Safety and Effectiveness Evaluation of the THERMOCOOL SMARTTOUCH™ SF Catheter with the TRUPULSE™ Generator for treatment of Paroxysmal Atrial Fibrillation (PAF)

SmartfIRE

Clinical Investigation Plan (CIP) Number: BWI202202

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.

Funded by: Biosense Webster, Inc., part of the Johnson & Johnson family of companies

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Eudamed number CIV-22-11-041528

History of Changes:

Version— Date	Description
V 1.0 —23SEP2022	Original Document
V 2.0 – 21Nov2022	Final Original Document for submission
V 2.1 – 05DEC2022	Minor Changes upon Belgian Competent Authority validation request
V 3.0 – 26JAN2023	Changes upon review Belgian and Danish Competent Authorities

The Biosense Webster THERMOCOOL SMARTTOUCH™ SF Bi-Directional Navigation Catheter (D-1348-05-SI-10) and TRUPULSE™ Generator (D-1417-01-IC) is for investigational device use only and is not commercially available anywhere in the world. THERMOCOOL SMARTTOUCH™ SF Bi-Directional Navigation Catheter and TRUPULSE™ Generator" are internal Biosense Webster project names and is not intended for any other external use. The final commercial or trade name of the investigational system (THERMOCOOL SMARTTOUCH™ SF Bi-Directional Navigation Catheter and TRUPULSE™ Generator) may be different.

1 Table of Contents

2 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
CEC	Clinical Events Committee
CF	Contact Force
CHF	Congestive Heart Failure
CIP	Clinical Investigation Plan
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatinine Phosphokinase
CRF	Case Report Form
CRO	Clinical Research Organization
CS	Coronary Sinus
CIR	Clinical Investigation Report
CT	Computed Tomography
CTI	Cavotricuspid Isthmus
CVA	Cerebrovascular Accident or Stroke
DD	Device Deficiency
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

Acronym/ Abbreviation	Expanded Term
FDA	Food and Drug Administration
Fr	French
FU	Follow-Up
GCP	Good Clinical Practices
GERD	Gastroesophageal Reflux Disease
HM	Holter Monitoring
HRS/EHRA/ECAS	Heart Rhythm Society / European Heart Rhythm Association / European Cardiac Arrhythmia Society
IB	Investigator Brochure
ICE	Intracardiac Echocardiography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instruction for Use
IRE	Irreversible Electroporation
ITD	Inter Tag Distance
ITT	Intention to Treat
LA	Left Atrium
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
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
NA	Neurological Assessment
NIHSS	National Institute of Health Stroke Scale
NYHA	New York Heart Association
PAF	Paroxysmal Atrial Fibrillation
PCI	Percutaneous Coronary Intervention
PFA	Pulsed Field Ablation
PF energy	Pulsed Electric Field Energy
PI	Principal Investigator
PN	Phrenic Nerve
PNP	Phrenic Nerve Paralysis
PP	Per Protocol
PPI	Proton Pump Inhibitors

Acronym/ Abbreviation	Expanded Term
PsAF	Persistent Atrial Fibrillation
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
RF	Radiofrequency
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
STSF	Thermocool Smarttouch Surroundflow
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

3 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 acknowledgment 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 Investigation 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 Investigation 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, core labs (if applicable) and Contract Research Organizations (if applicable). The definitive list shall be integrated into the clinical investigation report.

The current clinical investigation plan has been developed based on regulations applicable in Europe. For countries outside Europe, a country specific version of this clinical investigation plan may be developed, further defining regional regulations, if applicable.

4 Clinical Investigation Plan Summary

Full Title	Safety and Effectiveness Evaluation of the THERMOCOOL SMARTTOUCH™ SF Catheter with the TRUPULSE™ Generator for treatment of Paroxysmal Atrial Fibrillation (PAF)
Short Title	SmartfIRE
CIP Number	BWI202202
Eudamed number	CIV-22-11-041528
Sponsor	Biosense Webster, Inc.
Description of Investigational Devices	The Biosense Webster Pulsed Field (PF) /Radiofrequency (RF) Ablation System consists of the: - TRUPULSE™ Generator (D-1417-01-IC) - THERMOCOOL SMARTTOUCH™ SF (STSF) Catheter (D-1348-05-SI-10) - Related components and accessories [redacted]

	[redacted]
Premarket or Post market	Premarket
Study Design	Prospective, single arm, multi-center, pre-market clinical evaluation of the PF/RF ablation system (THERMOCOOL SMARTTOUCH™ SF (STSF) Catheter and TRUPULSE™ Generator) to demonstrate safety and effectiveness of the system for the treatment of Paroxysmal Atrial Fibrillation (PAF) comparing to corresponding performance goals. The study will enroll 135 subjects with drug refractory PAF who are candidates for atrial fibrillation ablation. Embedded within the main study will be a Neurological Assessment (NA) subset, a Cardiac Computed Tomography (CT) or Magnetic Resonance Angiogram (MRA) image subset, an Esophageal Endoscopy (EE) subset and a PVI durability subset in a prospective manner. These subsets are intended to delineate safety and assess lesion durability at 2-3 months following ablation. The same subjects will participate in all four (4) subsets. All subjects will be followed for 12 months and scheduled for evaluation at 7 days, 1-, 3-, 6- and 12-month following index ablation procedure.
Study Population	Patients scheduled to have a clinically indicated ablation procedure for the management of their drug refractory PAF.
Geographic areas to be included	Approximately 10 sites in Europe and potentially other regions.

Anticipated Study Timeline	Estimated 17-19 months total study duration: - Enrollment: Approximately 5-7 months - Primary endpoint evaluation: 3 months post procedure - Effectiveness evaluation: 12-months post procedure
Procedure(s) description	Subjects will arrive at 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 Left Atrium (LA) 2. Pulmonary Vein (PV) Isolation with PF/RF energy using the study device (THERMOCOOL SMARTTOUCH™ SF (STSF) Catheter and TRUPULSE™ Generator) 3. Confirmation of PV Isolation (entrance block) with adenosine/isoproterenol challenge 4. If necessary, treatment of acute reconnections with additional applications of PF/RF energy 5. Confirmation of entrance block of all targeted PVs at the end of procedure In this clinical investigation plan, PF modality is to be used as the primary mode for achieving PVI. Power controlled irrigated RF can be used for the anterior wall and ridge upon investigator discretion. All subjects will undergo PV ablation with the investigational device until PVI is achieved and isolation confirmed via entrance block. If PVI cannot be achieved with the investigational device, a commercial (RF) system can be used to complete the procedure. A right atrial Cavotricuspid Isthmus (CTI) linear ablation is allowed only in cases with documented typical atrial flutter (AFL) either prior to or during the index ablation procedure. The investigational system, the STSF catheter with the TRUPULSE™ Generator, should be used. If the CTI line cannot be achieved with the investigational system a commercially approved RF catheter and compatible commercially available RF generator should be used.
Major Objective	The major objective of this clinical investigation is to demonstrate safety and effectiveness of the ablation system (STSF Catheter and TRUPULSE™ Generator) when used for isolation of the atrial PVs in treatment of subjects with PAF. Safety and acute effectiveness will be evaluated through hypothesized primary endpoints and 12-month effectiveness will be evaluated through a hypothesized secondary endpoint.
Additional objectives	The additional objectives of this clinical investigation are to evaluate procedural data, quality of life and the incidence of (procedure and/or device related) serious adverse events during and after index ablation procedure up to 12 months.
Primary Hypothesized Endpoints	**Safety** Incidence of Primary Adverse Events (PAEs) (within seven (7) days of the index ablation procedure where the investigational STSF Catheter and TRUPULSE™ Generator are used per clinical investigation plan).

<table>
<tr><td></td><td>
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/Cerebrovascular Accident (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>Heart Block</td></tr>
<tr><td>Pulmonary Edema (Respiratory Insufficiency)</td><td>Vagal Nerve Injury/Gastroparesis</td></tr>
</table>
* Device or procedure related death, pulmonary vein stenosis and atrio-esophageal fistula that occur greater than one week (7 days) and less than or equal to 90 days post-procedure are considered and analyzed as PAEs.

Acute Effectiveness
Percentage of subjects with acute procedural success, defined as electrical isolation of clinically relevant targeted PVs (confirmed by entrance block) after adenosine/isoproterenol challenge at the end of the index ablation procedure. Use of a non-study device to achieve PVI is considered an acute procedural failure.
</td></tr>
<tr><td>Secondary Hypothesized Endpoint</td><td>
12-month Effectiveness
Freedom from documented (<u>symptomatic and asymptomatic</u>) atrial arrhythmia (Atrial Fibrillation (AF), Atrial Tachycardia (AT) or Atrial Flutter (AFL) of unknown origin*) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365) on or off antiarrhythmic therapy. Acute procedural failure (i.e., failure to achieve entrance block with the study device in any of the clinically relevant targeted PVs) will also be deemed a 12- month effectiveness failure.

*AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-lead electrocardiogram (ECG) or entrainment maneuvers in an EP study.
</td></tr>
<tr><td>Additional Effectiveness Endpoints</td><td>
• PVI Durability Rate
- Percentage of targeted PVs in the index ablation procedure being durably isolated as confirmed by the electroanatomical mapping 75 days (+/- 15 days) post index ablation procedure.
- Percentage of subjects with durably isolated targeted PVs, as confirmed by the electroanatomical mapping at 75 days (+/- 15 days) post index ablation procedure.
• Single Procedural Success: defined as freedom from documented symptomatic atrial arrhythmia (AF, AT or AFL of unknown origin*) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365) following a single index ablation procedure.
• Freedom from documented <u>symptomatic</u> atrial arrhythmia (AF, AT or AFL of unknown origin*) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness
</td></tr>
</table>

	evaluation period (Day 91-Day 365). Acute procedure failure will also be considered failure of 12-month symptomatic recurrence free endpoint. • **Freedom from documented <u>(symptomatic and asymptomatic)</u> atrial arrhythmia** (AF, AT or AFL of unknown origin*) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365) **<u>with extra failure modes</u>**. A subject who meets any of the following criteria will also be deemed an effectiveness failure: - Failure to achieve acute procedural success. - Taking a new Antiarrhythmic Drug (AAD) (Class I / Class III) for atrial tachyarrhythmia (AF, AT or AFL of unknown origin*) or taking a previously failed Class I/III AAD at a greater than the highest ineffective historical dose for AF/AFL/AT during the effectiveness evaluation period (Day of 3-month visit – Day 365). - Greater than 1 repeat ablation for AF/AT or AFL of unknown origin in the blanking period or any repeat ablation for AF/AT or AFL of unknown origin* during the effectiveness evaluation period. • **Use of a non-study device for** the purpose of - PVI (i.e., touch-up) among all clinically relevant targeted PVs and by subject - Ablation of left atrial non-PV AF targets (i.e., posterior wall) during index ablation procedure or for repeat procedures during blanking period. • **Acute reconnection** identified by adenosine/isoproterenol challenge among all clinically relevant targeted PVs and by subject • **Repeat ablation procedures** for left atrial arrhythmia (AF, AT or AFL of unknown origin*) within the 12-month FU period - Percentage of subjects with repeat ablation during blanking period (≤90 days post index ablation procedure) - Percentage of subjects with repeat ablation after blanking period (Day 91 - 365 post index ablation procedure) - Percentage PV reconnection observed during repeat ablation procedures by targeted PVs treated at index ablation procedure and by subject - Percentage of subjects with repeat ablations due to non- PV targets • **Quality of Life (QoL**): the change of QoL assessed by comparing the Atrial Fibrillation Effect on Quality-of-Life (AFEQT™) scores before and at 3, 6 and 12- months after the ablation procedure. • **Hospitalization for cardiovascular events** through 12 months follow-up compared to 12 months prior to baseline. **AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-lead electrocardiogram (ECG) or entrainment maneuvers in an EP study.*
Additional Safety Endpoints	**Safety** - Incidence of Serious Adverse Device Effects (SADEs) - Incidence of Unanticipated (Serious) Adverse Device Effects (UADEs and USADEs)

	- Incidence of Serious Adverse Events (SAEs) within 7 days (early-onset), 8 to 30 days (peri-procedural) and >30 days (late onset) of index ablation procedure - Incidence of non-serious adverse events (non-SAEs) **Neurological Assessment Subset** - Occurrence, anatomical location and size of new post-ablation asymptomatic and symptomatic cerebral emboli observed post-ablation as determined by Magnetic Resonance Imaging (MRI) evaluations - Incidence of new or worsening neurological deficits post-ablation and at follow-up, compared to baseline - 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 Subset** - Occurrence of PV stenosis up to 3 months post-ablation as determined by Computed Tomography (CT)/ Magnetic Resonance Angiogram (MRA) evaluations. **Esophageal Endoscopy Subset** - Occurrence of endoscopically detected esophageal thermal lesions in the region of the contact area between esophagus and LA as determined by post procedure endoscopy.
Additional Procedural Endpoints	**Procedural data, including but not limited to** - Total procedure time, PVI time, PF/RF application time and mapping time. - Number of PF/RF applications by left and right PV and by subject - Total fluoroscopy time - Total study catheter left atrial dwell time - Ablation settings used - Use of paralytics and type of anesthesia
Sample Size and Power Calculation	**Primary Safety Endpoint:** Based on a performance goal of 12% and assuming an anticipated primary safety event rate of 5% for the primary safety endpoint, a sample size of 135 subjects (with 5% missing data due to attrition) will provide above 80% power to reject the null hypothesis for the primary safety hypothesis test using a one-sided exact binominal test. The target significant level is 0.025. **Primary Effectiveness Endpoint:** Based on a performance goal of 90% and assuming an anticipated failure-free rate of 97% for the primary effectiveness endpoint, a sample size of 100 subjects will provide above 80% power to reject the null hypothesis for the primary effectiveness hypothesis test using a one-sided exact binominal test. The target significant level is 0.025.

