve effect. To allow for a wide range of physician skill level, up to three physicians per site will be able to participate. Because roll-in subjects are at the physician level, some physicians at a site may complete their roll-in subjects and move to the main study phase while other physicians at the site are still in the roll-in phase. A subject who is excluded or discontinued will not count toward the

roll-in subjects. Roll-in subjects will be followed for 12 months post index procedure. The results from the roll-in phase will be analyzed and presented separately from the main study phase.

8.1.3 Wave II: Main Study Phase Subjects

Eligible subjects who sign the Informed Consent Form (ICF) and who meet all eligibility will be enrolled and treated with the Circular IRE Catheter in conjunction with the IRE Generator. A maximum sample size of 330 subjects is planned the main phase. All main phase subjects will follow the same follow-up schedule as the other subjects namely be followed-up for 12 months after study procedure.

Planned statistical analyses of the endpoints and analysis populations are described in the Statistical Analysis section (section 20) of this clinical investigational plan and in the Statistical Analysis Plan (SAP).

8.2 Study Endpoints

Only Wave II subject data will be used for the purpose of primary hypothesis testing. Wave I and roll-in subject data will be separately analyzed (not part of the primary hypothesis testing), further described in the statistical section of this protocol (section 20).

8.2.1 Primary Endpoints

- **Acute Safety**
  The primary safety endpoint is the incidence of PAEs (within seven (7) days of the initial mapping and ablation procedure). PAEs include the following AEs:

Atrio-Esophageal Fistula*	Phrenic Nerve Paralysis (permanent)
Cardiac Tamponade/perforation	Pulmonary Vein Stenosis*
Device or procedure related death*	Stroke/CVA
Major Vascular Access Complication/Bleeding	Thromboembolism
Myocardial Infarction	Transient Ischemic Attack (TIA)
Pericarditis	

* Device or procedure related death, pulmonary vein stenosis and atrio-esophageal fistula that occur greater than one week (7 days) post-procedure are considered and analyzed as PAEs.

A 14% performance goal is set for the primary safety endpoint

- **Long term effectiveness:**

Freedom from documented (symptomatic and asymptomatic) atrial arrhythmia (AF, AT or AFL) episodes based on electrocardiographic data ($\geq$30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365). Acute procedural failure (i.e., failure to confirm entrance block, with or without touch-up, in all PVs except those that are silent and/or cannot be cannulated post-procedure) will be considered a long-term effectiveness failure.

A 50% performance goal is set for the primary long-term effectiveness endpoint

Further refer to appendix 1 for definitions on long term effectiveness terms.

8.2.2 Secondary Endpoints

- Acute Procedural Success defined as confirmation of entrance block in all clinically relevant targeted PVs after adenosine/isoproterenol challenge. Use of a non-study catheter to achieve PVI is considered an acute procedural success failure.

- Freedom from documented symptomatic atrial arrhythmia (AF, AT or AFL) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365).

- Quality of Life: the change of QoL assessed by comparing the Atrial Fibrillation Effect on Quality-of-Life (AFEQT™) scores before and after the ablation procedure. Note: Patient questionnaires will only be used in countries with validated languages.

8.2.3 Additional Endpoints

- **Safety**
  - Occurrence of individual PAEs from the primary composite
  - Occurrence of Serious Adverse Device Effects (SADEs)
  - 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
  - Occurrence of non-SAEs
  - Occurrence of clinically symptomatic severe PV stenosis as documented by CT/MRA

- **Effectiveness**
  - Ablation by a non-study catheter for PVI (touch-up) among all clinically relevant targeted PVs and by subject
  - Acute reconnection identified by adenosine/isoproterenol challenge.
  - % repeat ablation within the 12M FU period
    - Timing (blanking period or after blanking)
    - % PV reconnection
  - Freedom from documented (symptomatic and asymptomatic) atrial fibrillation (AF) episodes based on electrocardiographic data (>30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365).
  - Freedom from documented (symptomatic and asymptomatic) atrial arrhythmia (AF, AT or AFL) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365) with the following criteria also deemed failure (Appendix 1):
    - Taking a new class I/III AAD for AF or a previously failed class I/III AAD at a greater than the highest ineffective historical dose for AF during the effectiveness evaluation period
    - Greater than 2 repeat ablations for AF/AT/AFL in the blanking period or any repeat ablation for AF/AT/AFL during the effectiveness evaluation period

- **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

- **Neurological Assessment (Wave I)**
  - Occurrence of new post-ablation asymptomatic and symptomatic cerebral emboli as determined by MRI evaluations
  - Occurrence of new or worsening neurological deficits post-ablation and at follow-up, compared to baseline
  - Occurrence, anatomical location and size of asymptomatic and symptomatic cerebral emboli observed pre-and post-ablation as determined by MRI evaluations.
  - Summary of MMSE, NIHSS and mRS at baseline, post-ablation and during follow-up (if lesions were identified in prior evaluation).

- **CT/MRA (Wave I)**
  - Occurrence of severe PV stenosis at 3 months post-ablation as determined by CT/MRA evaluations

- **Endoscopy (Wave I)**
  - Occurrence of post-ablation esophageal lesions as determined by post-procedure endoscopy

9. Study Population

Patients scheduled to have a clinically-indicated ablation procedure for the management of their drug refractory PAF will be screened for enrollment per the study's inclusion and exclusion criteria. The "investigation population" (meeting all inclusion and exclusion criteria) represents the "target population" (drug resistant PAF subjects) indicated for catheter ablation per consensus guidelines, in addition the criteria listed below ensure mitigation of risks (as per instructions for use and user manual) associated with the patients' health status at the time of screening and contraindications for study assessments (as specified further in this protocol).

9.1 Participant Inclusion Criteria

Candidates for this study must meet ALL of the following criteria:

1. Diagnosed with Symptomatic PAF
2. Selected for AF ablation procedure by PVI
3. Failed at least one AAD (class I to IV) as evidenced by recurrent symptomatic AF, or intolerable or contraindicated to the AAD
4. Age 18-75 years
5. Willing and capable of providing consent
6. Able and willing to comply with all pre-, post- and follow-up testing and requirements.

9.2 Participant Exclusion Criteria

Candidates will be excluded if ANY of the following criteria apply:

1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
2. Previous LA ablation or surgery

3. Patients known to require ablation outside the PV region (e.g. CTI region, atrioventricular reentrant tachycardia, atrioventricular nodal reentry tachycardia, atrial tachycardia, ventricular tachycardia and Wolff-Parkinson-White).
4. Previously diagnosed with persistent AF (> 7 days in duration)
5. Severe dilatation of the LA (LAD >50mm antero-posterior diameter in case of Transthoracic Echocardiography (TTE))
6. Presence of LA thrombus
7. Severely compromised LVEF (LVEF <40%)
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 6 months
11. Previous PCI/MI within the past 2 months
12. Coronary Artery Bypass Grafting (CABG) in conjunction with valvular surgery, cardiac surgery (e.g. ventriculotomy, atriotomy) or valvular cardiac (surgical or percutaneous) procedure.
13. Unstable angina pectoris within the past 6 months
14. Anticipated cardiac transplantation, cardiac surgery or other major surgery within the next 12 months.
15. 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
16. Known significant PV anomaly that in the opinion of the investigator would preclude enrollment in this study
17. Has known pulmonary vein stenosis
18. Acute illness, active systemic infection or sepsis
19. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation.
20. Severe mitral regurgitation
21. Presence of implanted pacemaker or Implantable Cardioverter-Defibrillator (ICD) or other implanted metal cardiac device that may interfere with the IRE energy field.
22. Presence of a condition that precludes vascular access (such as IVC filter)
23. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this study
24. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being
25. Current enrollment in an investigational study evaluating another device or drug.
26. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of child bearing age and plan on becoming pregnant during the course of the clinical investigation.
27. Life expectancy less than 12 months
28. Presenting contra-indications for the devices used in the study, as indicated in the respective Instructions For Use (IFU)

Additional exclusion criteria for Wave I subjects:

29. Contraindication for MRI such as use of contrast agents due to advanced renal disease, claustrophobia etc. (at PI discretion)
30. Presence of iron-containing metal fragments in the body
31. Unresolved pre-existing neurological deficit.
32. Uncontrolled significant GastroEsophageal Reflux Disease (GERD)

10. Participant Withdrawal or Termination

10.1 Reasons for Withdrawal or Termination

Participants are free to withdraw from participation in the study at any time upon request without penalty or loss of benefits to which they may otherwise be entitled. Participants will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason without prejudice to their future medical care by a physician or the institution.

An investigator may terminate a subject's participation in the study if:

- Any clinical AE, laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant
- Withdrawal is in the subjects' best interest
- Subject withdraws consent
- Subject is lost to follow-up

Every subject should be encouraged to remain in the study until they have completed the protocol required follow-up period.

10.2 Handling of Participant Withdrawals or Termination

If a subject is removed or withdraws from the study, the date and reason for withdrawal will be recorded on the appropriate electronic Case Report Form (eCRF). If the subject is withdrawn due to an AE or SAE, the Investigator should follow the subject until the AE/SAE has resolved or is considered stable.

If a subject is unable to return for an office/clinic visit or cannot be contacted by telephone, 3 separate telephone calls should be made to obtain subject related safety information. All attempts should be documented in the source documents. If the subject does not respond to the 3 telephone calls, then the investigator must send a certified letter to the subject. If the subject does not respond to the letter, then the subject will be considered "lost to follow-up" for the study.

Subjects who have signed the ICF, but are later found not to be eligible PRIOR to insertion of the study catheter can be replaced. Replacement subjects will be recruited and enrolled following the same procedures as non-replacement subjects.

10.3 Subject Enrollment Disposition

- **Enrolled Subjects:** Patients who sign the ICF.
- **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. Subjects who signed the ICF but are 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.
  - Wave I discontinued subjects are not subjected to the additional Wave I study assessments (esophageal, neurological and PV).
  - 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.

11. Responsibilities

11.1 Investigator Responsibilities

Investigators at each participating clinical site will have the following responsibilities:

- Assuring compliance by site personnel with the provisions of the protocol
- Providing the Sponsor with:
  - Signed, dated Investigator Agreement
  - Written Ethics Committee (EC) approval letters and EC-approved consent forms
  - Signed, dated Financial Disclosure form for each participating investigator
  - Curriculum vitae for each investigator
- Maintain an accurate and current Delegation of Authority log which identifies individuals authorized to perform work for the study and assuring compliance by site personnel with the provisions of the protocol
- Completing the appropriate training on the device (ablating investigators only) and the study protocol prior to enrolling and treating subjects
- Maintain accurate and current logs for the study such as:
  - Subject log, Device Accountability Log
- Obtain initial and amendment (if applicable) EC approval and annual review/approval thereafter for the study protocol and informed consent as applicable
- Obtain ICF and enroll patients
- Perform medical procedures
- Order tests required by the study protocol
- Review pre-procedure imaging pertaining to the PV size prior to treatment
- Follow subjects until the end of the study protocol
- Accurately complete and sign eCRFs in a timely manner
- Maintain relevant source documentation and allow Sponsor direct access to perform monitoring or auditing duties
- Maintain records and provide reports according to prevailing regulatory requirements

- Share relevant study-related information with delegated study staff
- Inform the appropriate entities (e.g., Sponsor, Competent Authority (CA), EC) in a timely manner regarding the occurrence of AEs and/or product malfunctions.
- Making sufficient effort to maintain contact with treated subjects who fail to comply with the follow-up requirements
- Maintain study records for at least 5 years or as specified per country specific record retention requirements after the study is completed and or terminated. The Sponsor will notify the Investigator of either of these events.
- Complying with EC and Sponsor annual report requirements, including the final report.

11.2 Sponsor Responsibilities

The Sponsor (Biosense Webster, Inc.) will be responsible for the following:

- Conduct of pre-study site assessment and approval
- Preparation and modification (if applicable) of study documents including but not limited to the protocol, CRFs and informed consent
- Selection of appropriately qualified and trained individuals, including monitors, to conduct the study
- Conduct protocol and device training for investigators and research personnel as applicable
- Set-up of study-specific committees.
- Obtain signed study contracts from investigators/hospitals, Clinical Research Organizations (CROs) and other involved parties
- Ship study devices to each site
- Monitor sites for the duration of the study
- Maintain study database
- Inform investigator of his/her responsibilities
- Submit and obtain approval for study from applicable regulatory agencies
- Preparation of reports summarizing the status of the study no less than annually. These reports will be supplied to the PI at each site.
- Update Report of Priors, IFU, IB, and Risk Analyses, as applicable
- Update investigators on safety issues, if needed
- Report (including AE's and DDs) to study investigators and regulatory agencies, as required
- Have relevant safety information reviewed by the study-specific committees, as required
- Communications with the CA
- Submission of any amendments to the Clinical Study Protocol/Investigational Plan to the CA.