	Secondary Effectiveness Endpoint: Based on a performance goal of 50% and assuming an anticipated failure-free rate of 65% for the secondary effectiveness endpoint, a sample size of 100 subjects (with 10% missing data due to attrition) will provide above 80% power to reject the null hypothesis for the secondary effectiveness hypothesis test using a one-sided exact binominal test. The target significant level is 0.025. **Total Sample size:** A total of 135 evaluable subjects will be included in the study. Each of the four (4) subsets (NA, CT/MRA, EE and PVI durability) will consist of 30 subjects and will be integrated within the main study.
Inclusion Criteria	1. Diagnosed with Symptomatic Paroxysmal AF defined as AF that terminates spontaneously or with intervention within 7 days of onset. This PAF is considered to be symptomatic if symptoms related to AF are experienced by the patient. 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. Previously known AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause (e.g., documented obstructive sleep apnea, acute alcohol toxicity, morbid obesity (Body Mass Index >40 kg/m²), renal insufficiency (with an estimated creatinine clearance < 30 mL/min/1.73 m2), …). 2. Previous LA ablation or surgery 3. Patients known to require ablation outside the PV region (e.g., 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 Left Ventricular Ejection Fraction (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 Percutaneous Coronary Intervention (PCI) / Myocardial Infarction (MI) within the past 2 months

	12. Previous 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. Prior diagnosis of pulmonary vein stenosis 18. Pre-existing hemi diaphragmatic paralysis 19. Acute illness, active systemic infection, or sepsis 20. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation. 21. Severe mitral regurgitation 22. Presence of implanted pacemaker or Implantable Cardioverter-Defibrillator (ICD) or other implanted metal cardiac device that may interfere with the pulsed electric field energy. 23. Presence of a condition that precludes vascular access (such as inferior vena cava (IVC) filter). 24. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this study 25. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being 26. Current enrollment in an investigational study evaluating another device or drug. 27. 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. 28. Life expectancy less than 12 months 29. Presenting contra-indications for the devices used in the study, as indicated in the respective Instructions For Use (IFU) Additional exclusion criteria for Neurological Assessment (NA) subjects: 30. Contraindication for MRI such as use of contrast agents due to advanced renal disease, claustrophobia etc. (at PI discretion) 31. Presence of iron-containing metal fragments in the body 32. Unresolved pre-existing neurological deficit. Additional exclusion criteria for Esophageal Endoscopy (EE) subjects: 33. Uncontrolled significant Gastroesophageal Reflux Disease (GERD)
Statistical Analysis	**Primary Safety Endpoint:** The primary adverse event rate will be compared to a pre-specified threshold of 12% with an assumed true PAE composite rate of 5%.

	H_0: $P_S \geq 0.12$ vs. H_A: $P_S < 0.12$, where P_S denotes the rate of primary adverse event An exact binomial test of comparing PAE rate against the performance goal of 12% will be performed in the modified Intent To Treat (mITT) analysis set. **Primary Effectiveness Endpoint:** The primary effectiveness rate of confirmation of entrance block of all targeted PVs at the end of the index ablation procedure will be compared to a pre-specified threshold of 90% with an assumed true acute effectiveness rate of 97%. H_0: $P_E \leq 0.90$ vs. H_A: $P_E > 0.90$, where P_E denotes the rate of acute effectiveness success An exact binomial test for comparing acute effectiveness success against the performance goal of 90% will be performed in the Per Protocol (PP) analysis set. **Secondary Effectiveness Endpoint:** The rate of effectiveness success at 12 months, will be compared to a pre-specified threshold of 50% with an assumed true effectiveness rate of 65%. H_0: $P_1 \leq 0.50$ vs. H_A: $P_1 > 0.50$, where P_1 denotes the rate of secondary effectiveness success An exact binomial test of comparing 12-month effectiveness success against the performance goal of 50% will be performed in the PP analysis set. If the study success is met for both primary endpoints, then the secondary hypothesis for comparing the 12-month effectiveness success rate against the performance goal of 50% (with anticipated recurrence-free rate of 65%) will be tested.
Primary Endpoint Analysis	A primary endpoint analysis will be performed when all subjects completed their 3-month follow-up. This primary endpoint analysis report will be part of the CE mark application dossier.
Independent Committees/Reviewers	A Data Monitoring Committee (DMC) and Clinical Events Committee (CEC) will be established for this study - DMC will assess clinical safety data on regular intervals and make recommendations on study adaptations. - CEC will adjudicate primary safety endpoint events. Independent Core Laboratories will conduct objective evaluations of remote arrhythmia monitoring and ECG tracings for presence of atrial arrhythmia and will perform an independent analysis of collected images (Cerebral MRI, Endoscopy, CT/MRA) for evaluation of safety.

Time and Events Schedule	See Table 1 below

Table 1: Subject Treatment and Follow-up Schedule

Assessments[22]	**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	●	●	●[6]	●	●	●	●	●[21]
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]	●	●		●	●	●	●	●[21]
Atrial Arrhythmia monitoring (Remote)[7]				●	●	●	●	●[21]
Atrial Arrhythmia monitoring (24-hour Holter)[8]					●	●	●	●[21]
Repeat ablations[9]			●	●	●	●	●	●[21]
Concomitant Medication[10]	●	●	●	●	●	●	●	●[21]
Device Deficiencies		●						
Adverse Events[11]	●	●	●	●	●	●	●	●[21]
AFEQT[12]	●				●	●	●	
Cardiac CT/MRA[13]	●				●[13]			
PV Durability Subset								
3D Electro anatomical mapping[14]	●				●[14]			
Endoscopy Subset								
Endoscopy		●[15]						
Neurological Subset								
Cerebral MRI[16]	●[18]	●[19]		●[20]	●[20]	●[20]	●[20]	●[21]
Neurological Exam[17]	●[18]	●[19]		●[20]	●[20]	●[20]	●[20]	●[21]
NIH Stroke Scale[12]	●[18]	●[19]		●[20]	●[20]	●[20]	●[20]	●[21]
mRS	●[18]			●	●[20]	●[20]	●[20]	●[21]
MMSE[12]	●[18]			●	●[20]	●[20]	●[20]	●[21]

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, CHA2DS2 VASc Score 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 ablation 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. Data from 12-lead ECG recordings will be collected (For pre-procedure, can be performed before ICF signature)
7. Arrhythmia monitoring via remote monitoring once per week as from 1-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 ablation procedure will be collected
10. Concomitant medication: only cardiac (i.e., anti-arrhythmia drugs, anticoagulation regimen) & index ablation procedure related (i.e., adenosine, anticoagulation (i.e., heparin, pain medication)

11. AEs must be collected from the time the subject signs the informed consent onward.
12. Patient questionnaires will only be used in countries with validated languages.
13. For all subjects: CT/MRA to be completed within 6 months prior to the index ablation procedure. Post procedure: for CT/MRA subset to be repeated at 3M FU, for all subjects CT/MRA to be repeated post procedure in case subject presents with PV stenosis symptoms.
14. For PV Durability subset: an electro anatomical map, activation and voltage re-map is to be performed pre and post procedure and to be repeated at 75 days post procedure (+/- 15 days).
15. For Endoscopy subset: Endoscopy preferable between 1 day to 3 days (72hours) post procedure. For procedures on Friday a window of a maximum of 96 hours is justified.
16. 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.
17. 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.
18. To be completed within 72-hours pre-procedure. For procedures on Monday a window of a maximum of 96 hours is justified.
19. To be completed within 72-hours post-procedure. For procedures on Friday a window of a maximum of 96 hours is justified.
20. Full neurological follow-up to be undertaken if neurologic symptoms and/or cerebral ischemic lesions identified in a prior evaluation.
21. If subject returns for a potential study related cardiovascular or neurological visit outside of the CIP-defined visit schedule as deemed required per investigators discretion.
22. Assessments should not be repeated for the study if already done per standard of care within CIP defined time limits.

5 Background Information and Scientific Rationale

5.1 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. 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 2020 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."[1, 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]

The Biosense Webster THERMOCOOL SMARTTOUCH™ SF catheters provide real-time measurement of contact force (CF) between the catheter tip and heart wall, as well as location information, when used with CARTO™ 3 Navigation System and have been associated with increased acute and long-term procedural success in the paroxysmal AF population. Multiple studies have shown that a CF-guided ablation protocol aiming to enclose the veins with stable, contiguous and optimized RF lesions is associated with a high incidence of successful PVI, high single-procedure arrhythmia-free survival at 1 year, marked reduction in arrhythmia burden, and a high likelihood of finding four isolated veins at repeat ablation.[13, 14]

Most of the catheter ablation systems are thermal energy-based and use either heat or cold energy to destroy arrhythmogenic tissues. The ablation has been connected with arrhythmia recurrences due to incomplete lesion creation. It is also associated with severe complications such as pulmonary vein (PV) stenosis, phrenic nerve damage, coronary artery damage, atrio-esophageal fistula, steam pop, cardiac perforation and pericardial tamponade.[3, 15, 16]

In the past decades, extensive research on alternative energy forms for ablation has been conducted to improve ablation efficiencies and reduce ablation-related complications. One of the new technologies for lesion creation is based on electroporation by pulsed field (PF) ablation. Electroporation is a process in which an electric field is applied to the cell/tissue for a short period of time that results in pore formation in the cell membrane and a subsequent increase in cell permeability.[17] The electric field strength and duration could cause reversible or irreversible permeabilizations.[18] At low electric field strength and a short duration, the cell membrane forms nanosized pores, allowing small or medium sized molecules, such as drug and DNA, flow across the lipid bilayer. The pore formation is transient and reversible. The affected cells are able to survive from this reversible electroporation. At medium electric field strengths, the density of pore formation in the membrane increases to a certain level such that the process becomes irreversible. Free flows of water and ions in and out of the cell membrane result in the loss of cellular homeostasis, ultimately triggering cell apoptosis.

This irreversible aspect of the process is thus called “irreversible electroporation” or IRE.[15, 17] Finally, at high electric field strengths, the cell membrane quickly undergoes fragmentation resulting in necrotic cell death.[17]

The PFA system generally consists of an electric field generator and electric current applicators. The electric field required for IRE can be delivered by applying a high voltage or direct current (DC) across electrodes in contact with cardiac tissues.[17] Different kinds of electric currents, such as DC, alternate current (AC), pulsed DC, or a combination of these were used to generate the electric field for IRE in preclinical and clinical studies.[19] Pulsed DC was the most commonly used energy source in preclinical and clinical studies.[20, 21] Early studies found that the strength of the electric field delivered by pulsed DC is dictated by pulse shape, pulse duration, pulse height, pulse polarity, pulse interval, number of pulses per application or pulse train, number of pulse trains delivered, and interval between pulse train deliveries.[17, 18, 22]

The influence of PF energy 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.[23] The IRE effect on the phrenic nerve has been described to be recoverable , suggesting that permanent damage can be avoided with IRE.[24-27] A 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.[28]

A previous study with a lattice-tip catheter using combined RF/PF ablation showed the benefit of using PFA on the atrial myocardium without damage to adjacent structures.[29] In addition, the use of a focal PFA catheter was published to treat CTI and linear ablations in PAF and PsAF patients. Lesions were found to be durable.[30, 31] No safety concerns were outed[29]. However, transient coronary spasm was reported as a possible consequence of ablation of mitral isthmus line.[32, 33]

5.2 Previous Experience with the STSF Catheter

5.2.1 Pre-Clinical Experience with the STSF Catheter and TRUPULSE™ Generator

Bench and animal testing was performed using the THERMOCOOL SMARTTOUCH™ SF Bi-Directional Catheter and TRUPULSE™ generator. The animal testing validates the use of the STSF Catheter and TRUPULSE™ Generator at the targeted ablation locations, including CTI ablation line and met the acceptance criteria of safety and efficacy assessment. Refer to the Investigator Brochure (IB) for detailed description and outcomes of the testing performed.

5.2.2 Previous Clinical Evaluations with STSF catheter

The THERMOCOOL SMARTTOUCH™ SF Bi-Directional Catheters were placed on the EU market under Medical Device Directive (93/42/EEC) on April 12, 2010. The catheter received CE mark authorization under Medical Device Regulation (2017/745) on May 1, 2022. Since CE mark certification additional data has been published on the STSF catheters via post-market clinical follow-up studies. The SMART-SF[34, 35], PRECEPT[36], VISTAX[13] and SURPOINT[37] study provided supportive evidence on the safety and performance of the THERMOCOOL SMARTTOUCH™ SF catheter over defined device lifetime. The clinical literature data supports the safety and performance of the THERMOCOOL SMARTTOUCH™ SF catheters when used as intended to facilitate electrophysiological mapping of the heart and to transmit RF energy to the catheter tip electrode for ablation purposes.

5.2.3 Previous Clinical Evaluations with a similar Generator

Pulsed Field Ablation (PFA) System for the Treatment of Paroxysmal Atrial Fibrillation (PAF) by Irreversible Electroporation (IRE), the InspIRE clinical study (BWI2019_08)

The 'inspIRE' clinical study (NCT04524364, CIV-20-04-032584) is a pre-market, prospective, multicenter, single arm clinical evaluation utilizing the BWI Circular IRE Catheter and Multi-Channel IRE Generator. The study is conducted in Europe and Canada. The objective of the study is to demonstrate safety and long-term effectiveness of the IRE system (Circular IRE Catheter and IRE Generator) in the isolation of the atrial pulmonary veins in treatment of subjects with PAF. The inspIRE study consists of two sequential waves; WAVE I, the safety characterization phase, with intention to delineate safety and provide preliminary estimates for safety and acute effectiveness of the IRE system, enrolled 45 subjects between August 2020 and April 2021. Purpose of the WAVE II phase was to evaluate safety and long-term effectiveness. The sample size of WAVE II was determined based on accruing data and a successful interim analysis was performed in May 2022. A total of 227 subjects were enrolled between March 2021 and May 2022 and currently subjects are still in follow-up. Acute procedural success, defined as confirmation of entrance block in all clinically relevant targeted pulmonary veins after adenosine/isoproterenol challenge without use of a non-study catheter to achieve PVI, was achieved in all subjects treated with the study catheter. No primary adverse events including, atrio-esophageal fistula, phrenic nerve paralysis, cardiac tamponade/perforation, pulmonary vein stenosis, device or procedure- related death, or stroke/CVA have been reported in the study.