12. Study Device Description

12.1 Device Acquisition

After obtaining a fully executed clinical trial agreement and appropriate approvals, the sponsor will initiate shipment(s) of investigational devices to the site. The Sponsor will keep records of all investigational devices shipped to the site. Approved investigational devices will be shipped directly to the site and will be received by the site. Investigators are responsible for appropriate logging of the devices received, verification of packing slip information (i.e., lot numbers and quantity shipped), date and identity that each device was used in the study, disposition information regarding disposal or return to the Sponsor.

12.2 Device Storage and Stability

Devices are to be stored in a secure/locked location and in accordance with the catheter IFU and generator User Manual (UM). Do not use the (disposable) devices after the “Use By” date. Hardware should not be used past its preventative maintenance date.

12.3 Device Preparation

Information related to device preparation can be found in the catheter IFU and generator UM.

12.4 Instructions for Use

A comprehensive set of IFU and UM for the study system and all accessory cables/interface cables is contained in each product package and is also available upon request.

12.5 Device Description and Specific Considerations

12.5.1 Multi-Channel IRE Generator (D-1417-01-I)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Figure 1: Picture of the IRE Console

12.5.2 Circular IRE Catheter (D-1412-01-SI)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

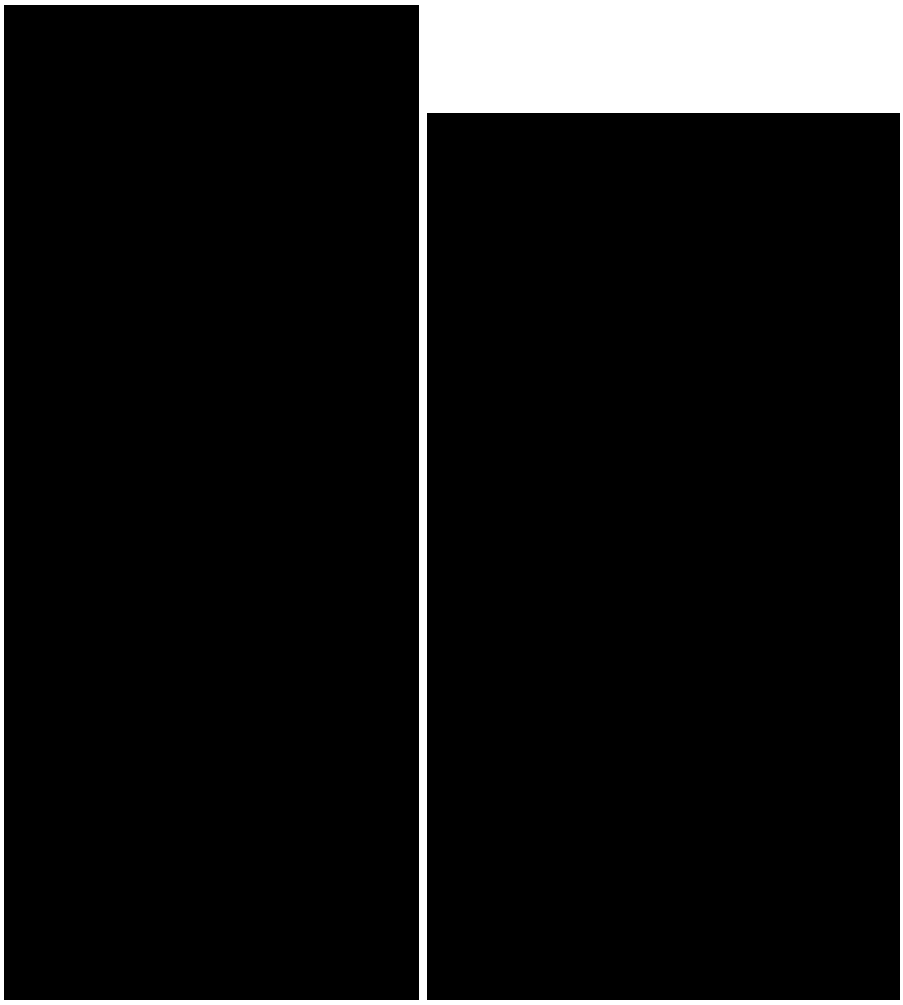


Figure 2: Picture of the Circular IRE Catheter and Circular Loop [redacted]

12.6 Equipment

12.6.1 System Components and Setup

The Circular IRE Catheter and Multi-Channel IRE Generator system are used in connectivity with the following devices to conduct an electrophysiology procedure:

To conduct an electrophysiology procedure, the Circular IRE Catheter and Multi-Channel IRE Generator System is used with the following Biosense Webster CE marked devices:

- nGEN™ Irrigation Pump (D-1397-01)
- Irrigation Tubing Sets (SAT001)
- CARTO®3 V7 workstation
- Multi-Electrode Catheter Connection Cable (D-1337-01)
- LASSO® or PentaRay® Catheter
- Carto®3 PIU
- 8.5F Compatible Sheath (Vizigo)

The following devices, CE marked by other companies, are also required for the procedure:

- 8.5F Compatible Sheath
- Electrophysiology (EP) Recording System
- Stimulator
- Body Surface ECG Patches
- Electrocardiogram (ECG) Leads
- Fluoroscopy/X-Ray System
- Cardiac Defibrillator
- Intracardiac Ultrasound (Investigator preference, not required)

A connectivity diagram for system set up is depicted in Figure 3 and the description of the connectivity is explained in table 2.

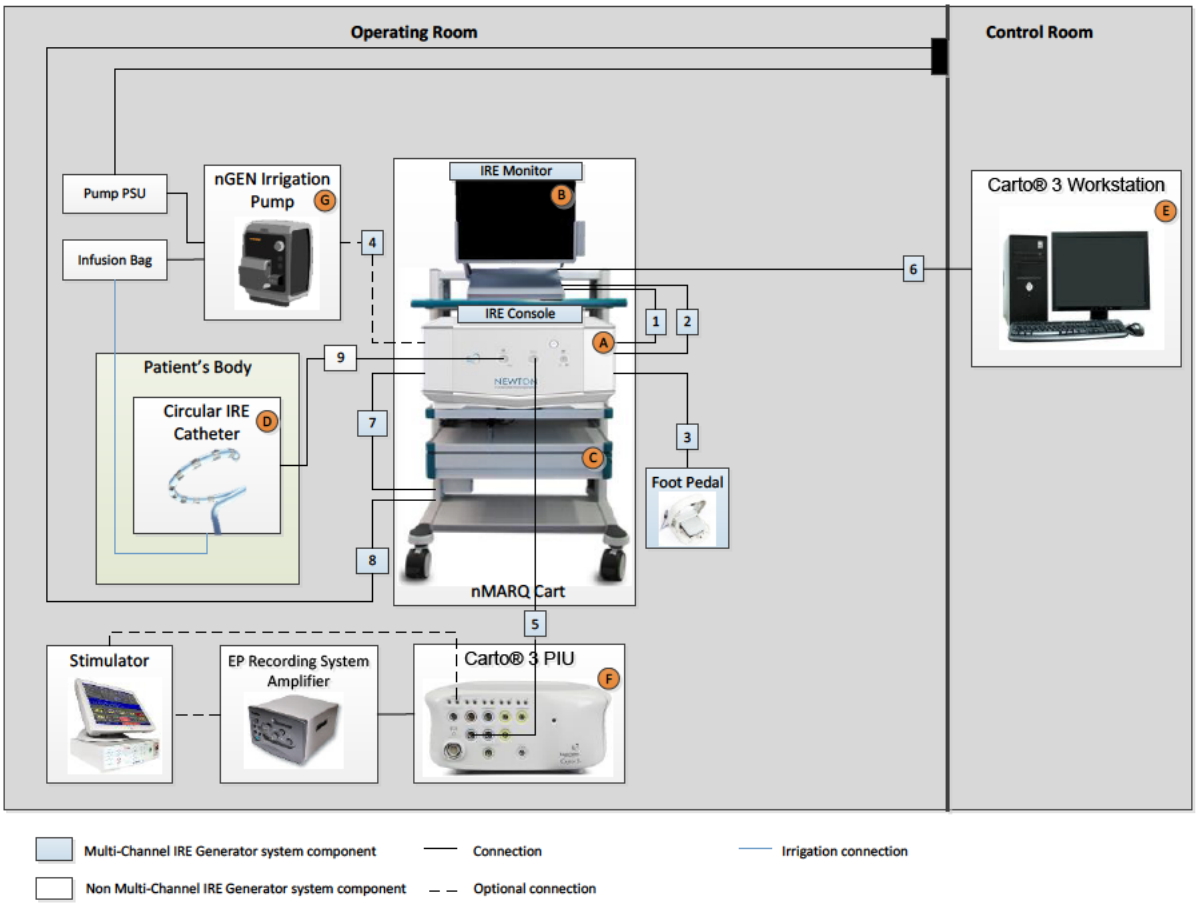


Figure 3: Connectivity diagram for system set-up

Table 2: Description of Connectivity

Number/Letter Connectivity Diagram	Description	Model
A	IRE Console	M-5968-26
B	IRE Monitor with Docking Station	M-5855-19
C	Cart	M-5831-61
D	Circular IRE Catheter	D-1412-01-SI
E, F	Carto® System	FG-5400-00
G	nGEN™ Pump	D-1397-01
1	USB communication cable between IRE Console and Monitor	M-5897-09
2	Power Supply Cable from IRE Console to Monitor	M-5831-109
3	Foot Pedal connection	M-5818-02
4	IRE Console to nGEN™ Irrigation Pump communication cable	M-6003-01
5	IRE Console to Carto® 3 PIU cable for Multi-Electrode configuration	M-5810-01
6	Ethernet communication cable between Monitor and CARTO® 3 Workstation, 25 m/10 m	M-5897-05/04
7	AC power cord between IRE Console to Cart	M-5831-63
8	AC power cord from Cart to Mains	M-6214-10
9	Multi-electrode Catheter Connection Cable	D-1337-01
N/A	ECG Stimulator Cable (Cable to connect the console to the stimulator, in case of emergency)	M-5811-01
N/A	nGEN PSU (Power Supply Unit) Power Cord (EU)	M-6214-10

Each site will have protocol-specified devices required for study participation (table 3). These devices must be used during the study to perform ablation procedures. Device set-up must be completed per the IFU and User Manual.

12.6.2 Required Study Devices

These devices must be used for the ablation procedure and are required Per Protocol (PP).

Table 3: Required Study Devices

Investigational Devices	**Function**
Circular IRE Catheter	Delivers biphasic high voltage to the target tissue.
Multi-Channel IRE Generator	Transmits biphasic high voltage to the Ablation Catheter
Non-investigational Devices/Standard Equipment	**Function**
CARTO®3 V7 workstation	For mapping and visualization information with software for Pulsed Field Ablation
nGEN™ Irrigation Pump	Delivers heparinized saline to the catheter during the voltage application (D-1397-01)
Multi-Electrode Catheter Connection Cable (D-1337-01)	Connects the Circular IRE Catheter with the Multi-Channel IRE Generator.
Carto®3 PIU	Patient Interface Unit for connectivity for therapeutic/diagnostic catheters and ultrasound.
SmartAblate Irrigation Tubing Sets (SAT001)	Delivers heparinized saline to the catheter during the voltage application
LASSO® or PentaRay® catheter	• Pre-ablation recording and mapping of the atria of the heart with the CARTO®3 system. • Confirmation of entrance block
8.5 F compatible sheath. Approved by the sponsor for use with the IRE catheter, including but not limited to Agilis™ and Vizigo.	Facilitate deployment of catheter into the atria.
EP Lab Recording Equipment	Records multiple intracardiac electrograms and signals from the Multi-Channel IRE generator (power, temperature, impedance) and performs electrical stimulation.
Esophageal Temperature Monitoring Device (OPTIONAL)	Esophageal temperature monitoring

For countries outside Europe the authorization status of non-investigational device may differ, which may be further clarified in a country specific version of this study protocol, if applicable.

12.6.3 Ablation Parameters

When used with the Circular IRE Catheter, the nGEN™ Irrigation Pump will deliver a continuous infusion of 4 mL/min of room temperature heparinized saline (1u heparin/1 mL saline) when not delivering IRE energy. The recommended operating parameters for the Circular IRE Catheter are presented in table 4.

13. Study Medication

The following medications are applicable for this protocol:

- PRIOR to the procedure
  - Uninterrupted anticoagulation therapy should be in place at least 3 weeks prior to ablation procedure.[5]
    - Recommendation: anticoagulation with warfarin (INR 2.0 to 3.0), a factor Xa inhibitor, or direct thrombin inhibitor is recommended for at least 3 weeks before and at least 4 weeks after ablation regardless of the CHA2DS2-VASc score or the method (electrical or pharmacological) used to restore sinus rhythm.
  - 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 or immediately after transseptal puncture.
  - Optimally target an Activated Clotting Time (ACT) of 350-400 seconds prior to inserting the study catheter and throughout the procedure.
    - An ACT below 350 requires additional bolus of heparin until a minimal targeted ACT of 350 is reached.
    - It's strongly recommended to check ACT levels on regular basis during the procedure to ensure an ACT target of 350-400 seconds.
  - Flush all tubing and sheath continuously with heparinized saline.

- FOLLOWING the procedure
  - Anticoagulation therapy is strongly recommended 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).
  - PPI administration following the procedure is MANDATORY if an endoscopy is performed post procedure.
  - AAD management during the study will be at the discretion of the investigator
  - Additional medications needed to treat clinical indications are at the discretion of the clinical investigation physician.

14. Study Schedule

14.1 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 60 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 International Conference on Harmonization-Good Clinical Practices (ICH-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.

14.2 Baseline Evaluation and Procedures

14.2.1 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 60 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.
    - **CHA_2DS_2 VASc Score.** Subjects will be scored against the CHA_2DS_2 VASc.

  - **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**: Uninterrupted anticoagulation management is mandatory for each study subject. For subjects on warfarin/coumadin therapy, subjects shall be maintained on Warfarin/Coumadin 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.

- **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 the day before or the day of the 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 or MRI
- **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.
- Quality of life via the **Atrial Fibrillation Effect on Quality-of-Life** (AFEQT™) questionnaire (non-Standard of Care). Note: Patient questionnaires will only be used in countries with validated languages
- **Cardiac CT/MRA** 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.

Additional Assessments for Wave I subjects:

- **Cerebral MRI, Neurological Exam and Neurological Evaluation using the MMSE, NIHSS and mRS (non-SOC)** are required to be performed within 72-hours pre-procedure (for procedures on Monday a window of a maximum of 96 hours is justified) to evaluate the neurological condition and presence of neurological deficits of the subjects before undergoing study ablation procedure. A certified/qualified physician expert must perform neurologic exams at pre-and post-ablation and possibly at other follow-up visits, pending previous findings of micro-emboli/neurologic deficits. Pre-and post-ablation cerebral MRIs will be analyzed by a central core lab to determine the frequency, size, and

anatomical location of cerebral micro-emboli, if any. Note: Patient questionnaires will only be used in countries with validated languages

14.2.2 Study Ablation Procedure Guidelines

14.2.2.1 Ablation Selections

There are 10 electrodes in the Circular IRE Catheter. The Multi-Channel IRE Generator creates pulsed electrical fields by delivering bipolar and biphasic energy though electrode pairs. Ablating with electrode pairs creates a closed electrical circuit between two adjacent electrodes and between two alternated electrodes. While the generator activates electrodes in groups of adjacent trios, only one electrode pair will deliver energy at a given time.

Ablations can be performed using a minimum of 3 adjacent electrodes or 1 electrode trio, and a maximum of 10 electrodes or 8 electrode trios to target desired regions of tissue. Multiple electrode trios can be activated during an ablation. When selecting multiple electrodes, the system will automatically activate electrode trios (up to two trios) in between the selected electrode trios to prevent gaps. For example, if you select electrode trios 1 3 and 4 6, the system will automatically activate electrode trios 2 4 and 3 5. See Figure 4 for an example of electrodes activated in adjacent trios. To activate all electrodes at once, use the All Electrodes toggle, as shown in Figure 5

The system delivers energy in pulses. The quantity of pulses is determined by the PFA levels: Min or Max. To adjust the level of energy delivered to the tissue, select the desired PFA level prior to starting ablation.

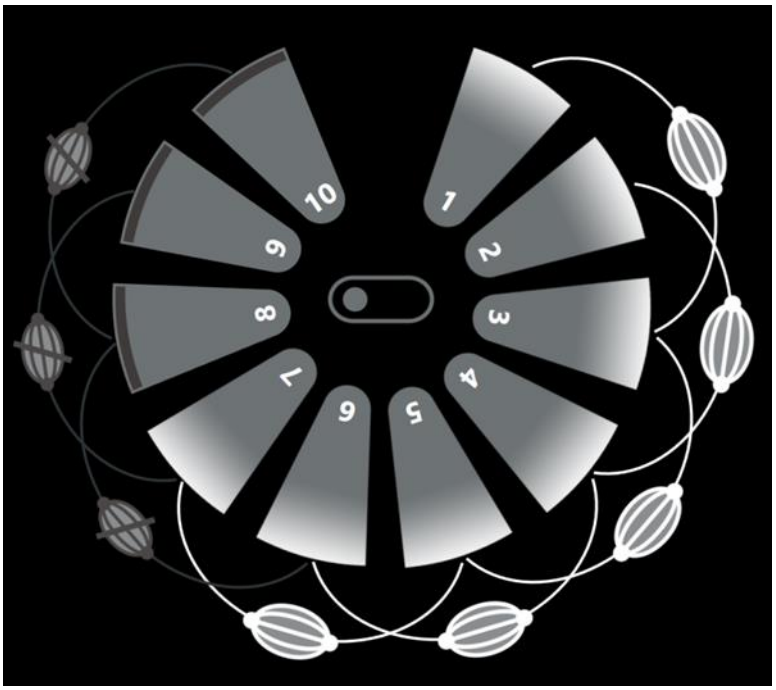


Figure 4: Electrode Selection

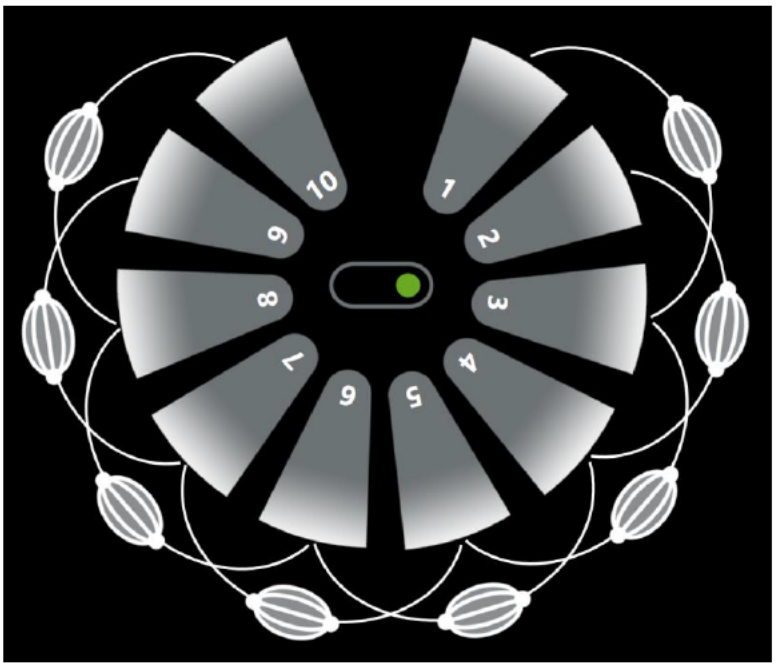


Figure 5: All Electrodes Toggle

Functional parameters and user adjustable settings for the device(s) are presented in table 4.

Table 4: Investigational Device- Functional Parameters and User adjustable settings

Functional Parameters	
Electrodes*	Adjacent + Alternate per trio
Type of Pulse	Bipolar, biphasic
PFA Measurement	900V between adjacent electrodes 1800V between alternated electrodes
Ablation Time	<1sec
Idle and Irrigation flow	4ml/min
User adjustable settings	
Pre-ablation time Post-ablation time	Range 0-2 sec (0/1/2) Range 0-2 sec (0/1/2)
Min/Max PFA Level	Max PFA level is twice the number of pulses than in Min PFA level
Electrode Trio(s)	User to select electrode trio(s) to activate

14.2.2.2 Study Ablation Procedure Sequence & Guidelines

Subjects will arrive to the EP laboratory for their ablation procedure and will undergo preparation for the procedure per the hospital's standard protocol (discretion of investigator).

<u>Electrophysiology Study, Mapping and Ablation Procedure</u>

- Preparation:
  - Anesthesia or sedation should be delivered per standard EP lab procedure.
    - It is highly recommended to ensure presence of anesthesiologist during the procedures.
  - The use of an appropriate strategy to minimize risk of esophageal injury (temperature probe, CARTOSOUND® and/or ICE, barium swallow) is OPTIONAL.

        - The type of monitoring method/device and clinical practice associated with the observations of this data will be collected in the CRFs.
    - Placement of diagnostic catheters:
        - Coronary sinus catheter in the CS for pacing purposes
        - Other catheters may be placed at the discretion of the investigator
    - At the discretion of the investigator, introduce an Intracardiac Echo (ICE) probe to review LA anatomy and PVs
    - Administration of heparin bolus prior to or immediately after transseptal puncture.
    - A single or double transseptal puncture should be performed per standard EP lab (at the discretion of the investigator).
- Mapping:
    - Following successful transseptal puncture, a left atrial map is required before ablating,
        - Wave I: it's highly recommended to use the Circular IRE catheter, possible substituted by the use of Lasso®, PentaRay® or 3D rotational angio (at investigator discretion).
        - Wave II: utilizing the Circular IRE Catheter, Lasso®, PentaRay®, or 3D rotational angio (at investigator discretion).
    - Create a voltage map, if SOC
- PVI:
    - Confirm targeted ACT 350-400 seconds. Systematic anticoagulation with heparin should be administrated with ACT level checked on regular basis during the procedure to ensure an ACT target range of 350-400 seconds.
    - Introduction of the 8.5 F compatible sheath, if not used for mapping.
    - Introduce the Circular IRE Catheter as per IFU, if not used for mapping.
    - Advance and position the Circular IRE Catheter at the targeted PV.
    - When position is satisfactory, commence energy delivery with the Circular IRE Catheter.
        - Recommended workflow:
            a) Left pulmonary veins and carina position and ablate with contracted and wider loop
            b) MANDATORY: prior to ablation in the region of the right sided PVs, precautionary measures to evaluate the proximity to the phrenic nerve.
                - Evaluate the diaphragm while pacing the phrenic nerve.
                - Assure diaphragmatic capture PRIOR to voltage delivery.
            c) Right pulmonary veins position and ablate with contracted and wider loop
        - Use the maximum PFA level. Consider using the minimum PFA level when repeated applications are applied. Use clinical judgment and consider patient anatomy and the catheter position to determine if minimum PFA level should be used.
        - Do not allow ablation electrodes to overlap during application of PFA energy. Doing so may cause an error message to appear and stop the ablation before completion. In case of overlap, change the catheter position or turn off overlapping electrodes on the monitor to perform ablation.
    - All subjects will undergo PV ablation with the Circular IRE Catheter until PVI is achieved in all targeted PV'.
        - IRE ablation is to be used as the primary mode for PVI.

        - If isolation is not obtained after circular PFA applications described above, review remaining signals and deliver PF energy with corresponding electrodes.
        - ONLY after the investigator deems IRE ablation unable to achieve PVI should the lab be switched to commercial RF setup to complete the procedure (PVI only). Note, to prevent any risk to the patient, the IRE system should be completely disconnected prior to use of an RF system.
    - Confirmation of entrance block (and exit block if SOC) (PVI) of all clinically relevant targeted PVs.
        - To verify entrance block, analyze electrograms in coronary sinus and/or atrial paced rhythm to confirm that no PV potentials are present.
    - Ablation outside the PV region is NOT allowed with IRE ablation modality (further details below).
- Post PVI:
    - Administer adenosine/isoproterenol for each clinically relevant targeted PV to rule out dormant conduction
        - If any, treat reconnected PV regions by reviewing remaining signals on reconnection location and deliver PF energy with corresponding electrodes.
    - Confirmation and documentation of final entrance block (exit block is optional) (PVI) of all clinically relevant targeted PVs
        - To verify entrance, analyze electrograms in coronary sinus and/or atrial paced rhythm to confirm that no PV potentials are present.
        - Wave I: use Circular IRE Catheter AND Lasso® or PentaRay® for confirmation
        - Wave II: use Circular IRE Catheter, Lasso® or PentaRay® for confirmation per investigators choice
    - The ablation procedure is considered complete when confirmation of <u>entrance</u> in clinically relevant targeted PVs is confirmed.
    - <u>Recommendation:</u> after confirmation of final entrance block (exit block is optional) block, evaluate diaphragmatic capture while pacing the phrenic nerve.