Assessment of Safety and Effectiveness in Treatment Management of Atrial Fibrillation with the BWI IRE Ablation System, the admIRE clinical study (BW2019_10).

The 'admIRE' clinical study (NCT05293639) is a prospective, non-randomized, multi-center, clinical evaluation of the BWI IRE Ablation System to demonstrate safety and long- term effectiveness for the treatment of drug refractory symptomatic paroxysmal atrial fibrillation. This study is conducted in the United States. The BWI IRE Ablation System consists of the VARIPULSE™ Bi-Directional catheter and TRUPULSE™ Generator. In conjunction with CARTO™ 3 system it is indicated for PVI of patients with drug refractory paroxysmal atrial fibrillation. Enrollment commenced on 20th April 2022 in the United States and was completed on 15th November 2022.

A summary of previous clinical investigations with similar devices are listed in Appendix 1.

5.3 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 Expert Consensus[38] 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[39-42] 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 12-month 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 Expert Consensus Statement[38] 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[39], Heartlight[40, 43], TOCCASTAR[41], ZERO-AF[44], and SMART-AF[42]. 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. This clinical investigation is intended to characterize safety and effectiveness of the investigational devices in scope. The study is not designed to include a comparator/control group since it is not intended to prove superiority.

5.4 Potential Risk and Benefit

The overall risks posed by use of the STSF Catheter, with the TRUPULSE™ 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 and are mentioned below. The STSF Catheter IFU and TRUPULSE™ User Manual warn users of all potential risks associated with the use of RF and PF energy, list all contraindications (i.e., myxoma, prosthetic valves, history of myocardial infarction, implanted (metal) device, active systemic infection, pregnancy), and provides the user with precautionary measures when using the devices for general risk mitigation. Additional specific mitigations are described with the associated risk below.

5.4.1 Known Potential Risks and Mitigation

Pericarditis: According to HRS guidelines 2017, the incidence of pericarditis incidence varies from 0%-50% as a complication of AF 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 invasive intervention.[3] The risk for pericarditis will be further minimized by the use of PF energy, which is minimal thermal.

Phrenic Nerve Palsy (PNP): Although injury to the Phrenic Nerve (PN) is rare for RF (<1%) and not expected with the PF energy provided, stimulation of the phrenic nerve that resolves acutely has been noted in the literature.[24] 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] Additionally, no new ablations should be delivered on or near the PN if evidence of PN impairment is observed and the catheter should be repositioned.

Atrio-Esophageal Fistula (AEF): AEF is a rare (0.02%-0.11%)[38] 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 is associated with a high mortality rate.[45] 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 PF energy is non-thermal, AEF is not an expected outcome and has not been reported in literature to date .[28, 46] Per CIP , PF energy is recommended on the posterior wall. Many investigators attempt to mitigate esophageal damage by monitoring endoluminal temperature during the ablation procedure.

Gastric Hypomotility and Periesophageal Vagal Nerve Injury: Injury to the vagal anterior esophageal plexus can occur with traditional thermal energy such as RF energy being applied to the posterior wall of the LA, which can cause acute pyloric spasm and gastric hypomotility. Vagal injury is unlikely with PF ablation and has not been reported in published data to date. To prevent the risk for vagal nerve injury, PF energy is recommended in the posterior wall per CIP workflow.

Pulmonary vein stenosis: Pulmonary vein stenosis (PVS) is a well-known complication of thermal catheter ablation of atrial fibrillation. In RF procedures, the risk of PV stenosis is small (<1%)[38]. The risk of pulmonary stenosis associated with a pulsed field energy ablation procedure is expected to be unlikely and to date has not been reported following pulsed field applications. PVS can be prevented by delivering energy outside the pulmonary vein ostium and by using a wide circumferential technique.

Thrombus formation: The incidence of thromboembolism associated with AF ablation is reported to be between 0% and 7%[38]. Thrombus generated during the ablation procedure may pose a serious and even life-threatening risk to the patient. Embolization of thrombus could produce stroke, Myocardial Infarction (MI), or other ischemic injury. The possible embolic sources include thrombus formation on the ablation catheter tip and sheath, debris from steam pop and charring, preexisting thrombus in the heart and air embolus. Thrombus could form due to temperature / impedance rise at the catheter-tissue region, insufficient level of anti-coagulation or lack of irrigation. The study catheter is irrigated and irrigation settings per the catheter's Instructions for Use should be maintained throughout the procedure. The CIP describes the pre-, peri- and -post procedural anticoagulation regimen to be followed. Imaging on the LA prior to the procedure to check on existing thrombus is a mandatory assessment in this CIP. These measurements in the CIP workflow should minimize the risk for thrombus formation.

Cardiac perforation/ Pericardial effusion/ Cardiac tamponade: Cardiac perforation may result from catheter manipulation or prolonged application of energy (risk is <1% for RF ablation and unknown for PF energy). Cardiac perforation may result in pericardial effusion or cardiac tamponade which requires percutaneous pericardial drainage or surgical repair.[3] Cardiac tamponade is a known complication of AF ablation and has a reported incidence of 0.2%-5%[38]. The occurrence of cardiac tamponade with PF technology is unknown. Physicians will be instructed to manipulate the catheter carefully in order to avoid cardiac damage (such as mitral valve incompetence, valve injury), perforation or tamponade. In addition, the amount of power and force at any one location should be limited.

Cerebral ischemic lesions: An Asymptomatic Cerebral Emboli (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 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 pulsed field ablation, leads to an unknown level of risk of ACE.[47] According to HRS guidelines, 2017, incidence of ACE is expected in 2%-15% as a complication to AF ablation.[3, 38] However, literature on asymptomatic cerebral lesions after existing ablation modalities for AF (RF, Cryo) reports large variations between publications with rates that range from 2-40%.[3, 48-55] Recent publications on detection of asymptomatic brain lesions when using PF energy for AF ablation show a similar trend and present rates from 3-40%.[56-59] With either energy modality, 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. To minimize the risk of air introduction, investigators will be trained on proper sheath handling, including removing air bubbles prior to insertion and will be instructed to minimize catheter exchange during the procedure.

Coronary Artery Spasm: Limited clinical data publications raised the potential for complication of coronary arterial spasm during ablation near the coronary arteries.[32, 60, 61] Coronary artery spasm may lead to coronary artery stenosis/occlusion, heart attack (ventricular tachycardia) and or chest pain.[3, 33, 60, 62] Energy application near the coronary arteries should be avoided to prevent coronary spasm. Per CIP, nitroglycerin (1-2mg) should be prepared when ablating near the coronary arteries. Administration of nitroglycerin, intravenous or intracoronary has been shown to be highly effective in attenuating the vasospasm.

Heart block: The application of RF or PF energy close to the atrioventricular (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. As per Instructions for Use, PF energy should not be used in close proximity to the AV node and extreme caution should be taken when delivering RF/PF energy in close proximity to the normal conduction system. The physician will be trained to closely monitor AV conduction during energy delivery and immediately terminate energy delivery if partial or complete AV block is observed, which will mitigate the risk for heart block.

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] The risk of vascular access complication can be minimized by using a compatible sheath, vascular access techniques, ultrasound-guided access and appropriate anticoagulation management.

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%).[63-65] The use of X-ray during the study procedure should be minimized or eliminated.

Infection: The percutaneous procedure carries risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%).[66, 67] Risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.[3]

Allergic, Anaphylactic and Toxic 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%).[65, 68-72] If an allergic reaction occurs, typical standard of care precautions should be taken. The product (s) should not be used where the packaging has been compromised, or already used, or reprocessed.

Ventricular Tachycardia, **Ventricular Fibrillation or other arrythmia**: The literature suggests that in some instances PF energy could induce ventricular tachycardia, ventricular fibrillation (ventricular rate usually >300 bpm), or another arrythmia induced by vagal response.[73-76] Vagal responses (VRs) such as brady cardia, sinus arrest, and atrioventricular block frequently occur, and are known to happen (0.1%-0.4%) with both RF and PF technologies.[30, 77, 78] Vagal responses may be associated with simultaneous modification of intrinsic cardiac autonomic nervous system expression. Extreme vagal response resulting in prolonged asystole should be treated using clinical standards of care. Risk for ventricular tachycardia has been minimized by the design of the catheter and generator, which uses unipolar energy with very short duration of pulses. Care should be taken to thoroughly monitor the patient's ECG recordings throughout the procedure. Physicians will be instructed to be extra cautious when ablating near other anatomical structures such as ganglia.

Muscular Nerve Injury: Pulse field ablations have been associated with muscular contraction in the literature.[79, 80] These contractions can cause acute or post procedural patient discomfort. Patient comfort should be maintained through proper administration of pharmaceuticals and through local pain management standards of care.

Hypervolemia/Fluid Overload: The STSF Catheter is an irrigated catheter. Excessive use of irrigation could cause hemodynamic imbalance. The risk of hypervolemia will be mitigated when irrigation settings are used per its instructions for use.

Risk due to Arcing: The hazard of arcing[81] 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. The likelihood for arcing has been mitigated by the specific design of the study devices. To further prevent the associated risks from arcing, do not operate the device in patients with metal cardiac implants or having metal in the same cardiac chamber with the ablation catheter.

Pulmonary injury: Pulmonary injuries, such as pneumothorax, may be caused by thermal injury during traditional RF ablation.[82] As PF is a minimally thermal modality, this injury is not expected to occur. However, to keep the risk of pulmonary injuries low, energy delivery should be halted after ECG signals have been sufficiently attenuated.[3]

In addition to the information in the IFU/UM and specific mitigation strategies for above mentioned potential risks, the criteria for subject selection, methods, personnel, facilities and training of the physicians are intended to minimize the risks to subjects undergoing this procedure.

Appropriate measures have been outlined in this **study 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.

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 8.2 for the Exclusion Criteria).[83]

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 17.1.1).

Post-procedural management: In accordance with the 2020 ESC AF Management Guidelines[84], all subjects will be recommended to be maintained on systemic oral anticoagulation therapy for at least two months 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 14) for more information on safety management.

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

5.4.2 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 cardiac ablation of AF is an improvement in QoL resulting from the elimination of arrhythmia-related symptoms such as palpitations, fatigue, or effort intolerance.[3]

Published animal and human studies demonstrate the potential for PF to be a safe and efficacious way to deliver energy for ablation via a non-thermal ablative modality.[47, 85] Influence on adjacent structures has been previously studied. The additional benefit of tissue selectivity of PF energy reduces the risk of collateral tissue injury[47] Of the well described complications in RF ablation techniques, the tissue specificity of IRE has been considered as a major advantage.[23]

The TRUPULSE™ generator provides a novel approach for the treatment of cardiac arrythmias by using radiofrequency (RF) or pulsed field (PF) energy to produce targeted intracardiac lesions and achieve the intended therapeutic effect. The novel investigational device system is intended to treat atrial fibrillation with the theoretical potential while minimizing thermal collateral damage.

The commercial THERMOCOOL SMARTTOUCH SF™ catheter has been shown to be safe and effective for electrophysiological mapping and treating structures in the heart by obtaining electrograms, providing location information, and delivering RF energy during cardiac ablation procedures. As STSF is an established commercialized single tip catheter, it will apply no operator learning curve. The catheter has force-sensing technology that provides a real-time measurement of contact force (CF) between the catheter tip and the heart. CF sensing technology include feedback to the user on tissue contact to prevent inappropriate energy applications and enhances efficient lesion formation.[42, 86] Additional benefit of confirmed tissue contact includes efficient creation of 3D anatomical maps with CARTO™ system and may translate to reduction of mapping fluoroscopy and procedure time. Irrigation of the RF catheter tip has been found to effectively reduce temperature at ablation sites and associated adverse events (e.g., thrombus, steam pop), there is a risk of volume overload from high volumes of perfused saline. The “surround flow” technology of the THERMOCOOL SMARTTOUCH® SF catheters allow a reduction in intraprocedural saline perfusion as well as in procedure time.[87-91]

Further reference can be made to the Risk Management Documentation for more information.

6 Objectives and Purpose

6.1 Objective

The primary objective of this clinical investigation is to demonstrate safety and effectiveness of the STSF Catheter when used in conjunction with the TRUPULSE™ Generator for Pulmonary Vein Isolation (PVI) in the treatment of subjects with Paroxysmal Atrial Fibrillation (PAF).
Specifically:

- To demonstrate safety based on early-onset Primary Adverse Events (PAEs) (within 7 days following the ablation procedure).
- To demonstrate 12-month effectiveness based on the 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).

Safety and acute effectiveness will be evaluated through hypothesized primary endpoints and long-term (12M) effectiveness will be evaluated through a hypothesized secondary endpoint. The results of this study provide evidence to support CE-mark registration of these devices.

6.2 Additional Objective

The additional objectives of this study are to evaluate procedural data, quality of life and the incidence of (procedure and/or device related) serious adverse events during and after procedure up to 12 months.

7 Study design and Endpoints

7.1 Description of the Study Design

The study will be carried out as an interventional, prospective, multicenter, single-arm safety and effectiveness evaluation using the THERMOCOOL SMARTTOUCH™ SF (STSF) catheter in conjunction with the TRUPULSE™ Generator.