<u>Ablation outside the PV region</u>

- **Prophylactic** ablation outside the PV region (in example SVC, roofline, CTI) is NOT allowed.
- If an arrhythmia requiring ablation outside the PV is identified.
    - **<u>prior</u>** to insertion of the study catheter (consistent with exclusion criteria) investigators will be required to switch to the commercial setup using a commercially available Biosense Webster catheter used with a commercially available RF generator. The subject will be considered a screen failure (<ICF signature or excluded from the study (> ICF signature).
    - **<u>after</u>** insertion of the study catheter, the subject will undergo PVI with IRE ablation modality followed by commercial RF therapy to complete the procedure (treatment of arrhythmia outside PV region). The subject will be evaluable for acute success but excluded from the long-term effectiveness cohort and followed till 3-months post procedure. Note: Ongoing AE(s) at month 3 shall be followed up until resolution (with or without sequelae).

14.2.3 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.

14.2.3.1 Data Collection during Study Ablation Procedure

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
- 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

14.2.4 Pre-Discharge Assessments

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

- Medication regimen (Cardiac, anti-coagulation, PPIs)
- Imaging assessment of pericardial fluid presence
- AEs events
- ECG in case standard of care

- **For Wave I subjects (non-SOC):**
    - Cerebral MRI, neurological exam and neurological evaluation using the NIH stroke scale within 72-hours post procedure, preferable prior to discharge. A certified/qualified physician expert must perform neurologic exams at pre- and post-ablation and possibly at other follow-up visits, pending previous findings of micro-emboli/neurologic deficits. For procedures on Friday a window of a maximum of 96 hours is justified. Note: Patient questionnaires will only be used in countries with validated languages
    - Endoscopy to check for any esophageal lesions and/or damage will be performed preferable prior to discharge and no later than 72 hours after procedure (for procedures on Friday a window of a maximum of 96 hours is justified). Endoscopy images will be transmitted to a central reader.

14.2.5 Repeat Ablation Procedures

Repeat procedures may be performed at the discretion of the investigator. It is highly recommended to collect arrhythmia documentation (in example documented recurrences) before performing a repeat procedure.
Repeat procedures during the blanking period (90 days post index procedure) must be conducted with the investigational device, with or without focal touch-up, if the arrhythmia is due to PV triggers. If the arrhythmia is due to non-PV triggers and the subject is treated with a commercially available ablation catheter and generator, the subject will be excluded from the long term effectiveness cohort.
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.

14.3 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 7 days (phone call or clinic visit), 1, 3, 6 and 12 months (clinic visit).

At 7-day follow-up visit, the following assessments will be performed:
Discharged subjects will receive a telephone call or have a clinic visit at 7 days (7D, day 7-9) post ablation procedure to assess any occurrence of Primary Adverse Events and any change in medication regimen;

Follow-up visits should be scheduled according to the following timeframes: 1 month (1M 23-37), 3 months (3M, day 76-104), 6 months (6M, day 166-194) and 12 months (12M, day 335-379). 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.

At 1, 3, 6 and, 12-month follow-up visits, the following assessments will be performed:

- Medical evaluation:
    - AEs
    - Cardiac and Anti-coagulation medication regimen
    - Cardiac related hospitalization and cardioversions
    - 12 Lead-ECG (if completed per standard of care)

- **Atrial arrhythmia monitoring as from month 3 (non-SOC)**
  - Remote Monitoring:
    Subjects will be provided with a remote monitoring device at the 3M FU visit and asked to record and transmit a minimum of 1 transmission (≥ 30 seconds) every week through the end of the month 5 of FU. Starting at month 6 of FU, subjects will be asked to record and transmit a minimum of 1 transmission (≥ 30 seconds) every month until the effectiveness evaluation period is completed (12 months post index procedure). Subjects will also be asked to transmit any symptom-triggered episode that occurs from the time they receive the remote monitoring device through the 12M FU visit. A core lab might be used to evaluate and assess the remote monitoring tracings.

    Remote monitoring will be conducted as follows:
    - Distribution and start by month 3
    - <6M: Weekly transmission of at least 1 scheduled recording
    - ≥6M: Monthly transmission of at least 1 scheduled recording
    - Conduct and transmit recording whenever symptoms are present

  - 24 Hour Holter:
    Holter monitor will be used at each follow-up visit to monitor the subjects' heart rhythm for 24 hours continuously. Following the 24h Holter, subjects will be contacted by the site to verify if symptoms are experienced during 24h Holter.
- Quality of life via the **Atrial Fibrillation Effect on Quality-of-Life** (AFEQT™) questionnaire (non-SOC), at Month 3, 6 and 12. Note: Patient questionnaires will only be used in countries with validated languages.
- **Cardiac CT/MRA**
  - **Wave I subjects:** is required to be performed at the 3M FU visit (non-SOC) or any other point in time when subject presents with symptoms of PV stenosis.
  - **Wave II subjects:** is only required to be performed if subject presents with symptoms of PV stenosis.
- **Wave I subjects only: Cerebral MRI, Neurological Exam and Neurological Evaluation using the MMSE, NIHSS and mRS (non-SOC)** are required to be performed if any neurological symptoms and/or cerebral ischemic lesions were identified at a prior evaluation. Note: Patient questionnaires will only be used in countries with validated languages.

14.4 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.

14.5 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 5, 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.

14.6 Core Laboratory for Evaluation

Independent central core laboratories or expert physician(s) will conduct objective evaluations of remote monitoring tracings, Holter, Cerebral MRI, endoscopy and will evaluate PV stenosis of all subjects enrolled in Wave I (independently of symptoms) and symptomatic subjects of Wave II.

14.7 Schedule of Events Table

Table 5 displays the required schedule for subject treatments and evaluations.

Table 5: Summary of Subject Visits and Assessments

Assessments	Pre-Procedure	Pre-Discharge	Follow-up					
			7 Day	1 Month	3 Month	6 Month	12 Month	UNS
Study Day			D7	D30	D90	D180	D365	
Visit window			D7-D9	D23-D37	D76-D104	D166-D194	D335-D379	
Clinic visit	●	●	(●)	●	●	●	●	●[18]
Phone call			●					
Patient Informed Consent[1]	●							
Demographics	●							
Medical History[2]	●							
Pregnancy test[3]	●							
LA and LVEF assessment[4]	●							
Left atrial thrombus detection[5]	●							
Pericardial fluid assessment		●						
12 Lead ECG[6]	●	●		●	●	●	●	●[18]
Atrial Arrhythmia monitoring (Remote)[7]					●	●	●	●[18]
Atrial Arrhythmia monitoring (24 hour Holter)[8]					●	●	●	●[18]
Repeat ablations[9]			●	●	●	●	●	●[18]
Concomitant Medication[10]		●	●	●	●	●	●	●[18]
Device Deficiencies		●						
Adverse Events[11]	●	●	●	●	●	●	●	●[18]
AFEQT[20]	●				●	●	●	
Cardiac CT/MRA	●				●[12]			
Wave I subjects ONLY additional assessments								
Endoscopy		●[13]						
Cerebral MRI[14]	●[16]	●[17]		●[18]	●[18]	●[18]	●[18]	●[19]
Neurological Exam[15]	●[16]	●[17]		●[18]	●[18]	●[18]	●[18]	●[19]
NIH Stroke Scale[20]	●[16]	●[17]		●[18]	●[18]	●[18]	●[18]	●[19]
mRS	●[16]			●	●[18]	●[18]	●[18]	●[19]
MMSE[20]	●[16]			●	●[18]	●[18]	●[18]	●[19]

1. Procedure must be done within 60 days of consent.
2. Medical history-including but not limited to arrhythmia, AAD therapy failure, heart disease (NYHA), vital signs, CHA2DS2score and thromboembolic events.
3. In all women of childbearing age and potential. To be completed within 72-hours prior to ablation procedure.
4. Imaging within 6 months prior to procedure to assess the LA and LVEF, in case 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.

5. Performed the day before procedure or day of ablation procedure to rule out the presence of atrial thrombus using one of the following modalities TEE, ICE, CT, MRI.
6. If Standard of care assessment (For pre-procedure, can be performed before ICF signature)
7. Arrhythmia monitoring via remote monitoring once per week as from 3-month follow-up visit to the end of 5-month follow-up and monthly as of 6-month follow-up visit and whenever subject feels symptoms.
8. Arrhythmia monitoring via 24H Holter, site to contact subject and verify if any symptoms experienced during the Holter monitoring.
9. Information on any repeat ablation after the index procedure will be collected
10. Concomitant medication: only cardiac (i.e. anti-arrhythmia drugs, anticoagulation regimen) & index procedure related (i.e. adenosine, pain medication)
11. AEs must be collected from the time the subject signs the informed consent onward.
12. To be completed within 6 months prior to ablation procedure, For Wave I subjects: CT-MRA to be repeated at 3M FU. For Wave I and Wave II subjects, CT-MRA to be repeated post procedure in case subject presents with PV stenosis symptoms.
13. Endoscopy preferable prior to discharge and no later than 72-hours after procedure. For procedures on Friday a window of a maximum of 96 hours is justified.
14. If observations are noted on the post-procedure MRI, the subject must have follow-up MRI at the next follow-up visit(s) until observations are resolved.
15. A certified/qualified physician expert must perform neurologic exams at pre-and post-ablation and possibly at other follow-up visits, pending previous findings of micro-emboli/neurologic deficits.
16. To be completed within 72-hours pre-procedure. For procedures on Monday a window of a maximum of 96 hours is justified.
17. To be completed within 72-hours post-procedure. For procedures on Friday a window of a maximum of 96 hours is justified.
18. Full neurological follow up to be undertaken if neurologic symptoms and/or cerebral ischemic lesions identified in a prior evaluation.
19. If subject returns for a potential study related cardiovascular or neurological visit outside of the protocol-defined visit schedule as deemed required per investigators discretion.
20. Patient questionnaires will only be used in countries with validated languages.

15. Assessment of Safety

15.1 Specific Safety Parameters

✪Pursuant MDR 2017/745, in the occasion relevant (local) regulations, guidance(s) and processes on safety determinations, definitions and reporting become in full force during the course of the study, the Sponsor shall adhere to the applicable definitions and processes.

15.1.1 Definition of Adverse Events (AE)

An AE is any untoward medical occurrence in a subject whether or not related to the investigational device.

Specifically, an AE is **any** undesirable experience (sign, symptom, illness, abnormal laboratory value, or other medical event) occurring to a subject during the course of the study, whether or not it is related to the investigational device or procedure. Physical findings (including vital signs) observed at follow-up, or pre-existing physical findings that worsen compared to baseline are considered AEs.

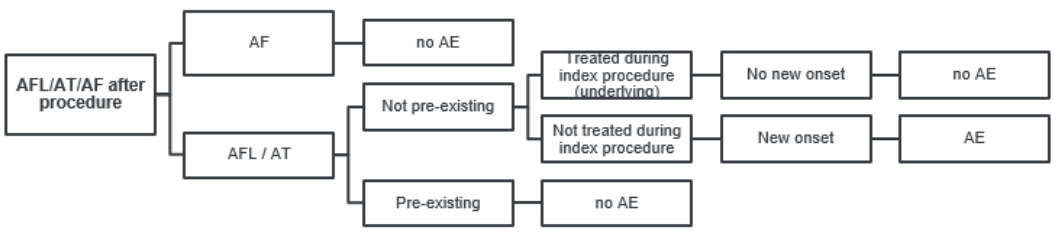
Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. Such conditions should be added to background medical history, if not previously reported. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Following arrhythmia's do not meet the definition of an AE:

- AF recurrence by itself is considered a recurrence of disease (pre-existing condition)
- Recurrence of pre-existing or underlying (treated during index procedure) AFL/AT is considered as a recurrence of disease
- Onset of non-previously identified AFL/AT which was treated during the index procedure as underlying arrhythmia (pre-existing condition)
- Re-ablation for AF or any pre-existing AFL/AT, however any procedural complication is considered an AE and shall be reported within the applicable timelines.
- Re-ablation for any non-pre-existing (underlying) AFL/AT which was treated during the index procedure, however any procedural complication is considered an AE and shall be reported within the applicable timelines.
- Cardioversion (pharmacological or synchronized electrical) for AF/AFL/AT recurrence during the hospitalization for the index ablation procedure, or throughout the duration of the study.

Following arrhythmia's meet the definition of an AE:

- Onset of non pre-existing AFL/AT which was not treated during the index procedure.



15.1.2 Definition of Serious Adverse Event (SAE)

A SAE is any event that meets one or more of the following criteria:

- Leads to a death
- Leads to a serious deterioration in the health of a subject that resulted in:
  - A life-threatening illness or injury
  - An injury or permanent impairment of a body structure or a body function
  - In-patient hospitalization or prolongation of an existing hospitalization*
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
  - Chronic disease (MDR2017/745) ✪
- Leads to fetal distress, fetal death or a congenital abnormality or birth defect.

*Planned hospitalization for a condition present prior to the participant's enrollment in the study will not meet the definition of an SAE. An AE would meet the criterion of "hospitalization" if the event necessitated an admission to a health care facility (e.g., 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.

15.1.3 Primary Adverse Event

A **Primary Adverse Event** is an event listed in table 6 which occurs within the first week (7 days) following an ablation procedure.

Table 6: Primary Adverse Events

Primary Adverse Event	Description / Criteria
Death*	Subject death directly related to the device or procedure and occurs at any time during or after the procedure.
Atrio-Esophageal Fistula*	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 AEF.
Myocardial Infarction	Presence of any one of the following criteria: – Detection of ECG changes indicative of new ischemia (new ST-T changes or new Left Bundle Branch Block [LBBB]) that persist for more than 1 hour – Development of new pathological Q waves on ECG – Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

Primary Adverse Event	Description / Criteria
Cardiac Tamponade**/Perforation	The development of a significant pericardial effusion during or within 30 days of undergoing the index AF ablation procedure. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1cm or more pericardial effusion as documented by echocardiography Cardiac tamponade/perforation should also be classified as: Early – diagnosed prior to discharge Late – following initial discharge from the hospital
Thromboembolism	Formation of a clot (thrombus) inside a blood vessel causing obstruction to blood flow accompanied by clinical symptoms. 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 purpose of this study silent (asymptomatic) cerebral embolism will not be considered a PAE.
Stroke/Cerebrovascular Accident (CVA)	Diagnosis: -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). Definition: 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

Primary Adverse Event	Description / Criteria
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 Paralysis	Absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis is considered to be permanent when it is documented to be present 12 months or longer following ablation.
Pulmonary Vein Stenosis*	A reduction of the diameter of a PV or PV branch. Severe PV stenosis (≥70% reduction in the diameter of the PV) will be considered a PAE and major complication of AF ablation.
Major Vascular Access Complication /Bleeding	Major Vascular Access Complication: Development of a hematoma, an AV fistula or a pseudoaneurysm which requires intervention, such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission. Major Bleeding: Requires and/or treated with transfusion or results in a 20% or greater fall in hematocrit.
Pericarditis	Pericarditis should be considered a major complication following ablation if it results in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization, or persists for more than 30 days following the ablation procedure.

* Device or procedure related death, atrio-esophageal fistula and pulmonary vein stenosis that occur greater than one week (7 days) post-procedure shall be deemed Primary AE.

** Hemodynamic compromise or instability is defined as Systolic blood pressure < 80 mmHg

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

†† mRS assessments should be made by qualified individuals according to a certification process. If there is discordance between the 30 and 90 day mRS, a final determination of major versus minor stroke will be adjudicated by an independent physician/committee.

15.1.4 Adverse Device Effect / Serious Adverse Device Effect

An adverse device effect is an AE related to the use of the investigational medical device.

NOTE 1- This includes any AE resulting from insufficiencies or inadequacies in the IFU, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.
NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

15.1.5 Unanticipated (Serious) Adverse Device Effect

An Unanticipated Adverse Device Effect (UADE) or Unanticipated Serious Adverse Device Effect (USADE) is any SAE on health, safety, any life-threatening problem, or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or risk analysis report, or any other unanticipated serious problem associated with a device that relates to rights, safety, or welfare of subjects. Refer to table 10 for a comprehensive list of foreseeable and anticipated AEs.

15.1.6 Study Device Deficiency, Failure or Malfunction

A device deficiency means any inadequacy in the identity, quality, durability, reliability, usability, safety or performance, including of an investigational device, including

- Malfunction (failure to perform in accordance to its intended purpose when used in accordance with the IFU/CIP/IB),
- Use errors,
- Inadequacy in labelling (for studies under MDR2017/745✪ inadequacy in information supplied by the manufacturer (including labelling)).

If a device failure is detected or suspected, it should be documented on the appropriate eCRF and device failure and AE must be reported per section 15.4.1 AE documentation and reporting requirements.

15.2 Classification of an Adverse Event

15.2.1 Severity of Event

The intensity or severity of each AE must be assessed according to the following classifications:

Table 7: Intensity or Severity Definitions

Mild	Awareness of signs, symptoms, or events that are otherwise easily tolerated that may result in minimal transient impairment of a body function or damage to a body structure, but do not require intervention other than monitoring.
Moderate	Any event that results in moderate transient impairment of a body function or damage to a body structure that causes interference with usual activities, or that warrants possible intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure.
Severe	Any event that is incapacitating (an inability to do usual activities) or is life-threatening and results in permanent impairment of a body function or damage to a body structure, or requires intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

15.2.2 Relationship to Study Device

For all collected AEs, the clinician who examines and evaluates the participant will determine the AEs causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below as described per Medical Device Directive Guidance (MEDDEV) 2.7/3✪.

Table 8: Adverse Event Causality Classifications

Caused By	Relation	Definition of Relation
Device	Definitely (Causal Relationship)	The event is associated with the investigational device beyond reasonable doubt
	Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained
	Possibly	The relationship with the use of the investigational device is weak but cannot be ruled out completely
	Unlikely	The relationship with the use of the investigational device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained
	Not related	Relationship to the investigational device can be excluded
Study Procedure	Definitely (Causal Relationship)	The event is associated with the study procedure beyond reasonable doubt
	Probable	The relationship with the study procedure seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained
	Possibly	The relationship with the study procedure is weak but cannot be ruled out completely
	Unlikely	The relationship to the study procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained
	Not related	Relationship to the procedure can be excluded

15.2.3 Outcome

The outcome of each AE must be assessed according to the following classifications:

Table 9: Adverse Event Outcome Classifications

Classification		Definition
Resolved without sequelae		Subject fully recovered with no observable residual effects
Resolved with sequelae		Subject recovered with observable residual effects
Ongoing	**Improved**	Subject's condition improved, but residual effects remain
	Unchanged	AE is ongoing without changes in the overall condition
	Worsened	Subject's overall condition worsened
Death		Subject died as a result of the AE (whether or not the AE is related to the device or procedure)

15.2.4 Expectedness (Anticipatedness)

An anticipated AE is an effect which by nature, incidence, severity or outcome has been identified as a possible complication associated with the investigational medical device and/or intervention procedure.

Potential AEs that are reasonably anticipated to occur during the cardiac EP procedure are listed in table 10. These events should be reported via EDC as anticipated AEs. Anticipated AEs are to be reported to the sponsor via EDC as indicated in section 15.4.

Table 10: Comprehensive List of Anticipated Adverse Events

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	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 position or propofol
Diaphragmatic paralysis	Sedation induced CO_2 retention with lethargy and cholecystitis
Dislodgement/Malfunction of pacemaker/defibrillator 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
Infection, localized	

*Atrial Fibrillation and exacerbation of an existing arrhythmia are anticipated adverse events. However, they will not be captured as such under this protocol, as they are considered recurrence of disease.

15.3 Time Period and Frequency for Event Assessment and Follow-up

The investigator, or designated individual, will record all reportable events with start dates occurring any time after informed consent is obtained. At each study visit, the investigator will inquire about the occurrence of AEs/SAEs since the last visit.

All AEs, especially SAE's, need to be followed until the event is resolved (with or without sequelae), stabilization, or until the event is adequately explained. The medical monitor or designee of this clinical investigation will decide if more follow-up information is needed in case the event is not resolved at study completion. All required treatments and outcomes of the SAE must be recorded in the eCRF.

15.4 Reporting Procedures

15.4.1 Adverse Event Documentation and Reporting Requirements

Subjects should be encouraged to report AEs spontaneously or in response to general, non-directed questioning (e.g. "How was your health been since last visit?"). Anytime during the study, the subject may volunteer information that resembles an AE.

Each AE must be reported to the sponsor regardless of classification, seriousness, intensity, outcome or causality. The investigator is responsible for ensuring that all AEs observed by the investigator, or reported by the subject, that occur from the time that the subject has signed the informed consent through the end of the study are properly assessed, recorded, and reported as defined and described in the AEs, Adverse Device Effects and Device Deficiencies section of this protocol (section 15). All AEs must be documented by completing subject's medical records (source documents) and appropriate eCRF by the investigator or study coordinator throughout the study and provided to the Sponsor. All AEs will be monitored until they are adequately resolved or explained.

Anonymized documentation pertaining to the AE (e.g. laboratory tests, consultation reports, post-mortem reports, new information relating to a previously reported AE, correspondence with the local EC, etc.) will be provided by the investigator to the sponsor or designee in a timely manner, when requested. Follow-up reports relative to the subject's subsequent course must be submitted to the sponsor or designee until the event has resolved or, in case of permanent impairment, until the condition stabilizes. If the subject is withdrawn from the study because of the AE, the information must be included on the appropriate eCRFs.

The Sponsor is responsible for the classification of AEs and ongoing safety evaluation of the study and shall review the investigator's assessment of all AEs. The sponsor will determine and document in writing their seriousness and relationship to the investigational device. In case of disagreement between the sponsor and the PIs, the sponsor shall communicate both opinions to the concerned parties.

Biosense Webster will ensure that investigators are instructed to return devices suspected of causing an AE or SAE (i.e., definitely (causal relationship) device-related or possibly device-related) in accordance with relevant regulations and current company procedures.

In the case of serious device effects and device deficiencies that could have led to SADEs, the Sponsor will determine whether the risk analysis needs to be updated and whether corrective or preventative action is required.

Timing for reporting the different types of AEs is described in table 11.

Table 11: AE Reporting Requirements

Type of Adverse Event	Reporting Requirements
Serious Adverse Events	Report to Sponsor immediately upon awareness of event but no later than 72 hours
USADE & SADE	Report to Sponsor immediately upon awareness of event but no later than 72 hours
Primary AEs	Report to Sponsor immediately upon awareness of event but no later than 72 hours
Study device failure/malfunction associated with an AE	Report both study device failure and AE to Sponsor immediately upon awareness of event but no later than 72 hours
Study device failure/malfunction that could have led to a SAE *	Report to Sponsor immediately upon awareness of event but no later than 72 hours
All other Adverse Events	Report to Sponsor immediately upon awareness of event but no later than 2 weeks

* If a) suitable action had not been taken, or b) intervention had not been made or, c) if circumstances had been less fortunate.

15.4.2 Serious Adverse Events Reporting

All

- SAEs (SADEs for studies under MDR2017/742✪)
- Investigational DD that might have led to a SAE if
  a) suitable action had not been taken or
  b) intervention had not been made or
  c) if circumstances had been less fortunate, whether or not they are related to the device or procedure,
- new findings/updates in relation to already reported events.

must be reported to the Sponsor, via eCRF, **immediately upon awareness of event but no later than 72 hours** by the study site personnel.

The sponsor will ensure that investigators are instructed to return devices suspected of causing an AE or SAE (i.e., definitely (causal relationship) device-related or possibly device-related) in accordance with relevant regulations and current company procedures.

In the case of serious device effects and device deficiencies that could have led to SADEs, the Sponsor will determine whether the risk analysis needs to be updated and whether corrective or preventative action is required.

The sponsor will report or ensure reporting all reportable events and updates to the reportable events to the EC (by the principal investigator) as per national or site specific

requirements. Event reporting to relevant CAs for non CE-marked devices will occur by the sponsor and if indicated per local country requirements by the investigator.

15.4.3 Unanticipated Device Effect Reporting

All UADE/SADE/USADE **must be reported** to the Sponsor, via eCRF, **immediately upon awareness of event but no later than 72 hours** by the study site personnel. An investigator shall submit to the reviewing EC a report of any UADE occurring during an investigation according to EC requirements.