The study will enroll subjects with drug refractory, symptomatic PAF who are candidates for catheter ablation. Subjects who sign the Informed Consent Form (ICF) and who meet all eligibility criteria will be enrolled and treated with the STSF Catheter and the TRUPULSE™ Generator. A maximum sample size of 135 evaluable subjects is planned in the study. To ensure generalizability of study results, no more than 25% of the total enrollment in the study will be allowed at a single site. All study subjects will be followed-up for 12 months after study procedure.

For the purpose of characterization of safety and to provide an assessment of lesion durability of the investigational ablation system four (4) subsets will be embedded in the study; the Neurological Assessment (NA), a Cardiac Computed Tomography (CT) or Magnetic Resonance Angiogram (MRA) imaging (CT/MRA), an Esophageal Endoscopy evaluation (EE) and a PVI durability subset in a prospective manner. Each subset will consist of 30 subjects, who will undergo the index ablation procedure and additional neurological, PV, esophageal and PVI durability assessments. The same subjects will participate in all four (4) subsets.

All 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).

Planned statistical analyses of the endpoints and analysis populations are described in the Statistical Analysis section (section 19) of this clinical investigational plan and in the Statistical Analysis Plan (SAP).

7.2 Study Subsets

7.2.1 Neurological Assessment (NA) subset

A focused neuropathological evaluation will be integrated within the study. This subset of subjects will represent the neurological assessment (NA) subgroup. Subjects will be assessed for incidences of post-ablation cerebral emboli with either an absence (asymptomatic) or presence (symptomatic) of neurological symptoms. Specifically, an asymptomatic cerebral embolism 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. The presence (symptomatic) or absence (asymptomatic) of neurological symptoms will be determined by the site neurologist of the participating hospitals. The Cerebral MRI data will be analyzed by an independent Core Laboratory.

A total of 30 subjects will be prospectively included in this subset at sites with accessible MRI capabilities and a certified neurologist available to participate in the study. All subjects enrolled in the NA subset will meet all inclusion and exclusion criteria, including the additional exclusion criteria specific for the NA subset.

NA subset subjects will, in addition to the general follow-up schedule, undergo additional assessments including, 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.

7.2.2 Esophageal Endoscopy (EE) Subset

A subset of study subjects will be enrolled in the EE subgroup and will, in addition to the general follow-up schedule, undergo an esophageal endoscopy within 1 to 3 days post ablation procedure to assess the presence of endoscopically detected thermal esophageal lesions (EDEL) in the region of the contact area between esophagus and LA. The presence or absence of EDEL post ablation will be determined by independent gastroenterologists of the Core Laboratory.

These 30 subjects will be prospectively included by sites with accessible endoscopy capabilities and a certified gastroenterologist available to participate in the study. All subjects who are enrolled in the EE subset will meet all inclusion and exclusion criteria, including the additional exclusion criteria specific for the EE subset.

7.2.3 Cardiac CT/MRA subset

An additional subset of study subjects will be enrolled in the cardiac CT/MRA subset and undergo a 3-month CT/MRA in addition to the baseline CT/MRA (all subjects will have a baseline CT/MRA) to assess incidence of post-ablation PV stenosis. A total of 30 subjects will be included in the CT/MRA subset at sites that have the appropriate equipment for CT/MRA imaging.

In addition to this subset, any subjects with signs or symptoms of PV stenosis will undergo a post ablation CT/MRA. These subjects will not be included in the CT/MRA subset analysis. If severe PV stenosis is present, it will be reported as adverse event. The CT/MRA data will be analyzed for PV stenosis by an independent Core Laboratory.

7.2.4 PVI Durability Subset

A subset of 30 study subjects will be enrolled in the PVI Durability subset and will, in addition to the index ablation procedure and general follow up schedule, undergo an electro-anatomical re-map procedure at 75 days (+/- 15days) post index ablation procedure. The re-map is intended to evaluate the durability of the pulmonary vein isolation generated at the index ablation procedure. The assessment of lesion durability will be done by the ablating physician at the participating sites.

7.3 Study Endpoints

7.3.1 Primary Hypothesized Endpoints

Safety

The primary safety endpoint is the incidence of Primary Adverse Events (PAEs) (within seven (7) days of the index ablation procedure where the investigational STSF catheter and TRUPULSE™ generator are used per clinical investigation plan).

PAEs include the following Adverse Events (AEs):

Atrio-Esophageal Fistula*	Phrenic Nerve Paralysis (permanent)
Cardiac Tamponade/perforation	Pulmonary Vein Stenosis*
Device or procedure related death*	Stroke/Cerebrovascular Accident (CVA)
Major Vascular Access Complication/Bleeding	Thromboembolism
Myocardial Infarction	Transient Ischemic Attack (TIA)
Pericarditis	Heart Block
Pulmonary Edema (Respiratory Insufficiency)	Vagal Nerve injury/Gastroparesis

**Device or procedure related death, pulmonary vein stenosis and atrio-esophageal fistula that occur greater than one week (7 days) and less than or equal to 90 days post-procedure are considered and analyzed as PAEs.*

Acute Effectiveness:

Percentage of subjects with acute procedural success, defined as electrical isolation of clinically relevant targeted PVs (confirmed by entrance block) after adenosine/isoproterenol challenge at the end of the index ablation procedure. Use of a non-study device to achieve PVI is considered an acute procedural failure.

NOTE: Subjects who have the study catheter inserted but do not undergo ablation due to Study Device (SMARTTOUCH™ SF (STSF) and TRUPULSE™ Generator) related reasons will be considered acute effectiveness failures; subjects who are discontinued due to Non-Study Device related reasons (e.g., pump, other equipment or anatomy that precludes treatment with THERMOCOOL SMARTTOUCH™ SF (STSF) Catheter and TRUPULSE™ Generator or a commercially available device) will not be considered as acute effectiveness failures.

7.3.2 Secondary Hypothesized Endpoints

12-Month Effectiveness

Freedom from documented (symptomatic and asymptomatic) atrial arrhythmia (AF, AT or AFL of unknown origin*) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365) on or off antiarrhythmic therapy. Acute procedural failure (i.e., failure to achieve entrance block with the study device in any of the clinically relevant targeted PVs) will also be deemed a 12-month effectiveness failure.

**AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-lead electrocardiogram (ECG) or entrainment maneuvers in an EP study.*

Further refer to Appendix 2 for definitions on effectiveness terms.

7.3.3 Additional Effectiveness Endpoints

PVI Durability Rate

- Percentage of targeted PVs in the index ablation procedure being durably isolated as confirmed by the electroanatomical mapping 75 days (+/- 15days) post index ablation procedure.
- Percentage of subjects with durably isolated targeted PVs as confirmed by the electroanatomical mapping at 75 days (+/- 15days) post index ablation procedure.

Single Procedural Success: defined as freedom from documented symptomatic atrial arrhythmia (AF, AT or AFL of unknown origin*) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365) following a single index ablation procedure.

Freedom from documented symptomatic atrial arrythmia (AF, AT or AFL of unknown origin *) episodes based on electrocardiographic data (≥30 seconds on arrythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365). Acute procedural failure will also be considered failure of 12-month symptomatic recurrence free endpoint.

Freedom from documented (symptomatic and asymptomatic) atrial arrhythmia (AF, AT or AFL of unknown origin*) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365) **with extra failure modes**. A subject who meets any of the following criteria will also be deemed an effectiveness failure:

- Failure to achieve acute procedural success.
- Taking a new Antiarrhythmic Drug (AAD) (Class I / Class III) for atrial tachyarrhythmia (AF, AT or AFL of unknown origin*) or taking a previously failed Class I/III AAD at a greater than the highest ineffective historical dose for AF/AFL/AT during the effectiveness evaluation period (Day of 3-month visit – Day 365).
- Greater than 1 repeat ablation for AF/AT or AFL of unknown origin* in the blanking period or any repeat ablation for AF/AT or AFL of unknown origin* during the effectiveness evaluation period.

Use of a non-study device for the purpose of:

- PVI (i.e., touch-up) among all clinically relevant targeted PVs and by subject
- Ablation of left atrial non-PV AF targets (i.e., posterior wall) during index ablation procedure or for repeat procedures during blanking period.

Acute reconnection identified by adenosine/isoproterenol challenge among all clinically relevant targeted PVs

Repeat ablation procedures for left atrial arrhythmia (AF, AT or AFL of unknown origin*) within the 12-month FU period

- Percentage of subjects with repeat ablation during blanking period (≤90 days post index ablation procedure)
- Percentage of subjects with repeat ablation after blanking period (Day 91 – 365 post index ablation procedure)
- Percentage PV reconnection observed during repeat ablation procedures by targeted PVs treated at index ablation procedure and by subject
- Percentage of subject with repeat ablations due to non-PV targets

Quality of Life (QoL): the change of QoL assessed by comparing the Atrial Fibrillation Effect on Quality-of-Life (AFEQT™) scores before and at 3, 6 and 12- months after the ablation procedure.

Hospitalization for cardiovascular events through 12 months follow-up compared to 12 months prior to baseline.

NOTE: hospitalization is defined as prolonged stay > 2 nights post index ablation procedure or in-patient stay not concurrent with index ablation procedure > 1 calendar day; Excluding emergency room visits that do not result in admission to the hospital. Excluding social or administrative reasons for (prolonged) hospitalization.

**AFL of unknown origin is defined as all AFL except those CTI dependent AFL as confirmed by 12-lead electrocardiogram (ECG) or entrainment maneuvers in an EP study.*

7.3.4 Additional Safety Endpoints

Safety

- Incidence of Serious Adverse Device Effects (SADEs)
- Incidence of Unanticipated (Serious) Adverse Device Effects (UADEs and USADEs)
- Incidence of Serious Adverse Events (SAEs) within 7 days (early-onset), 8 to 30 days (peri-procedural) and >30 days (late onset) of index ablation procedure
- Incidence of non-serious adverse events (non-SAEs)

Neurological Assessment Subset

- Occurrence, anatomical location and size of new post-ablation asymptomatic and symptomatic cerebral emboli observed post-ablation as determined by Magnetic Resonance Imaging (MRI) evaluations
- Incidence of new or worsening neurological deficits post-ablation and at follow-up, compared to baseline
- 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 Subset

- Occurrence of PV stenosis up to 3 months post-ablation as determined by Computed Tomography (CT)/ Magnetic Resonance Angiogram (MRA) evaluations.

Esophageal Endoscopy Subset

- Occurrence of endoscopically detected esophageal thermal lesions in the region of the contact area between esophagus and LA as determined by post procedure endoscopy.

7.3.5 Additional Procedural Endpoints

Procedural data, including but not limited to

- Total procedure time, PVI time, PF/RF application time and mapping time
- Number of PF/RF applications by left and right PV and by subject
- Total fluoroscopy time
- Total study catheter left atrial dwell time
- Ablation settings used
- Use of paralytics and type of anesthesia

8 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.

8.1 Participant Inclusion Criteria

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

1. Diagnosed with Symptomatic Paroxysmal AF defined as AF that terminates spontaneously or with intervention within 7 days of onset. This PAF is considered to be symptomatic if symptoms related to AF are experienced by the patient.
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.

8.2 Participant Exclusion Criteria

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

1. Previously known AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause (e.g., documented obstructive sleep apnea, acute alcohol toxicity, morbid obesity (Body Mass Index >40 kg/m²), renal insufficiency (with an estimated creatinine clearance < 30 mL/min/1.73 m2) ….).
2. Previous LA ablation or surgery
3. Patients known to require ablation outside the PV region (e.g., 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 Left Ventricular Ejection Fraction (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 Percutaneous Coronary Intervention (PCI) / Myocardial Infarction (MI) within the past 2 months
12. Previous 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. Prior diagnosis of pulmonary vein stenosis
18. Pre-existing hemi diaphragmatic paralysis
19. Acute illness, active systemic infection, or sepsis
20. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation.
21. Severe mitral regurgitation
22. Presence of implanted pacemaker or Implantable Cardioverter-Defibrillator (ICD) or other implanted metal cardiac device that may interfere with the pulsed electric field energy.
23. Presence of a condition that precludes vascular access (such as Inferior Vena Cava (IVC) filter)
24. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this study
25. Categorized as vulnerable population and requires special treatment with respect to safeguards of well-being
26. Current enrollment in an investigational study evaluating another device or drug.
27. 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.
28. Life expectancy less than 12 months
29. Presenting contra-indications for the devices used in the study, as indicated in the respective Instructions For Use (IFU)

Additional exclusion criteria for Neurological Assessment (NA) subjects:

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

Additional exclusion criteria for Esophageal Endoscopy (EE) subjects:

33. Uncontrolled significant GastroEsophageal Reflux Disease (GERD)

9 Participant Withdrawal or Termination

9.1 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 CIP required follow-up period.

9.2 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) and the applicable on-site source documentation. 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 Responsibilities

10.1 Investigator Responsibilities

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

- Assuring compliance by site personnel with the provisions of the CIP
- 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 CIP
- Completing the appropriate training on the device (ablating investigators only) and the CIP 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 CIP and informed consent as applicable
- Obtain ICF and enroll patients
- Perform medical procedures
- Order tests required by the CIP
- Review pre-procedure imaging pertaining to the PV size prior to treatment
- Follow subjects until the end of the CIP
- 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 10 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 clinical investigation report.

10.2 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 CIP, CRFs and informed consent
- Selection of appropriately qualified and trained individuals, including monitors, to conduct the study
- Conduct CIP 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
- Substantial modifications to the study will be submitted to CAs and/or ECs for approval before implementation. A response of no objections will be awaited as per ISO 14155, MDR article 75. Non-substantial modifications will be notified to the CAs and/or ECs but do not require a formal approval before implementation.
- Maintain study records for at least 10 years or as specified per country specific record retention requirements after the study is completed and/or terminated.