15.4.4 Events of Special Interest

All study device failure/malfunction must be reported to the Sponsor, via eCRF, as soon as possible, within 72 hours by the study site personnel. If a device failure is detected or suspected, it should be documented on the eCRF and the device returned according to the Sponsor's instructions**.**

The investigational device should be sent to appropriate R&D team or designated Quality engineer. Complaints related to non-investigational products manufactured and/or distributed by Biosense Webster, used during the procedure related to other devices (other than the study device under investigation), are to be reported according to current Biosense Webster procedures and other policies as necessary (i.e., institutional policies, EC policies, and local regulations). Investigators are instructed to return devices in accordance with current company procedures and other relevant regulations.

Event reporting to relevant CAs in accordance with the jurisdictional regulations will occur by the sponsor and/or by the investigator, depending upon the local requirements and will be done in EU per MEDDEV 2.12/1 guidelines✪ for CE-marked devices manufactured by Biosense Webster and per MEDDEV 2.7/3 guidelines✪ for non CE-marked devices manufactured by Biosense Webster.

A device deficiency related to a medical device not manufactured by Biosense Webster should be reported by the investigator to their respective manufacturer as per relevant regulation. Complaints related to non-Biosense Webster, Inc. products must be handled according to institutional policies, EC policies, and local regulations.

15.5 Safety Oversight

Safety oversight will be conducted as described in the Safety Management Plan. Aggregate safety data will be reviewed during enrollment by the study safety lead in order to promptly identify new issues or trends which may have an impact on the conduct of the study and/or subject safety. Under the rules of an approved study-specific charter, safety events will be reviewed by an established committee which may recommend appropriate action(s) to ensure subject safety.

16. Administrative Responsibilities

16.1 Ethics Committee and Competent Authority Application

The study protocol (or amendment[s]), ICF, and other applicable study related documents must be approved by the EC and CAs before enrollment of subjects. Any additional requirement imposed by the EC or CA shall be discussed, agreed upon, and followed. A signed copy of the EC and CA approval letters addressed to the investigator must be submitted to Biosense Webster certifying study approval prior to subject enrollment. Biosense Webster and the EC must approve, in writing, any changes to the protocol that affect the rights safety and/or welfare of the subjects or may adversely affect the validity of the study.

In addition, Biosense Webster, Inc. is responsible for notifying the relevant CA of the intention to perform a clinical investigation under this protocol and ensure to get the official response/ approval before starting the clinical investigation.

16.2 Audits and Inspections

The sponsor and/or designee and/or CAs may contact the participating institution to inform the investigator of an upcoming audit/inspection. The investigator should immediately notify the sponsor of any CA audits/inspection at the study site. The audit/inspection can include the review of documents, facilities, records and any other resources deemed by the authorities to be related to study.

17. Deviations from the Clinical Study Plan

The investigator is responsible for ensuring that the clinical investigation is conducted in accordance with the procedures and evaluations described in this protocol. The study monitors shall verify that the conduct of the study is in compliance with the currently approved protocol and applicable regulations and shall identify any issues of non-compliance with regulations or guidelines.

Issues of non-compliance include but are not limited to repeated protocol deviations; failure to obtain proper informed consent; non-conformance to EC requirements; failure to report AEs, product malfunctions and other product issues; and other non-conformance to GCP.

A protocol deviation is defined as an instance of failure to follow, intentionally or unintentionally, the requirements of the protocol (e.g. missed test or procedure, visit out of window, non-adherence to inclusion/exclusion criteria). Investigators are not allowed to deviate from the protocol. Waivers are prohibited for this clinical study. Protocol deviations will be monitored closely and will be reported per EC/CA requirement.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of a subject may proceed without prior approval of the sponsor and EC. Such deviations shall be documented and reported to the sponsor and the EC as required.

All instructions described in this study protocol are to be followed. If an amendment is required, it must be made in written form and receive approval from all persons and

authorities who approved the original protocol. Administrative changes (do not affect subject's benefits/risks ratio) may be inserted with abbreviated approval. All amendments will be distributed to all original protocol recipients.

18. Investigational Product

18.1 Use of the Investigational Device and Investigator Experience

18.1.1 Training

The training of applicable clinical site personnel will be the responsibility of the Sponsor. Prior to initiating subject enrollment at a site, appropriate study training will be provided. Investigators selected to participate in the study will be experienced in intracardiac mapping and AF ablation. Investigators will undergo device and IRE technology training in accordance with the physician training charter.

To ensure uniform data collection and protocol compliance, the Sponsor will conduct a training session that will include reviewing the protocol, eCRF and data collection process, and the AE reporting process. The sponsor will reinforce the training or provide clarification throughout the study, as needed.

18.1.2 Materials

IRE Generator

Biosense Webster, Inc. USA, is the legal manufacturer of the generator to be used in this study in a manner similar to standard, commercially approved Biosense Webster products.

Complete manufacturing records of each generator manufactured for human use during this study are maintained at the respective manufacturing location. Each generator is released for human use under a Confirmation of Conformity from Regulatory Affairs that will certify that the investigational generator conforms to the Essential Requirements for product release apart from those features, that are being investigated in this clinical investigation. And that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.

Circular IRE Catheter

Biosense Webster, Inc. USA, is the legal manufacturer of the catheters to be used in this study. The investigational devices were built in a clean room environment, and sterilized using EtO gas, in a manner similar to standard, commercially approved Biosense Webster products. Further detail of catheter components coming into contact with the human body are described in the Investigator Brochure.

Complete manufacturing records of every lot of catheter manufactured for human use during this study are maintained at the respective manufacturing location. Each lot of catheters is released for human use under a Confirmation of Conformity from Regulatory Affairs that will certify that the investigational catheters conforms to the Essential Requirements for product release apart from those features, that are being investigated in this clinical investigation. And that, with regard to these aspects, every precaution has been taken to protect the health and safety of the patient.

18.2 Device Acquisition and Accountability

After obtaining a fully executed clinical trial agreement and appropriate CA/EC approvals, the study site will receive the necessary amount of study-related materials prior to commencement. Study-related devices (investigational and non-investigational) will be shipped to the site upon completion of required documentation. Investigational Study Devices will be labeled as "**Investigational Device**" and are only to be used for subjects enrolled in this clinical study.

The Sponsor will keep records of all investigational devices shipped to the site. Investigational site personnel are responsible for appropriate logging of devices received, verification of packing slip information (i.e. lot numbers and quantity shipped) and date and identifying that each device was used in the study and disposition information completed when returned to the Sponsor.

The Investigational Device Accountability Log shall record the following information:

- Date of receipt
- Person in receipt of the devices
- Quantity received
- Catalog number
- Serial/lot numbers
- Expiry Date
- Date device was used
- Subject ID on whom device was used
- Date of return
- Reason for return (i.e. used without incident, malfunction, expired, end of study, …)

18.3 Device Returns

All investigational devices (**used and unused**) will be returned to the Sponsor's attention and per Sponsor's Instructions. The Circular IRE catheter shall be returned to the below address. Device deficiencies should be properly documented on the eCRF. Any suspected malfunctioning device or device associated with an AE (device related or possibly device related) will undergo a thorough complaint analysis All returned devices must be properly labeled with the study name, the subject identification number, date of issue, identified as a defective return, non-defective return, or AE (as applicable). All tracking information must be retained in the event the package has been lost and requires tracking. All investigational devices should be returned to:

ATTN: Complaints Lab
Biosense Webster, Inc.
15715 Arrow Highway
Irwindale, CA 91706 USA

19. Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved

protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Each site will undergo periodic monitoring of the study, which involves a visit from a Sponsor representative, qualified to perform such visit. Monitoring visits may include, but are not limited to, the following:

- Protocol adherence
- Source documentation verification and accuracy of the eCRFs
- Verification that informed consent is being obtained for all subjects participating in the study in accordance with requirements described in the study protocol
- Verification of completeness of the site file
- Verification of accuracy of all study logs such as the Delegation of Responsibility Log, etc.
- Compliance with applicable regulations
- Identification and action to resolve any issues or problems with the study.

Data are to be submitted promptly via e-CRF after collection. Missing or unclear data will be corrected as necessary throughout the trial. Biosense Webster will request further documentation such as physician and/or cardiac EP lab procedure notes when complications or malfunctions are observed and reported.

Further details on clinical monitoring are provided in the study specific monitoring plan.

20. Statistical Methodology

The Sponsor will be responsible for the overall analysis of data from this protocol. A separate Statistical Analysis Plan (SAP) will be written and approved prior to database lock. The SAP will describe all planned analyses based on the statistical design of this study and the subsequent data collected. A brief statistical overview of key statistical analyses is provided below.

Wave I will serve as characterization of safety and provide preliminary estimates for safety and acute effectiveness of the system under study, accordingly all analyses of Wave I data are planned to be descriptive. Only Wave II subject data will be used for the purpose of primary hypothesis testing.

20.1 Levels of Significance

Significance levels and the type-I error control for the interim and final analyses of the primary endpoints are specified below in the applicable sections describing the analyses.

20.2 Sample Size Justification

As Wave I of the study is a safety characterization phase, a sample size of 40 subjects is intended to delineate safety and provide preliminary estimates for safety and acute effectiveness of the IRE system. The maximum enrollment of 40 subjects will provide greater than 90% probability of observing at least one primary AE, assuming the PAE rate is 7% and that 35 of the enrolled subjects have the study catheter inserted.

A Bayesian adaptive design will be utilized to select the final sample size for Wave II of the study. The sample size for Wave II is primarily driven by the long-term effectiveness endpoint.

Two interim analyses will be performed for sample size selection and the details will be provided in the statistical analysis plan (SAP). Predictive probabilities of success for the primary effectiveness endpoint will be used to determine whether the sample size at the time of the interim analysis will be sufficient or if Wave II enrollment will continue to the full sample size of 330.

Trial simulations were performed to estimate the power for the success of the trial under a range of assumptions for the true safety and effectiveness rates. Based on the simulation results for the most likely scenario (assumed safety rate of 7.0% and effectiveness rate of 65%), the power for showing success for both safety and effectiveness endpoints is above 80.0% and adequate.

Simulations were also performed to estimate the overall Type-I error for the trial under various hypothetical scenarios. The highest Type-I error rates were reached in the following two scenarios:

1. The true primary safety rate was on the decision boundary (i.e. equal to 14%) and the device was assumed to be effective. The Type-I error for this scenario was estimated to be 0.0191 with a 95% confidence interval of (0.0156 , 0.0189).
2. The true primary effectiveness rate was on the decision boundary (i.e. equal to 50%) and the devices was assumed to be safe. The Type-I error for this scenario was estimated to be 0.0145 with a 95% confidence interval of (0.0152 , 0.0185).

As the primary safety or effectiveness rates moves away from the decision boundary, the overall Type-I error decreases. Therefore, considering all scenarios, the overall Type-I error for claiming success for both safety and effectiveness endpoints was controlled at 2.5%. Additional details on the simulation results will be provided in the SAP and the study Simulation Report.

Based on the simulation results, the study is adequately powered to meet the primary safety and effectiveness endpoints and overall Type-I error is controlled at 2.5%.

20.3 Analysis Sets

20.3.1 Wave I Analysis Sets

- **Modified Intent-To-Treat (mITT-Wave I) Analysis Set**: The mITT-Wave I analysis set will consist of enrolled Wave I subjects who meet eligibility criteria and have had insertion of the study catheter. Subjects in this analysis set who are discontinued due to:
  - study catheter related reasons will be considered acute effectiveness failures
  - non-study catheter related reasons (other equipment, pump, anatomy that precludes treatment with the study catheter or commercially available catheter) will be excluded from the effectiveness analysis.

- **Full Analysis Set (FAS- Wave I):** The FAS-Wave I Analysis Set will consist of all enrolled Wave I subjects who have had insertion of the study catheter (with or without delivery of PFA).

- **Per Protocol Analysis Set (PP-Wave I)**: The PP-Wave I analysis set will consist of Wave I subjects who satisfy the following criteria:
  - are enrolled and without major protocol deviations that would affect the integrity of the data
  - have undergone ablation (PFA) with the study catheter
  - are treated for the study-related arrhythmia
  - did not require the use of a non-study catheter for Pulmonary Vein Isolation (PVI)
  - did not require ablations outside the PV region

20.3.2 Wave II Analysis Sets

- **Modified Intent-To-Treat (mITT-Wave II) Analysis Set**: The mITT-Wave II analysis set will consist of enrolled Wave II main study phase subjects who meet eligibility criteria and have had insertion of the study catheter. Subjects in this analysis set who are discontinued due to:
  - study catheter related reasons will be considered acute effectiveness failures
  - non-study catheter related reasons (other equipment, pump, anatomy that precludes treatment with the study catheter or commercially available catheter) will be excluded from the effectiveness analysis.

- **Full Analysis set (FAS-Wave II):** The FAS-Wave II Analysis Set will consist of all enrolled Wave II main study phase subjects who have had insertion of the study catheter (with or without delivery of PFA).

- **Per Protocol (PP-Wave II) Analysis Set**: The PP-Wave II analysis set will consist of Wave II main study phase subjects who satisfy the following criteria:
  - are enrolled and without major protocol deviations that would affect the integrity of the data
  - have undergone ablation (PFA) with the study catheter
  - are treated for the study-related arrhythmia
  - did not require the use of a non-study catheter for Pulmonary Vein Isolation (PVI)
  - did not require ablations outside the PV region

- **Roll-In Analysis Set**: The Roll-In analysis set will include all subjects who are enrolled in the roll-in phase. All endpoints will be analyzed for the roll-in analysis set separately.

20.4 Analyses to be Conducted

20.4.1 General Conventions

Standard descriptive summaries for continuous data include the number of observations with data, number of observations with missing data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum, and maximum values. For categorical data, the count

and percent will be provided. Percentages will be based on the number of subjects without missing data.

20.4.2 Disposition and Study Subjects

Disposition and accountability of the study subjects will be summarized descriptively for the subject categories defined in section 10.3.

20.4.3 Demographic and Baseline Characteristics

Subject demographics, medical history, previously failed AADs, active AAD use (still administered) and other baseline data will be summarized descriptively for subjects in the mITT-Wave I and FAS-Wave I analysis sets. These characteristics will also be summarized descriptively for subjects in mITT-Wave II, FAS-Wave II, PP-Wave II, and Roll-in analysis set for Wave II subjects.

20.4.4 Primary Endpoint Analyses and Associated Hypotheses

The primary safety endpoint will be summarized descriptively in the mITT-Wave I analysis set after all Wave I subjects complete the 12-month follow-up. Similarly, the primary effectiveness endpoint will be summarized descriptively in the PP-Wave I analysis set after all Wave I subjects complete the 12-month follow-up.

For the main study phase, the PAE rate will be formally compared against a performance goal of 14%. Additionally, the primary effectiveness success rate will be compared to a performance goal of 50% for the main study phase. The primary safety endpoint analysis for the main phase will be performed in the mITT-Wave II analysis set and the primary effectiveness analysis will be performed in the PP-Wave II analysis set.

20.4.4.1 Interim Analysis for Sample Size Selection for the Main Study Phase

The sample size for the main study phase is primarily driven by the primary effectiveness endpoint. The methods described in Broglio *et al.*[71] will be used for adaptive determination of the sample size based on the effectiveness endpoint alone. Mutiple sample size selection interim analyses will be performed when pre-specified enrollment targets described in the SAP are reached in the mITT-Wave II analysis set.

To estimate the predictive probability of success at each sample size selection interim analysis, time-to-failure during the 9-month (39 weeks) post-blanking period will be modeled using a piecewise exponential model with three distinct intervals (from (0,2], (2,8], and (8,39] weeks). The time intervals were chosen to adequately capture the functional form of the survival function by taking into account the timing of the occurrence of documented AF/AT or AFL events based on previous studies. The probability of a failure during each interval is assumed to be exponentially distributed, with a different hazard rate. The model is:

$$f(t) = \exp\big(-t * h(t)\big)$$

Where

$$h(t) = \begin{cases} \lambda_1 & 0 < t \leq 2 \\ \lambda_2 & 2 < t \leq 8 \\ \lambda_3 & 8 < t \leq 39 \end{cases}$$

Vague Gamma prior distributions will be assumed for λ_1, λ_2 and λ_3.

The predictive probabilities of success for the effectiveness endpoint will be estimated using Monte Carlo integration (details will be provided in the SAP). Enrollment will be stopped at an interim if the predictive probability of success for the effectiveness endpoint with the sample size at the time of the interim is greater than 90.0%, or if the predictive probability of success for the effectiveness endpoint with the maximum sample size of 330 subjects is less than a futility threshold of 2.5%. Otherwise, enrollment will continue to the next sample size selection interim or the final sample size of 330 subjects.

Additional details on estimation of the predictive probabilities will be provided in a separate simulation report and in the Statistical Analysis Plan.

Analysis of the primary safety endpoint will be performed using the final sample size that is selected adaptively based on the primary effectiveness endpoint. All sample sizes from the interim sample selections will provide greater than 80% power for the primary safety endpoint assuming a PAE composite rate of $\leq$7% and a performance goal of 14%.

20.4.4.2 Early Success Interim Analysis for the Main Study Phase

An interim analysis will be performed for claiming early trial success in Wave II when 30 subjects in the PP-Wave II analysis set reach full 12-month of follow-up and all subjects in the mITT-Wave II analysis set reach three months of follow-up. At this interim, the trial will declare early success if both safety and effectiveness objectives are met:

1. The posterior probability of the safety rate being less than 14% is greater than 0.975
2. The posterior probability of the effectiveness proportion p_E being greater than 50% is greater than 0.9975.

For Primary Safety Endpoint:

The primary safety endpoint analysis performed at this interim will include 3-month safety follow-up for all mITT-Wave II subjects and will be the same as the final safety endpoint analysis.

A beta-binomial model with a non-informative uniform prior will be used for the primary safety rate. The uniform prior for the safety rate will be updated based on the observed number of events to obtain the posterior distribution for the primary safety rate. If the posterior probability of the safety rate being less than 14% is greater than 0.975, the early success primary safety endpoint will have been met.

The null and alternative hypotheses for the safety endpoint for the early success interim analysis are:

$$H_0: \Pr(P_s < 0.14) \leq 0.975$$

$$H_a: \Pr(P_s < 0.14) > 0.975$$

Primary Effectiveness Endpoint

In case early success is achieved, the study will continue to follow up the subjects for the full follow-up duration, and the primary effectiveness endpoints based on full 12-month follow-up data will be descriptively summarized in subjects in the PP-Wave II analysis set. The early success effectiveness analysis will be performed in the PP-Wave II analysis set. At the time of the early success interim analysis, the posterior distribution for the 12-month effectiveness proportion will be estimated by using the piecewise exponential model described in 20.4.4.1. Early success effectiveness will be demonstrated if the p_E being greater than 50% is greater than 0.9975.

For the early success interim analysis, the total number of primary effectiveness events and the total subject exposure time will be used to update the vague Gamma priors for the hazard rates and obtain posterior Gamma distributions for three segments of the effectiveness model. Next, 10,000 random hazard rates will be sampled from the posterior distribution for each segment and each triplet set of hazard rates will be used to estimate a single 12-month effectiveness rate. The posterior distribution of the 12-month rate is estimated based on the 10,000 simulated rates. Using this distribution, if the probability of the 12-month effectiveness rate being greater than 50% is greater than 0.9975(99.75%), the trial will declare early success for the effectiveness endpoint.

The null and alternative hypotheses for the primary effectiveness endpoint for the early success interim analysis are:

$$H_0: \Pr(P_E > 0.50) \leq 0.9975$$

$$H_a: \Pr(P_E > 0.50) > 0.9975$$

where P_E is the 12-month effectiveness rate.

20.4.4.3 Final Analysis for the Main Study Phase

If early success is not achieved, then the final effectiveness analysis will be based on complete follow-up data for the primary effectiveness endpoint as described in this section. If trial success is achieved at the early success interim analysis, then the final analysis for the effectiveness endpoint will involve descriptive statistics on the full follow-up effectiveness data in the mITT-Wave II and PP-Wave II analysis sets.

For Primary Safety Endpoint:

The final primary safety endpoint analysis is the same analysis performed at the early success interim as all safety data is available at the time of the early success interim look. A beta-binomial model will be used for this analysis. A non-informative uniform prior will be assumed for the primary safety proportion. The primary safety endpoint will be considered a success if

$$\Pr(P_S < 0.14) > 0.975$$

The analysis population for the primary safety endpoint will be the mITT-Wave II analysis set. If the posterior probability of the safety rate being less than 14% is greater than 0.975, then the study will be considered to have demonstrated safety of the device.

For Primary Effectiveness Endpoint:

If trial success is not declared at the early success interim, the final analysis for the primary effectiveness endpoint will use a beta-binomial model similar to the primary safety endpoint analysis. A non-informative uniform prior will be assumed for the primary effectiveness rate.

At the time of the final analysis, the trial will be considered a success if

$$Pr(P_E > 0.50) > 0.9775$$

The analysis population for the primary effectiveness endpoint will be the PP-II analysis set. If the posterior probability of the effectiveness rate being greater than 50% is higher than 0.9775, the study will be considered to have demonstrated effectiveness of the device.

20.4.4.4 Handling of Missing Data

If a subject has not completed 12 months of follow-up but has had a PAE, then the subject will be considered an event for the final primary safety analysis. If a subject's follow-up time is less than 12 months and the subject has not had a PAE, then that subject will be excluded from the primary safety analysis.

For the early success interim analysis of the primary effectiveness endpoint, the subjects with incomplete follow-up data who are event free will be censored at the time of their last follow-up visit, and only their observed partial follow-up time will contribute to estimating model parameters.

For the final primary effectiveness analysis, if a subject has an effectiveness failure at any time during the evaluation period, then the subject will be considered an event. Subjects without an effectiveness failure who do not have full 12 months of follow-up will be excluded from the final primary effectiveness analysis.

20.4.4.5 Sensitivity Analyses

To investigate the robustness of the analysis result for the primary endpoints, several sensitivity analyses will be performed. Details on these analyses will be provided in SAP.

20.4.4.6 Subgroup Analyses

Subgroup analyses by clinically relevant factors will be performed and details will be provided in SAP.

20.4.5 Secondary Endpoint Analysis

All secondary endpoints will be summarized based on the full 12-month follow-up data of subjects in the mITT-Wave II analysis sets.

Acute Procedural Success: The rate of acute procedural success (defined in section 8.2.2) will be summarized descriptively.

Freedom from Documented Symptomatic Recurrence: The rate of freedom from documented symptomatic atrial arrhythmia (atrial fibrillation (AF), atrial tachycardia (AT) or atrial flutter (AFL)) episodes will be summarized descriptively.

Quality of Life (QOL): AFEQT scores assessed at baseline and follow-up visits will be summarized and compared descriptively.

20.4.6 Additional Endpoint Analyses

No formal statistical hypothesis and inferential statistics will be formulated and performed for the additional endpoints. Additional safety endpoints will be analyzed in Roll-in, Safety and mITT analysis sets for respectively Wave I and Wave II. Effectiveness endpoints and procedural data will be analyzed in FAS and PP analysis sets for respectively Wave I and Wave II. NAE, CT/MRA, and esophageal lesion endpoints will be analyzed in the mITT-Wave I analysis set. All endpoints will be analyzed for the roll-in analysis set separately. Details of the analyses will be described in the SAP.

21. Ethics and Protection of Human Subjects

21.1 Ethical Standard

As the Sponsor of this study, Biosense Webster has the overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements of the Food and Drug Administration (FDA), applicable European medical device regulation and the local government. For study under MDR, MDR2017/745 will be applicable, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC.
The Sponsor will also maintain compliance with GCP (ICH E6 (R2), 9 November 2016), the European standard EN ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects), the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Fortaleza 2013), Sponsor general duties (21 CFR 812.40), selection of investigators (21 CFR 812.43), monitoring (21 CFR 812.46), supplemental applications (21 CFR 812.35 [a] and [b]), maintaining records (21 CFR 812.140 [b]), and submitting reports (21 CFR 812.150 [b)]), and to local regulations where required.

- General Duties
  Biosense Webster's general duties consist of submitting the clinical investigation application to appropriate regulatory agencies, assuring that sites have received EC

approvals prior to shipping the devices, selecting investigators, ensuring proper clinical site monitoring and ensuring subject informed consent is obtained.

- Data Quality and Reporting
  Biosense Webster is responsible for providing quality data that satisfy federal regulations and informing proper authorities of serious unanticipated AEs and deviations from the protocol.

- Selection of Investigators
  All potential investigational sites will undergo an evaluation to ensure that the site has the appropriate facilities and personnel to conduct the study in compliance with the clinical investigational plan. Based on outcome of evaluation process, Biosense Webster will select qualified investigators, ship devices only to participating investigators, obtain a signed Investigator's Agreement and provide the investigators with the information necessary to conduct the study.