11 Study Device Description

11.1 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.

11.2 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.

11.3 Device Preparation

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

11.4 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.

11.5 Device Description and Specific Considerations

[redacted]

[redacted]

[redacted]

[redacted]

11.5.3 System Components and Setup

To conduct an electrophysiology procedure, the THERMOCOOL SMARTTOUCH™ SF Bi-Directional Navigation Catheter and TRUPULSE™ Generator is used with the following Biosense Webster CE marked devices:

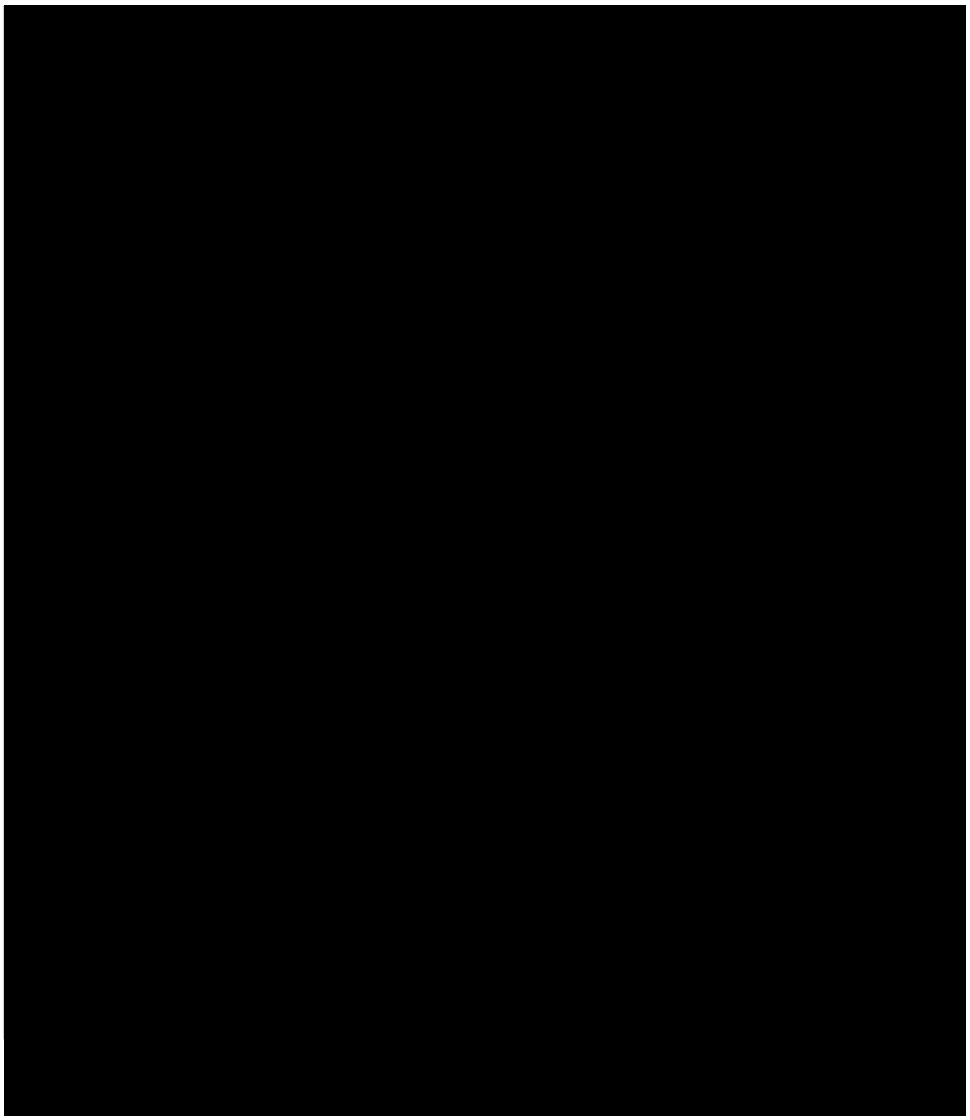
- nGEN™ Pump (D139701)
- SmartAblate Irrigation Tubing Sets (SAT001)
- Patient Interface Unit (PIU) of CARTO™ 3 system
- CARTO™ 3 System and CARTO™ V7.9 workstation
- Sterile Catheter Connection Cable (CR3434CT)
- BWI multi-electrode mapping Catheter
- ≥8.5Fr Compatible Sheath

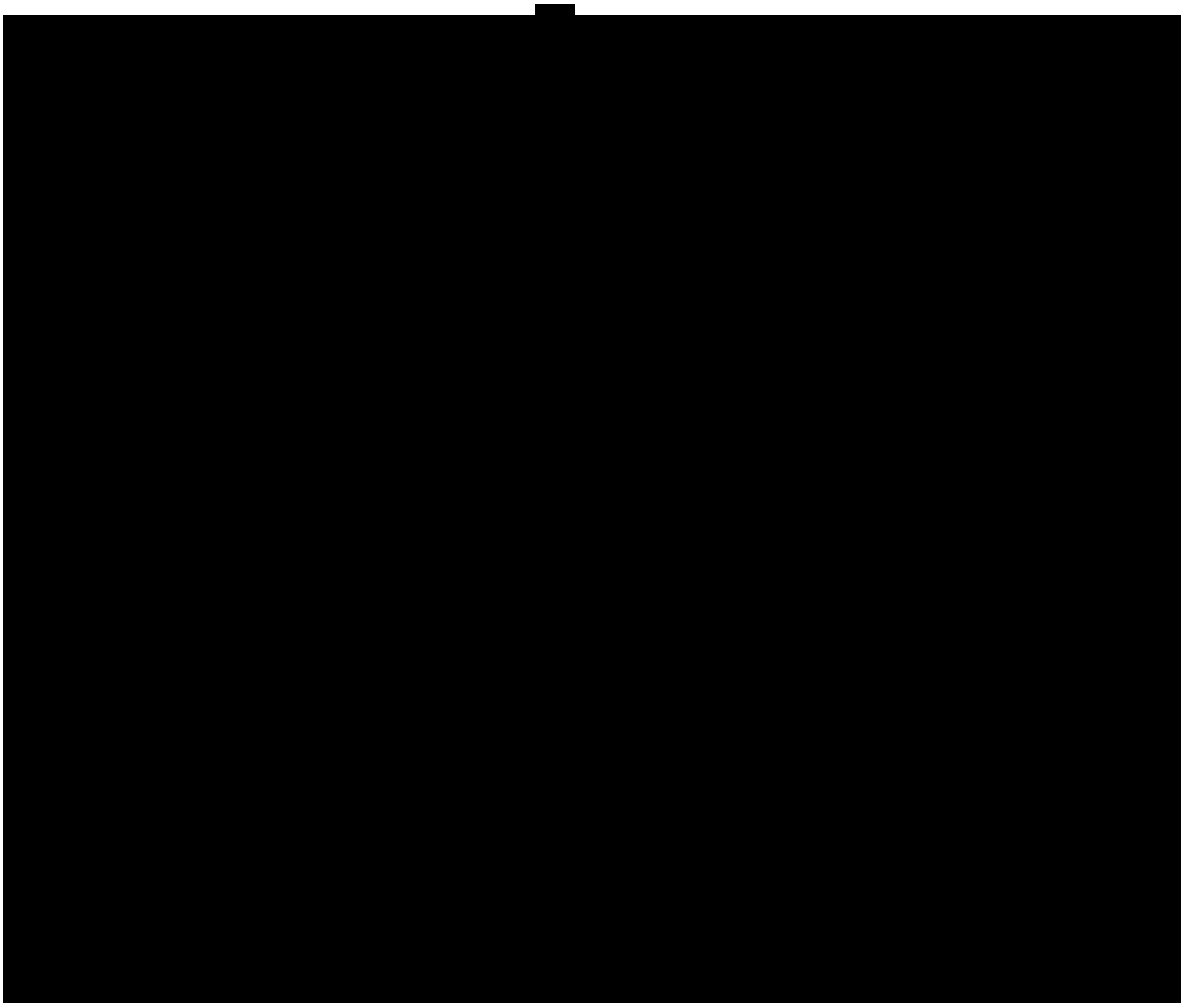
The following devices, CE marked by other companies, are also required for the procedure:
- ≥8.5Fr Compatible Sheath
- Electrophysiology (EP) Recording System
- Stimulator
- Body Surface Electrocardiogram (ECG) Patches and Leads
- Indifferent electrode patches
- Fluoroscopy/X-Ray System
- Cardiac Defibrillator
- Intracardiac Ultrasound (Investigator preference, not required)

11.5.4 System Connectivity

Each site will have CIP specified devices required for study participation. These devices must be used during the study to perform ablation procedures. Device set-up must be complete per the IFU and User Manual.

Below figures displaying a connectivity diagram from the front view (Figure 3) and back view (Figure 4) for system set up and a description of the connectivity respectively.





11.5.5 Required Study Devices

Table 2 displays the devices which must be used for the ablation procedure and are required per protocol.

Table 2: Required Study Devices

Investigational Devices	**Function**
THERMOCOOL SMARTTOUCH™ SF Bi-Directional Navigation Catheter	Transmits energy to the target tissue.
TRUPULSE ™ Generator	Delivers PF and RF energy to compatible ablation catheter
Non-investigational Devices/Standard Equipment	**Function**
CARTO™ 3 SYSTEM V7.9 workstation	For mapping and visualization information with software for PF and RF
nGEN™ Pump	Delivers heparinized saline to the catheter
Sterile Catheter Connection Cable (CR3434CT)	Connects the STSF Catheter with the TRUPULSE™ Generator.
SmartAblate Irrigation Tubing Sets (SAT001)	Delivers heparinized saline to the catheter
BW Multi-Electrode mapping Catheter	• Pre-ablation recording and mapping of the atria of the heart with the CARTO™ 3 System. • Confirmation of entrance block
≥8.5 Fr compatible sheath used with STSF catheter.	Facilitate deployment of catheter into the atria.
Adhesive electrical dispersive pads/indifferent split electrode (with a surface area of ≥ 124 cm^2 that conform with IEC/EN 60601-2-2)	Component of the RF / PF current return path (Valley Lab recommended)
EP Lab Recording Equipment	Records multiple intracardiac electrograms and signals from the TRUPULSE™ generator 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 clinical investigation plan, if applicable.

12 Study Medication

The following medications are applicable for this CIP:

PRIOR to the procedure

- Uninterrupted anticoagulation therapy should be in place at least 3 weeks prior to ablation procedure
    - Recommended: anticoagulation with Warfarin/Coumadin (INR≥ 2.0), 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.
- Anticoagulation therapy should not be interrupted or stopped prior to the procedure (this means no doses should be missed or omitted) and daily regimen should be continued. One dose can be omitted on the evening prior- or day of procedure as per standard of care.
- AAD therapy and administration of Proton Pump Inhibitors (PPI) should be managed as per the institution's standard of care

DURING the procedure, provided in the Study Ablation Procedure Guidelines (section 13.3.3)

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[3] 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 for at least 6 weeks 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.

13 Study Schedule

13.1 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 CIP 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 or jointly given approval from CAs and independent 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.

13.2 Baseline Evaluation and Procedures

13.2.1 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.)
    - **Cardiovascular Hospitalization history**: information on hospitalization for cardiovascular reason (including arrhythmia, cardioversion, …) from 12 months prior to enrollment will be collected from medical records and recorded in the eCRF.
    - **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.
- **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/MRA) 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 ablation 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 on 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.
- **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 for all subjects 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 **NA subset** 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.

13.3 Study Ablation Procedure Guidelines

13.3.1 Energy and Ablation Selections

The TRUPULSE™ Generator is capable of controlling the delivery of RF and PF energy to the THERMOCOOL SMARTTOUCH™ SF catheter. The generator includes a touch screen that allows the user to select the energy type and apply ablations. Before energy delivery it is required to verify if RF or PF is selected on the ablation screen. The start button contains a drag feature. After the start button is dragged or the pedal is pressed, there is a countdown until ablation begins. When the stop button is pressed or the pedal is released, the delivery of energy is terminated. To preform RF ablation, the user selects target power and time from the ablation screen. The user may configure the cutoff temperature and warning temperature from the setup screen. For more general operation of the TRUPULSE™ Generator, refer to the user manual for detailed information.

13.3.2 Ablation Parameters

When used with the THERMOCOOL SMARTTOUCH™ SF Catheter, the nGEN™ Pump will deliver a continuous infusion of 2 mL/min of room temperature heparinized saline (1u heparin/1 mL saline) when the catheter is in the body. The recommended operating flow settings for the THERMOCOOL SMARTTOUCH™ SF Catheter are presented in Table 3. Recommended instructions for RF and PF energy applications are presented in the IFU and per physician training.

Table 3: Recommended Flow Settings for PF and RF mode

	PF mode	RF mode
Idle mode	2 ml/min	2 ml/min
During ablation	4 ml/min	Dependent on target power ≤30W: 8ml/min >30W: 15ml/min

13.3.3 Study Ablation Procedure Sequence & Guidelines

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).

PREPARATION of the ablation procedure:

- Anesthesia or sedation should be delivered per standard EP lab procedure. It is highly recommended to ensure presence of an anesthesiologist during the procedures.
- **REQUIRED:** Placement of two indifferent electrodes on the patient prior to mapping.
- Esophageal monitoring/localization (investigator discretion) with CARTOSOUND® and/or ICE, barium swallow or temperature probe (CIRCA™ or Single Thermistor™ probes ONLY).
- CARTO™ Respiratory gating recommended (unless using Jet Ventilation).
- Introduce an Intracardiac Echo (ICE) probe to review LA anatomy and PVs (at investigator discretion).
- Diagnostic catheter placement:
    - Coronary sinus catheter in the CS for pacing purposes is recommended
    - Other catheters may be placed at the discretion of investigator
- **REQUIRED:** Administration of heparin bolus prior to or immediately following transseptal puncture.
- A double or single transseptal puncture should be performed per standard EP lab (at the discretion of the investigator).
- Cardioversion if subject is in AF (at discretion of investigator).