- Supplemental Applications
  As appropriate, Biosense Webster will submit changes in the Clinical Investigational Plan to the investigators to obtain all applicable re-approvals.

- Maintaining Records
  Biosense Webster will maintain copies of correspondence, data, adverse device effects and other records related to the study. Biosense Webster will maintain records related to the signed Investigator Agreements.

- Submitting Reports
  Biosense Webster will submit any required regulatory reports identified in this section of the regulation. This may include UADEs, withdrawal of EC approval, current investigators list, annual progress reports, recall information, final reports and protocol deviations.

21.2 Informed Consent Process

21.2.1 Informed Consent Procedure and Documentation

Subjects informed consent must be obtained and documented according to the principles of informed consent in the latest version of the Declaration of Helsinki (Fortaleza, 2013), ISO 14155, and approved by the reviewing CA and EC.

Informed consent is mandatory and must be obtained from all subjects prior to their participation in the study.

Prior to screening or performing any study related procedures that are solely for the purpose of determining eligibility for this study, any potential benefits and risks of the study must be explained to the subject. Subjects will be informed about aspects of the study that are relevant to the subject's decision to participate. Subjects should be made aware that by signing the ICF, they are granting approval for study personnel to review their medical records and to collect/analyze personal medical information. Subjects should also be informed that study personnel will maintain confidentiality of the medical records at all times.

The ICF will be written in a native, non-technical, language that is understandable to the subject and is to be approved by the applicable EC prior to enrolling subjects. The subject or designee will be provided with ample time to read and understand the ICF and to consider participation in the study. Informed consent will be requested prior to enrollment and must be personally signed and dated by the subject, or subject's legal representative, prior to performance of any study related activity or procedure. If a subject is unable to read or write, informed consent shall be obtained through the aid of an independent witness who will be present throughout the process. The written ICF and any other information shall be read aloud and explained to the prospective subject and, whenever possible, subject shall sign and date the ICF. The witness must also sign and date the ICF attesting that the information was accurately explained, and that informed consent was freely given. The point of enrollment corresponds with the time that subjects signs the informed consent.

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 obtaining 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 ICH-GCP and, where applicable, local and federal regulations. Subjects should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the trial. Subjects or his/her legal representative must be given ample time and opportunity to inquire about details of the trial and all questions about the trial should be answered to the satisfaction of the patient or the representative. Failure to provide written informed consent renders the subject ineligible for the study. 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 the amended ICF.

21.3 Participant and Data Confidentiality

During this clinical investigation, all representatives of the Sponsor will comply with all in-country privacy laws and regulations regarding contact with subjects, their medical record information, copying of information, and protection of the subject identities.

All information and data sent to Biosense Webster concerning subjects or their participation in this clinical investigation will be considered confidential. Only authorized Biosense Webster personnel or representatives (including contracted service providers, i.e. Core Lab, Clinical Research Associate, CRO, etc.), representatives of the FDA or CAs acting in their official capacities will have access to these confidential files upon request (including, but not limited to, laboratory test result reports, ECG reports, admissions/discharge summaries for hospital admission occurring during a patient's study participation and autopsy reports for deaths occurring during the clinical investigation). Some of the countries to which the study subjects and investigators personal data may be transferred may not offer as comprehensive a level of protection of personal data as within the European Union but Sponsor will take all reasonable steps to ensure a sufficient level of data protection. All data used in the analysis and reporting of this evaluation will exclude identifiable reference to the subject.

21.3.1 Research Use of Stored Data

- Intended Use: Data collected under this protocol may be used to study AF.
- Storage: Access to stored data will be limited. Data will be stored using codes assigned by the sponsor. Data will be kept in password-protected computers. Only investigators and the sponsor will have access to the data.

22. Source Documents and Access to Source Data/Documents

Data entered on to the eCRFs will be taken from source documentation, such as hospital procedure reports, admission and discharge summaries, other hospital or investigator office/clinic documents, and system data (CARTO, generator system). If unique study parameters are not documented on standard hospital or office reports, a worksheet may be developed to record this information. The worksheet shall be signed by the PI or authorized designee and will serve as source document and as basis for monitoring the eCRFs. Electronic subject records will be considered as source documents on the condition that the hospital's database is a validated system. If this is not the case, electronic records should be printed and added to the subject's paper file. A print-out of a completed eCRF cannot be used as source documentation.

Investigators should maintain information in the subject's medical records, which corroborate data collected on the eCRFs. In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained.

- Medical history/physical condition of the study subject before involvement in the study sufficient to verify protocol selection criteria (if not already present).
- Dated and signed notes from the day of entry into the study including the study Sponsor (Biosense Webster), protocol number, clinical site, subject number assigned and a statement that consent to participate in the study was obtained.
- Dated and signed notes from each study visit with reference to the eCRFs for further information, if appropriate (for specific results of procedures and exams).
- Reports on AEs and their resolution, including supporting documents such as discharge summaries, EP lab reports, ECGs, lab results.
- Notes regarding protocol-required medication and prescription medications taken during the study (including start and stop dates).
- Notes on subject's condition upon completion of or withdrawal from the study.

Only authorized Biosense Webster personnel or representatives, authorized site personnel, local government authorities, or the FDA, acting in their official capacities, will have access to these confidential files.

23. Quality Assurance and Quality Control

Quality Control (QC) procedures will be implemented beginning with the data entry system and ongoing QC checks will be run on the database. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written SOPs, monitors will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the

applicable regulatory requirements. If noncompliance is identified, Sponsor is required by regulation to implement measures to secure compliance.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and CAs.

24. Data Handling and Record Keeping

24.1 Data Collection and Management Responsibility

The Sponsor will be responsible for all data management activities. These activities include development of an EDC system and utilizing a validated EDC system into which all study data will be entered. The Sponsor will be responsible for reviewing all data to ensure the overall integrity of the database.

24.1.1 Data Collection

eCRFs will be used to collect all subject data during this clinical investigation. eCRFs have been developed to capture the information outlined in this clinical investigation Plan. Modification to the eCRF will only be made if deemed necessary by the sponsor. Data on these eCRFs will be monitored (source verified) and the monitor will ask the site representative to correct if necessary, to match the source documents. All changes made to the data will be tracked in the electronic audit trail. The investigator will be required to sign designated eCRFs as verification that they have been reviewed and the data entered are correct. Data from these eCRFs will be used to provide analysis of this clinical investigation.

24.1.2 Data Reporting

The investigator, or a designated individual, is responsible for ensuring that clinical investigation data are timely and properly recorded on each subject's eCRF and related documents. The investigator, or a designated individual, is required to electronically sign the eCRF on the appropriate pages to verify that he/she has reviewed and attests to the correctness of the recorded data. Completed eCRF will be reviewed and monitored by the sponsor personnel, or an appropriately qualified and trained designee, throughout the clinical investigation. To this end, the Investigator and institution must permit inspection of the trial files and subject eCRFs by such representatives and/or responsible government agencies.

Investigators are required to prepare and submit accurate and timely reports on this study to the governing EC and Biosense Webster.

Table 12: Responsibilities for Preparing and Submitting Reports

Type of Report	Prepared by Investigator For	Time of Notification
Subject withdrawal	Biosense Webster	Should report within 5 working days
Withdrawal of EC approval	Biosense Webster	Should report within 5 working days
Final report	Biosense Webster, EC	Will prepare a final report for the clinical investigation as required per national regulations.
Informed consent not obtained from subject	Biosense Webster, EC	Should report within 5 working days

It is recommended that all eCRF data be entered by the designated site personnel as soon as possible. For AE reporting, refer to the Adverse Event Reporting Requirements and timelines noted within this clinical investigation protocol.

24.1.3 Data Verification and Review

Biosense Webster will track the amount of missing data and contact sites as appropriate to instruct them on steps to minimize missing data and remain compliant with protocol required assessments. Missing or unclear data will be queried as necessary throughout the trial. Biosense Webster will request further documentation such as physician and/or cardiac EP lab procedure notes when complications or device malfunctions/complaints are observed and reported. Biosense Webster will be responsible for auditing the database and confirming the overall integrity of the data.

24.1.4 Final Data Analysis

All exported datasets for analyses will undergo a final data review before final database lock. Once all critical data are monitored and locked, the final analyses of clinical investigation data will be performed.

24.2 Study Record Retention and Archiving

Records and reports for the study will remain on file at the site for a minimum of 5 years or per country specific record retention requirements following notification by the sponsor that all investigations have been terminated or completed. This documentation must be accessible upon request by the CAs, the sponsor, or a designee. The sponsor must approve archiving, transfer, and destruction of the documentation, in writing, prior to the actual archiving, transfer, and destruction. The investigator must notify the sponsor, in writing, of transfer location, duration, and the procedure for accessing the study documentation.

If the investigator retires, relocates, or withdraws from assuming primary responsibility for keeping the study records, custody transfer per written notice must be submitted to the sponsor indicating the name and address of the person accepting primary responsibility. The EC must be notified in writing of the name and address of the new custodian. Record retention dates must be provided to all parties by the sponsor's corporation.

25. Study Suspension or Termination

This study may be temporarily suspended or prematurely terminated at the discretion of the Sponsor. The Sponsor may also terminate a site prior to study completion if the Sponsor believes the site is no longer capable of participating (e.g., cannot fulfill subject enrollment or protocol compliance goals, site suspension by EC). If the study is prematurely terminated or suspended, the PI will promptly inform the EC and will provide the reason(s) for the termination or suspension.

If suspension or premature termination occurs, the terminating party shall justify its decision in writing and promptly inform the other parties with whom they are in direct communication. The PI and sponsor shall keep each other informed of any communication received from either the EC or the CA.

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.

If, for any reason, the sponsor suspends or prematurely terminates the study at an individual study site, the sponsor shall inform the responsible CA as appropriate and ensure that the EC is notified, either by the PI or by the sponsor. If the suspension or premature termination was in the interest of safety, the sponsor shall inform all other PIs.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, protocol compliance, data quality is addressed and satisfy the sponsor, EC and regulatory agency.

26. Data and Publication Policy

Publications and/or presentation of clinical investigation results will be coordinated and governed between Biosense Webster, Inc., the clinical investigation author(s) and if applicable local law. Authorship will be determined prior to development of any manuscript. All information concerning the study, investigational medical device, sponsor operations, patent application, manufacturing processes, and basic scientific data supplied by the sponsor to the investigator and not previously published, are considered confidential and remain the sole property of the sponsor.

27. Document Filing

A copy of all approved versions of the Investigation Protocol will be kept, by the site, in the Investigator Site File and in the Sponsor Trial Master File.

28. Scientific References

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29. Appendix 1

Definitions on (long term) effectiveness terms are mentioned below

Term	Definition
Recurrent AF/AT/AFL	Recurrent AF/AFL/AT is defined as AF/AFL/AT of at least 30 seconds' duration that is documented by an ECG or device recording system and occurs following catheter ablation. Recurrent AF/AFL/AT may occur within or following the post ablation blanking period. Recurrent AF/AFL/AT that occurs within the post-ablation blanking period is not considered a failure of AF ablation.
Early recurrence of AF/AFL/AT	Early recurrence of AF/AFL/AT is defined as a recurrence of atrial fibrillation within three months of ablation. Episodes of atrial tachycardia or atrial flutter should also be classified as a "recurrence." These are not counted toward the success rate if a blanking period is specified.
Recurrence of AF/AT/AFL	Recurrence of AF/AFL/AT postablation is defined as a recurrence of atrial fibrillation more than 3 months following AF ablation. Episodes of atrial tachycardia or atrial flutter should also be classified as a "recurrence." Electrocardiographical occurrences of new onset non left atrial arrhytmia's, if confirmed by entrainment maneuvers during electrophysiology testing, should not be considered an ablation failure or primary effectiveness endpoint. Examples are: • CTI dependant AFL. Cavotricuspid isthmus-dependent atrial flutter is easily treated with cavotricuspid isthmus ablation and is not an iatrogenic arrhythmia following a left atrial ablation procedure for AF. • Atrioventricular nodal reentry tachycardia (AVNRT)
Off AAD	As assessed from the end of the 3-month blanking period (Day 91 or Day of the visit whatever comes last) to 12 months following the ablation procedure. Class I and III antiarrhythmic drug therapy, same dose as before procedure is not considered as failure Class I and III antiarrhythmic drug therapy, higher dose or newly prescribed after procedure is considered as failure Class I and III antiarrhythmic drug therapy prescribed for other arrhythmia's than AF/AT/AFL is not considered as failure