MAPPING prior to the ablation procedure**:**

- **REQUIRED:** Creation of a left atrial anatomical map, including PV anatomy prior to ablation, utilizing a multi-electrode BWI mapping catheter.
- Additional imaging techniques such as 3D rotational angio (at investigator discretion), or CT integration can be used to supplement the map.
- A pre-ablation paced activation and bi-polar voltage map may be created at physician discretion and if SOC.
- For subjects participating in PVI durability subset:
    - **REQUIRED:** creation of paced activation map and bipolar voltage map, utilizing a BWI multi-electrode mapping catheter.
- Pace the phrenic nerve prior to ablation in the region of the right sided PV's in order to evaluate the proximity. NOTE: in case of deep sedation a fluoroscopic evaluation of the diaphragm may be used.

ABLATION Procedure:

- **REQUIRED:** Confirmation of ACT ≥300 seconds PRIOR to start ablation with investigational catheter and systematic anticoagulation with heparin should be administrated.
    - ACT must be targeted to be maintained ≥300 seconds throughout the ablation.
    - ACT level must be checked on regular basis while investigational device is in the left atrium.
    - If ACT is below 300 seconds, systematic anticoagulation with heparin should be administrated to ensure an ACT target of 300 seconds without pausing ablation procedure.
- Introduction of the compatible 8.5 Fr or greater sheath, if not used for mapping. Before inserting the sheath into the patient, flush the sheath with heparinized normal saline to remove air bubbles.
- Introduce the investigational THERMOCOOL SMARTTOUCH™ SF catheter as per IFU.
- NOTE: Usage of a diagnostic catheter or any metal device in the same chamber during PF ablation is strictly prohibited and diagnostic catheter should be disconnected from CARTO™ system prior to starting ablation.
- When position is satisfactory, commence energy delivery with the investigational catheter per recommended workflow.

Pulmonary Vein Isolation (PVI)

- Use point-by-point ablation to obtain a contiguous lesion set for ipsilateral PV isolation.
- Create VISITAG™ settings in order to segment the left atrium during the procedure according to below image (Figure 5).

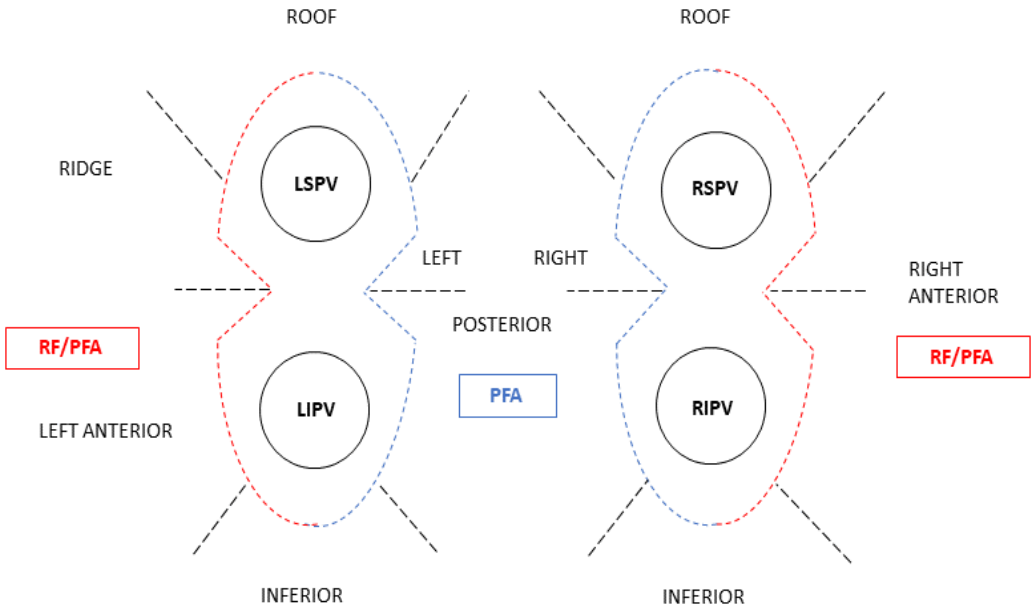


Figure 5: VISITAG™ settings

- Use the ablation parameters, and VISITAG™ targets as recommended by IFU and per physician training.
- Evaluate the Inter-tag Distance (ITD) using the VISITAG™ Module distance tool. An ITD of ≤ 6mm is recommended.[13]
- Prepare 1-2mg nitroglycerine for either intravenous or intracoronary administration to limit /reduce coronary spasm when ablating near the coronary artery.
- All subjects will undergo PV ablation with the investigational device until PVI is achieved in all targeted PV's:
    - PF is recommended to be used as the primary ablation modality for achieving PVI
    - Power controlled irrigated RF can be used for the anterior wall and ridge upon clinical judgement and per investigator discretion.
    - ONLY after investigator deems unable to achieve PVI with the investigational device, a commercial (RF) system can be used to complete the procedure (PVI only).
- **REQUIRED:** Confirmation of entrance block (exit block is optional) (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.

Post Pulmonary Vein Isolation:

- 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 energy in corresponding locations. As per above recommendation, PF is the primary modality, but RF can be used based on clinical judgement.

- **REQUIRED:** Confirmation and documentation of final entrance block (exit block is optional) (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.
    - Use a BWI multi-electrode mapping catheter for confirmation per investigators choice
- The ablation procedure is considered complete when confirmation of entrance block in all clinically relevant targeted PVs is confirmed.
- **REQUIRED**: after last application or confirmation of final entrance block (exit block is optional) at the right sided PVs, evaluate diaphragmatic capture while pacing the phrenic nerve. NOTE: in case of deep sedation a fluoroscopic evaluation of the diaphragm might be used.
- A post paced activation and bipolar voltage map may be created at physician discretion and if SOC.
- For subjects participating in PVI durability subset:
    - **REQUIRED:** creation of paced activation map and bipolar voltage map, utilizing the same BWI multi-electrode mapping catheter as pre-procedure.

Ablation outside the PV region

- **A right atrial CTI linear** ablation is allowed only in cases with documented typical atrial flutter identified either prior to or during the procedure. The investigational system, the STSF catheter with the TRUPULSE™ generator in RF and/ or PF mode should be used based upon investigator decision. If block of CTI line cannot be achieved with the investigational system, a commercially approved RF catheter with a compatible commercially available RF generator may be used.
- **Prophylactic ablation** outside the PV region (in example SVC, PW, roofline) is NOT allowed.
- If an arrhythmia is requiring ablations outside the PV or CTI line:
    - **Prior** 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).
    - **After** insertion of the study catheter, the subject will undergo PVI and/or CTI line with study set up 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 12-month 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)

13.3.4 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™ 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.

13.3.5 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 PF/RF applications
- Energy delivered
- PF/RF application time
- Ablation settings used
- Ablation information will be collected in the CARTO™ 3 system and investigational Generator
- Contact force values

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 PF/RF applications per left and right PV per left and right PV
- Number of PF/RF applications per target PV and by subject
- Number of PF/RF applications required with a non-study catheter
- PVI confirmed with BWI multi-electrode mapping 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)
- Use of paralytics and type of anesthesia

13.3.6 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**
- **12- Lead -ECG**
- Additional Assessments for **NA subset** 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. Cerebral MRI images will be transmitted to an independent

core laboratory. NOTE: Patient questionnaires will only be used in countries with validated languages.

- Additional Assessments for **EE subset** subjects (non-SOC): **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 an independent core laboratory.

13.4 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 ablation 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. Procedures for CTI dependent flutter in the follow up period are not considered repeat procedures per CIP.

Repeat procedures performed **after the blanking period** (≥90- 365days post index ablation procedure) may be managed per investigator discretion using a commercially available ablation catheter and generator.

For the repeat procedures, the investigator must collect and provide information on location of reconnections of PVs and in case of atrial flutter recurrence, confirm if CTI dependent flutter or not. The follow-up schedule will remain based on the index ablation procedure.

13.5 Post-Ablation Follow-up Schedule

The subjects will be required to complete follow-up visits through 12 months post index ablation procedure. Follow-up will be done at 7 days (phone call or clinic visit), 1, 3, 6 and 12 months (clinic visit). 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 ablation procedure and will not reset if subject undergoes a repeat AF ablation procedure.

13.5.1 Seven (7) day follow-up visit

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 **Adverse Events** and any change in **medication regimen.** If subject is coming for a clinic visit at day 7, data from 12 lead ECG will be collected.

13.5.2 Monthly follow-up visit

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

- **As from 1-month: Atrial arrhythmia monitoring (non-SOC)**
  - **Remote Monitoring**: subjects will be provided with a remote monitoring device at the 1M 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 ablation 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. Remote monitoring will be **conducted as follows:**
    - Distribution and start by month 1
    - <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 Monitoring**: per CIP a Holter monitor will be used at the 3-, 6- and 12-months 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. An independent core laboratory will be used to evaluate and assess the remote and 24h Holter monitoring tracings.

- Additional Assessments for Cardiac **CT/MRA** subset subjects: A **cardiac CT/MRA** is required to be performed at the 3M FU (non-SOC) visit or any other point in time when the subject presents with symptoms of PV stenosis. For other subjects, a cardiac CT/MRA is only required to be performed if the subject presents with symptoms of PV stenosis.

- Additional Assessments for **NA** subset subjects (non-SOC): A **Cerebral MRI, Neurological Exam and Neurological Evaluation using the MMSE, NIHSS and mRS** 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.

- Additional Assessments for **PVI Durability subset** subjects (non-SOC):

- A repeat electro anatomical creation of a paced activation map and bipolar voltage map will be performed by the ablating physician* in the enrolling hospital at 75 days (+/-15days) post index ablation procedure to verify isolation durability of the treated pulmonary vein during the index ablation procedure.
- A BWI multi-electrode mapping catheter should be used for the remap procedure. It is **REQUIRED** to use the same mapping catheter that was used during the index ablation procedure.
- Additional ablations may be performed at the discretion of the investigator.
- NOTE*: preference to have the PVI durability assessment performed by the same ablation physician that treated the subject during index ablation procedure.

- **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.

13.6 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 CIP requirements. In case of early termination due to safety concerns, reporting to EC and CA may be required per local regulations.

13.7 Unscheduled Visit

If a subject returns for a potential study related cardiovascular or neurological visit outside of the CIP -defined visit schedule provided in Table 3, 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 CIP 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.

13.8 Core Laboratory for Evaluation

Independent central core laboratories and/or expert physician(s) will conduct objective evaluations of remote arrhythmia monitoring tracings, ECGs, Holter, Cerebral MRI, endoscopy and will evaluate PV stenosis of all subjects requiring the applicable assessments per CIP.

13.9 Schedule of Events Table

Table 3 displays the required schedule for subject treatments and evaluations.

Table 3: Summary of Subject Visits and Assessments

Assessments[22]	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	●	●	●[6]	●	●	●	●	●[21]
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]	●	●		●	●	●	●	●[21]
Atrial Arrhythmia monitoring (Remote)[7]				●	●	●	●	●[21]
Atrial Arrhythmia monitoring (24-hour Holter)[8]					●	●	●	●[21]
Repeat ablations[9]			●	●	●	●	●	●[21]
Concomitant Medication[10]	●	●	●	●	●	●	●	●[21]
Device Deficiencies		●						
Adverse Events[11]	●	●	●	●	●	●	●	●[21]
AFEQT[12]	●				●	●	●	
Cardiac CT/MRA[13]	●				●[13]			
PV Durability Subset								
3D Electro anatomical mapping[14]	●				●[14]			
Endoscopy Subset								
Endoscopy		●[15]						
Neurological Subset								
Cerebral MRI[16]	●[18]	●[19]		●[20]	●[20]	●[20]	●[20]	●[21]
Neurological Exam[17]	●[18]	●[19]		●[20]	●[20]	●[20]	●[20]	●[21]
NIH Stroke Scale[12]	●[18]	●[19]		●[20]	●[20]	●[20]	●[20]	●[21]
mRS	●[18]			●	●[20]	●[20]	●[20]	●[21]
MMSE[12]	●[18]			●	●[20]	●[20]	●[20]	●[21]

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, CHA2DS2 VASc Score 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 ablation 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. Data from 12-lead ECG recordings will be collected (For pre-procedure, can be performed before ICF signature)
7. Arrhythmia monitoring via remote monitoring once per week as from 1-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 ablation procedure will be collected
10. Concomitant medication: only cardiac (i.e., anti-arrhythmia drugs, anticoagulation regimen) & index ablation procedure related (i.e., adenosine, anticoagulation (e.g., heparin, pain medication)

11. AEs must be collected from the time the subject signs the informed consent onward.
12. Patient questionnaires will only be used in countries with validated languages.
13. For all subjects: CT/MRA to be completed within 6 months prior to the index ablation procedure. Post procedure: for CT/MRA subset to be repeated at 3M FU, for all subjects CT/MRA to be repeated post procedure in case subject presents with PV stenosis symptoms.
14. For PV Durability subset: an electro anatomical map, activation and voltage re-map is to be performed pre and post procedure and to be repeated at 75 days post procedure (+/- 15 days).
15. For Endoscopy subset: Endoscopy preferable between 1 day to 3 days (72hours) post procedure. For procedures on Friday a window of a maximum of 96 hours is justified.
16. 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.
17. 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.
18. To be completed within 72-hours pre-procedure. For procedures on Monday a window of a maximum of 96 hours is justified.
19. To be completed within 72-hours post-procedure. For procedures on Friday a window of a maximum of 96 hours is justified.
20. Full neurological follow-up to be undertaken if neurologic symptoms and/or cerebral ischemic lesions identified in a prior evaluation.
21. If subject returns for a potential study related cardiovascular or neurological visit outside of the CIP defined visit schedule as deemed required per investigators discretion.
22. Assessments should not be repeated for the study if already done per standard of care within CIP defined time limits.

14 Assessment of Safety

14.1 Specific Safety Parameters

14.1.1 Definition of Adverse Events (AE)

An Adverse Event (AE) means any untoward medical occurrence, unintended disease or injury or any untoward clinical signs, including an abnormal laboratory finding, in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational device (MDR Article 2(57))

NOTE:
a. This definition includes events that are anticipated as well as unanticipated events
b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

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.

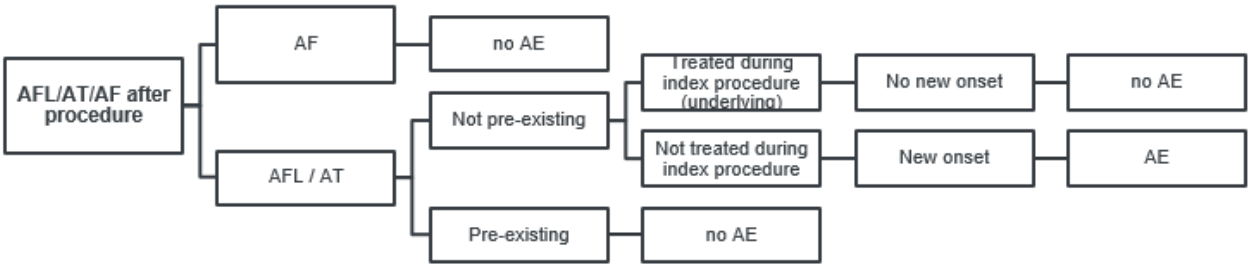
Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. Such conditions should be added to background medical history, if not previously reported. However, if the study participant's condition deteriorates at any time 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 ablation procedure) AFL/AT is considered as a recurrence of disease
- Onset of non-previously identified AFL/AT which was treated during the index ablation 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 ablation 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 <u>not</u> treated during the index ablation procedure.



14.1.2 Definition of Serious Adverse Event (SAE)

A SAE is any event that led to any of the following:

- Death
- Serious deterioration in the health of a subject that resulted in any of the following:
  - Life-threatening illness or injury
  - permanent impairment of a body structure or a body function
  - In-patient hospitalization or prolongation of patient hospitalization*
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function
  - Chronic disease
- Fetal distress, fetal death or a congenital physical or mental impairment 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.*

14.1.3 Primary Adverse Event

A **Primary Adverse Event** is an event listed in Table 5 which occurs within the first week (7days) following the study index ablation procedure.

Table 4: Primary Adverse Events

Primary Adverse Event	Description / Criteria
Death[1]	Subject death directly related to the device or procedure and occurs at any time during or after the procedure.
Atrio-Esophageal Fistula[1]	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
Cardiac Tamponade[2]/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.

Primary Adverse Event	Description / Criteria
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). [3] -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[4] Major—Modified Rankin score ≥2 at 30 and 90 days
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. Under this protocol, diaphragmatic paralysis/phrenic nerve palsy will be considered a Primary AE if specified symptoms have not improved at the 3-month visit.
Pulmonary Vein Stenosis[1]	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.

Primary Adverse Event	Description / Criteria
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.
Heart Block	Impairment of AV conduction requiring intervention (e.g., temporary, or permanent pacemaker) due to iatrogenic cause (e.g., inappropriate energy application, traumatic maneuvering of catheter or other intracardiac devices)
Pulmonary Edema (Respiratory Insufficiency)	Respiratory insufficiency resulting in pulmonary complications necessitating intubation or other significant intervention (including diuretics administered specifically for treating pulmonary edema or ICU hospitalization requiring oxygen administration but not intubation). Exclusion criteria include: • Pneumonia – infiltrate, fever, and leukocytosis • Acute Respiratory Distress Syndrome
Vagal Nerve Injury/ Gastroparesis	Injury to the vagal nerve that results in esophageal dysmotility or gastroparesis. Vagal nerve injury is considered to be a major complication if it requires or prolongs hospitalization[5], or results in ongoing symptoms for more than 30 days following an ablation procedure.

1 Device or procedure related death, atrio-esophageal fistula and pulmonary vein stenosis that occur greater than one week (7 days) and less than or equal to 90 days post-procedure are considered and analyzed as Primary AE.

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

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

4 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.

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

14.1.4 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.

14.1.5 Unanticipated (Serious) Adverse Device Effect

An Unanticipated Adverse Device Effect (UADE) or Unanticipated Serious Adverse Device Effect (USADE) is any (S)AE 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, outcome, or degree of incidence in the current 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 11 for a comprehensive list of foreseeable and anticipated AEs.

14.1.6 Study Device Deficiency, Failure or Malfunction

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

- Malfunction (failure to perform on its intended purpose when used in accordance with the IFU/CIP/IB),
- Use errors,
- 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 14 AE documentation and reporting requirements.

14.1.7 Serious Public Health Threat

Signal from any adverse event or device deficiency that indicates an imminent risk of death, serious illness, or a serious deterioration in a person's state of health in subjects, users or other persons, and that may require prompt remedial action for other subjects, users or other persons and that may cause significant morbidity or mortality in humans, or that is unusual or unexpected for the given place and time.

NOTE: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

14.2 Classification of an Adverse Event

14.2.1 Severity of Event

The intensity or severity of each AE must be assessed according to the classifications as described in Table 5.

Table 5: 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.

14.2.2 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 EU Medical Device Regulations (MDR) and MDCG 2020-10/1 guidance (Table 6).

Table 6: Adverse Event Causality Classifications (Ref. MDCG 2020-10/1 guidance)

Relation	Definition of Relation to device/procedure
Causal Relationship	The serious adverse event is associated with the investigational device or with procedures beyond reasonable doubt when: – the event is a known side effect of the product category the device belongs to or of similar devices and procedures, – the event has a temporal relationship with investigational device use/application or procedures, – the event involves a body-site or organ that ▪ the investigational device or procedures are applied to, ▪ the investigational device or procedures have an effect on, – the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known); the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible),

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

14.2.3 Outcome

The outcome of each AE must be assessed according to the classifications as described in Table 7.

Table 7: 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)

14.2.4 Anticipated Adverse Event

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 the table in Appendix 3, including standard of care practice. The probability of occurrence may vary as it depends on technique used, patient selection, operator and hospital experience. The published clinical studies reported lower complication rates than real-world data. [3, 92] An increase of overall incidence of complications associated with atrial fibrillation (AF) ablation was observed from 5.3% in 2000 to 7.5% in 2010 (In-hospital complications associated with catheter ablation of atrial fibrillation in the United States between 2000 and 2010: analysis of 93 801 procedures).[82]

Table 8) includes the incidence of the complications of AF ablation reported in the 2017HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation.[3] The probability of occurrence of potential hazard/harm related to the investigational device is provided in the Investigator Brochure.

Table 8: The incidence of the complications of AF ablation

Anticipated Adverse Event	Incidence*
Air embolism	<1%
Asymptomatic Cerebral Emboli (ACE)	2%-15% (literature reports out to 40%)
Atrio-Esophageal fistula	0.02%-0.11%
Cardiac tamponade	0.2% to 5%
Cardiac Coronary artery stenosis/occlusion	<0.1%
Death	<0.1%-0.4%
Gastric hypomotility	0%-17%
Mitral valve entrapment	<0.1%

Pericarditis	0%-50%
Permanent phrenic nerve paralysis	0% to 0.4%
Pulmonary vein stenosis	<1%
Radiation injury	<0.1%
Stiff left atrial syndrome	<1.5%
Stroke and TIA	0% to 2%
Vascular complications	0.2% to 1.5%
* Data from 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation[3]	

Anticipated AEs are to be reported to the sponsor via EDC as indicated in section 14.

14.3 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.

14.4 Reporting Procedures

14.4.1 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 CIP (section 14). 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 malfunctioning or causing an AE or SAE (i.e., definitely (causal relationship) device-related or probably/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 9.

Table 9: 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.

14.4.2 Serious Adverse Events Reporting

14.4.2.1 Serious Adverse Events Reporting by the study site personnel to the Sponsor

All

- Serious Adverse Events
- Investigational DD that might have led to a SAE if
  a) Appropriate action had not been taken or
  b) intervention had not occurred or
  c) if circumstances had been less fortunate, whether or not they are related to the device or procedure,
- Any 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.

14.4.2.2 Serious Adverse Events Reporting by the Sponsor to the CA/EC

As per MDCG 2021-10/1, following events are considered reportable events:

a. Any serious adverse event (SAE) that has a causal relationship with the investigational device, the comparator or the investigation procedure of where such causal relationship is reasonably possible.

b. Any device deficiency that might have led to a serious adverse event if:
   - Appropriate action had not been taken or
   - Intervention had not occurred or
   - If circumstances had been less fortunate

c. Any new finding/updates in relation to any event referred to in point a) and b)

Both the relationship between the occurrence of each adverse event and the use of the medical investigational device, and the relationship between the occurrence of each adverse event and the investigational procedure must be assessed and categorized (see section 14.2.2). Only causality level (not related) is excluded from reporting. If either the sponsor or the investigator has assigned a higher causality level than 'not related', the event will be reported.

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 or serious health threat, 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 and CA as per national, site-specific or EC specific requirements. A list of applicable Competent Authorities is included in Appendix 4. The reportable events will be reported through the Eudamed web form once fully functional. Until then, the template for the Clinical Investigation Summary Safety Report Form will be used (MDCG 2020-10/1 or its next revisions). 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.

14.4.3 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.

14.4.4 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 CA's 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 MDR 2017/745. Event reporting will be done through the Eudamed web form once fully functional. Until then, the template for the Clinical Investigation Summary Safety Report Form will be used (MDCG 2020-10/1 or next revisions).

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.

14.5 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 as defined in the Safety Management Plan, safety events will be reviewed by the Safety Management Team which may recommend appropriate action(s) to ensure subject safety.

15 Administrative Responsibilities

15.1 Ethics Committee and Competent Authority Application

The CIP (or amendment[s]), ICF, and other applicable study related documents must be approved by the EC and CAs before enrollment of subjects. The application shall be submitted by means of the electronic system referred to in Article 73 (MDR [EU - 2020/561]), which shall generate a Union-Wide unique single identification number for the Clinical Investigation. 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 countries with a centralized submission process, a single submission will be performed in order to obtain the joint opinion from EC and CA. This applies for the initial application and for substantial modifications.

In addition, Biosense Webster, Inc. is responsible for notifying the relevant CA of the intention to perform a clinical investigation under this CIP and ensure to get the official response/ approval before starting the clinical investigation. For all relevant communication in relation to the clinical investigation the Union-Wide unique single identification number shall be used as a reference.

15.2 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.

16 Deviations from the Clinical Investigation Plan

The investigator is responsible for ensuring that the clinical investigation is conducted in accordance with the procedures and evaluations described in this CIP. The study monitors shall verify that the conduct of the study is in compliance with the currently approved CIP 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 CIP deviations; failure to obtain proper informed consent; non-conformance to EC requirements; failure to report AEs, product malfunctions and other product issues; and another non-conformance to GCP.

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

Under emergency circumstances, deviations from the CIP 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 CIP 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 CIP. Administrative changes (do not affect subject's benefits/risks ratio) may be inserted with abbreviated approval. All amendments will be distributed to all original CIP recipients.

17 Investigational Product

17.1 Use of the Investigational Device and Investigator Experience

17.1.1 Training

Investigators selected to participate in the study will be experienced in intracardiac mapping and AF ablation. 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. The study training in includes following:

- All investigators who will be performing the ablation procedures for this study will be required to attend device and PF technology training in accordance with the physician training charter. Investigators will also undergo a didactic training, which includes detailed reviews of the study catheter and the results of preclinical studies completed. This training will occur prior to first treatment of the subject and will take 2 hours on average.

- To ensure uniform data collection and CIP compliance, the Sponsor will conduct a training session that will include reviewing the CIP, eCRF and data collection process, and the AE reporting process. This training will occur during the site initiation visit, prior to site activation and will take on average 3 to 4 hours. The sponsor will reinforce the training or provide clarification throughout the study, as needed.

17.1.2 Materials

TRUPULSE™ 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.

STSF Catheter
Biosense Webster, Inc. USA, is the legal manufacturer of the catheters to be used in this study. There is no change to the approved manufacturing process to the THERMOCOOL SMARTTOUCH™ SF Catheter. An investigational label will be applied to the devices for use with the TRUPULSE™ Generator for this study.

17.2 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, …)

17.3 Device Returns

All investigational devices (used and unused) will be returned to the Sponsor's attention and per Sponsor's Instructions. The THERMOCOOL SMARTTOUCH™ SF Bi-Directional Navigation 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 probably/ 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
C. G Laboratories, Inc.
2449 Bob White Drive
Granbury, TX 76049 USA

18 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 CIP /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:

- Adherence to the CIP
- 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 CIP
- 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. Specific monitoring requirements are provided in the study specific monitoring plan.

19 Statistical Methodology

The Sponsor will be responsible for the overall analysis of data from this CIP. 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.

19.1 Levels of Significance

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

19.2 Sample Size Justification

Primary Safety Endpoint:
Based on a performance goal of 12% and assuming an anticipated primary safety event rate of 5% for the primary safety endpoint, a sample size of 135 subjects (with 5% missing data due to attrition) will provide above 80% power to reject the null hypothesis for the primary safety hypothesis test using a one-sided exact binominal test. The target significant level is 0.025.

Primary Effectiveness Endpoint:
Based on a performance goal of 90% and assuming an anticipated failure-free rate of 97% for the primary effectiveness endpoint, a sample size of 100 subjects will provide above 80% power to reject the null hypothesis for the primary effectiveness hypothesis test using a one-sided exact binomial test. The target significant level is 0.025.

Secondary Effectiveness Endpoint:
Based on a performance goal of 50% and assuming an anticipated failure-free rate of 65% for the secondary effectiveness endpoint, a sample size of 100 subjects (with 10% missing data due to attrition) will provide above 80% power to reject the null hypothesis test for the secondary effectiveness hypothesis using a one-sided exact binominal test. The target significant level is 0.025.

Total Sample size:
The sample size of this study is mainly driven by the hypothesis test for the primary safety endpoint. The total sample size for this study will be 135 subjects, based on the 135 subjects needed for the primary safety endpoint evaluation, 100 subjects for the primary acute effectiveness endpoint evaluation, and 100 subjects for the secondary effectiveness endpoint evaluation. A 5% attrition rate of the subjects for the primary safety endpoint and no attribution of the subjects for the primary effectiveness endpoints were assumed for the total sample size estimation.

A total of 135 evaluable subjects will be included in the study. Each of the four (4) subsets (NAE, CT/MRA, EE and PVI durability) will consist of 30 subjects and will be integrated within the study.

19.3 Analysis Sets

Safety Population Analysis Set (SP): The SP analysis set will consist of all enrolled subjects who have had insertion of the study catheter, regardless of energy delivery.

Modified Intention-To- Treat (mITT) Analysis Set: The mITT analysis set will consist of enrolled subjects who meet eligibility criteria and have had insertion of the study catheter.

Per Protocol (PP) Analysis Set: The PP analysis set will consist of subjects who satisfy the following criteria:

- Have undergone ablation using PF and/or RF energy via the investigational ablation system per CIP
- Are treated for the study-related arrythmia
- Are enrolled and without major CIP deviation that would affect the scientific integrity of the safety and effectiveness, including but not limited to the following:
    - Subjects found not meeting eligibility criteria
    - Failure to check for entrance block for each targeted PV after adenosine/isoproterenol challenge.

- Use of the investigational ablation system outside the PV region. A CTI line for documented typical AFL identified prior to or during the procedure using investigational system or commercial RF devices to complete the procedure is allowed during index or repeat ablation procedure (within blanking). For the treatment of arrhythmia outside the PV region, using commercial RF devices to complete the procedure is allowed. However, subjects using commercial RF devices for the non-PV regions and/or CTI lines will be excluded from the 12-month effectiveness analysis.
- Missing all CIP specified electrocardiographic effectiveness monitoring

Neurological Assessment (NA) Analysis Set: The NA analysis set will include 30 subjects who have had pre-and post-index-ablation procedure MRI and neurological assessments completed. Subjects with no pre-index ablation procedure MRI assessment and no lesions observed on post-MRI assessment will be included for analysis.

Esophageal Endoscopy (EE) Analysis Set: The EE analysis set will include 30 subjects who have had a readable 1 to 3 days post index-ablation procedure esophageal endoscopy assessment.

Cardiac CT/MRA Analysis Set: The CT/MRA analysis set will include 30 subjects who have readable outcomes at baseline and 3 months.

PVI Durability Analysis Set: The PVI durability analysis set will include 30 subjects who have readable electro-anatomical mapping at index ablation procedure and 75 days (+/-15 days) post index ablation procedure.

19.4 Analyses to be Conducted

19.4.1 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.

19.4.2 Subject Disposition

Disposition and accountability of the study subjects will be summarized descriptively for the subject categories defined as following,

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 who have the catheter inserted, 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.
- Discontinued subset subjects are not subjected to the additional subset assessments (esophageal, neurological, PV and PVI durability).

- 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.

19.4.3 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 all enrolled subjects.

19.4.4 Primary Endpoint Analyses and Associated Hypotheses

The number and percentage of primary safety events will be summarized in the mITT analysis set after all study subjects completed the 3 -month follow-up. Similarly, the number and percentage of primary acute effectiveness events will be summarized in the PP analysis set after all subjects completed the index ablation procedure. The primary endpoint analysis will be part of the CE mark application dossier.

The PAE rate will be formally compared against a performance goal of 12%. Additionally, the primary effectiveness success rate will be compared to a performance goal of 90%. The primary safety endpoint analysis will be performed in the mITT analysis set and the primary effectiveness analysis will be performed in the PP analysis set.

Primary Safety Endpoint:

The null and alternative hypotheses are:

H_0: $P_S \geq 0.12$ vs. H_A: $P_S < 0.12$,
where P_S denotes the rate of early onset Primary Adverse Events

The primary safety endpoint will be evaluated using an exact test for a binomial proportion at a one-sided significance level of 2.5%. If the upper bound of the exact two-sided 95% confidence interval of the primary safety endpoint rate is less than the performance goal of 12%, the study will be considered to have demonstrated safety.

Primary Effectiveness Endpoint:
The null and alternative hypotheses are:

H_0: $P_E \leq 0.90$ vs. H_A: $P_E > 0.90$,
where P_E denotes the rate of acute effectiveness success

The primary effectiveness endpoint will be evaluated using the exact test for a binomial proportion at a one-sided significance level of 2.5%. If the lower bound of the exact two-sided 95% confidence interval of the primary effectiveness endpoint rate is greater than the performance goal of 90% %, the study will be considered to have demonstrated effectiveness.

The study will be declared a success if both primary safety and acute effectiveness endpoints are met. The secondary endpoint will be tested only if the primary endpoints are met.

19.4.4.1 Subgroup Analyses

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

19.4.5 Secondary Effectiveness Endpoint Analysis

The null and alternative hypotheses are:

H_0: $P_1 \leq 0.50$ vs. H_A: $P_1 > 0.50$,
where P_1 denotes the rate of secondary effectiveness success.

Percentage (%) of subjects with freedom from documented symptomatic and asymptomatic atrial arrhythmia (AF, AT or AFL of unknown origin) episodes based on electrocardiographic data (≥30 seconds on arrhythmia monitoring device) during the effectiveness evaluation period (Day 91-Day 365) will be estimated in the PP population at 365 days with the corresponding two-sided 95% exact binomial lower bound. 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 also be deemed an effectiveness failure The secondary effectiveness endpoint will be evaluated using the exact test for a binomial proportion at a one-sided significance level of 2.5%. If the lower bound of the exact two-sided 95% confidence interval of the secondary effectiveness endpoint rate is greater than the performance goal of 50%, the study will be considered to have demonstrated effectiveness.

19.4.6 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 SP and mITT analysis sets. Effectiveness endpoints and procedural data will be analyzed in the PP and mITT analysis sets respectively. NA, EE, CT/MRA, and PVI Durability endpoints will be analyzed in the NA, EE, CT/MRA, and PVI Durability analysis sets, correspondingly. Details of the analyses will be elaborated in the SAP.

19.4.6.1 Handling of Missing Data

- For the final primary safety analysis, if a subject does not have full 12 months of follow-up and the subjects has had a PAE at any time during the follow-up, then the subject will be considered an event. If a subject does not have 12 months of follow-up but has at least 3 months of follow-up, then their last observed status will be carried forward for the 12-month safety endpoint as a conservative proxy. If a subject does not have at least 3 months of follow-up for the primary safety endpoint, then this subject will be excluded from the final primary safety analysis.

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

- 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 Ethics and Protection of Human Subjects

20.1 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 this study, 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 CIP.
- **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 CIP deviations.

20.2 Informed Consent Process

20.2.1 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 and maintain the investigational site's signed informed consent with the essential 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.

20.3 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.

20.3.1 Research Use of Stored Data

- Intended Use: Data collected under this CIP 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.

21 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 CIP selection criteria (if not already present).
- Dated and signed notes from the day of entry into the study including the study Sponsor (Biosense Webster), CIP 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 CIP -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.

22 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 CIP, 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.

23 Data Handling and Record Keeping

23.1 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.

23.1.1 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.

23.1.2 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 as described in Table 10.

Table 10: 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
Clinical Investigation l 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 plan.

23.1.3 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 CIP 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.

23.1.4 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.

23.2 Study Record Retention and Archiving

Records and reports for the study will remain on file at the site for a minimum of 10 years or per country specific record retention requirements following notification by the sponsor that all investigations have been terminated or completed, or in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market. 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.

Each Member State shall require that this documentation is kept at the disposal of the competent authorities for the period referred to in the first section of the paragraph, in case the Sponsor, or its contact person or legal representative as referred to in Article 62 (2) (MDR [EU - 2020/561]) established within its territory, goes bankrupt or ceases its activity prior to the end of this period.

24 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 CIP 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 CIP 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:

- If suspicion of an unacceptable risk, including serious health threat, to subjects arises during the clinical investigation, or when so instructed by the EC or regulatory authorities, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the EC or regulatory authority to suspend or prematurely terminate participation in a clinical investigation at the investigation sites for which they are responsible.
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to CIP requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

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

The Sponsor must notify the CA in case of a temporary halt or early termination of the clinical investigation. This notification must be made within 15 days of the temporary halt or early termination, providing a justification for the event. In the event that the sponsor has temporarily halted or terminated early the investigation on safety grounds, the CA must be informed within 24 hours of the event.

25 Study Completion

The study end shall be deemed to coincide with the last visit of the last subject. The sponsor will inform the responsible CA within 15 days of the study end in a participating country. In addition, each CA will be notified within 15 days of the global study end.

Within one year of the end of the clinical investigation, the full final clinical investigational report must be submitted to the CA. A clinical investigation ends with the last visit of the last subject unless another endpoint is specifically set out in the clinical investigation plan.

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. As per ISO 14155:2020 paragraph 5.4. a description of this clinical investigation will be registered in publicly accessible database (http://www.ClincialTrials.gov) and content will be updated throughout the study. Results will be entered at completion of the clinical investigation.

27 Document Filing

A copy of all approved versions of the Clinical Investigation Plan 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

Summary of previous clinical investigations with similar devices

Name of the previous Clinical Investigation (CI)	NCT# (CIV-ID, if applicable)	Manufacturer	Investigational Medical Device (IMD)	Model of IMD	Indication	Target population in the study	Duration of use	Any other important differences between the previous CIs and the current CI
SMART-SF	NCT01385202	Biosense Webster, Inc.	THERMOCOOL SMARTTOUCH™ SF Catheter	D-1348-XX-SI curves DD, FF, JJ, DJ and DF D-1347-XX-SI curves D, F, J	It is indicated for catheter-based cardiac electrophysiological mapping (stimulation and recording) and, when used in conjunction with an RF generator, for cardiac ablation. It provides a real-time measurement of contact force between the catheter tip and heart wall, as well as location information when used with the CARTO™ 3 System.	Adult patients with symptomatic paroxysmal atrial fibrillations	It is non-implanted catheter intended for single-patient, single-use only. There is no specific limitation in duration of use; however, cardiac ablation procedures typically last 2 to 4 hours.	The study was testing the catheter when used in conjunction with an RF generator. It was conducted at 17 US sites.
PRECEPT	NCT02817776	Biosense Webster, Inc.	THERMOCOOL SMARTTOUCH™ SF catheter	D-1348-XX-SI curves DF, FF and FJ D-1347-XX-SI curves D, F, J	It is indicated for catheter-based cardiac electrophysiological mapping (stimulation and recording) and, when used in conjunction with an RF generator, for cardiac ablation. It provides a real-time measurement of contact force between the catheter tip and heart wall, as well as location information when used with the CARTO™ 3 System.	Adult patients with relatively early persistent atrial fibrillations, with episodes lasting >7 days but not more than 1 year.	It is non-implanted catheter intended for single-patient, single-use only. There is no specific limitation in duration of use; however, cardiac ablation procedures typically last 2 to 4 hours.	The study was testing the catheter when used in conjunction with an RF generator. It was conducted at 30 sites in US and Canada with total enrolment of 381 subjects. The PRECEPT study used both a 3-month “medication adjustment period” and an additional 3-month “therapy consolidation” period, creating a 6-month “blanking period” during which: 1) additional ablations could be performed; and/or 2) antiarrhythmic medications could be added or adjusted.
VISTAX	NCT03062046 CIV-17-03-018764	Biosense Webster, Inc.	Ablation Index and VISITAG™ software in combination with a THERMOCOOL SMARTTOUCH™ (ST) or SmartTouch Surroundflow™ (STSF) catheter	Ablation Index module V4 was investigational, STSF not investigational and could be used from the shelf	During RF application, when the VISITAG™ filter thresholds are met, the Tag Index value appears on the Readings Dashboard.	Adult patients with symptomatic paroxysmal atrial fibrillations	Ablation Index and VISITAG™ software is installed in The CARTO™ 3 System, which is a multiple-use medical device provided non-sterile, and as such it has no therapeutic use lifetime.	This study was conducted to evaluate safety and effectiveness of a standardized RF ablation workflow.

Name of the previous Clinical Investigation (CI)	NCT# (CIV-ID, if applicable)	Manufacturer	Investigational Medical Device (IMD)	Model of IMD	Indication	Target population in the study	Duration of use	Any other important differences between the previous CIs and the current CI
SURPOINT	NCT03624881	Biosense Webster, Inc.	VISITAG SURPOINT Module with External Processing Unit (EPU) in combination with THERMOCOOL SMARTTOUCH™ SF (STSF) and THERMOCOOL SMARTTOUCH™ (ST) catheters	D-1348-XX-S curves DF, FF, and FJ D-1347-XX-S	During RF application, when the VISITAG™ filter thresholds are met, the Tag Index value appears on the Readings Dashboard.	Adult patients with drug-resistant symptomatic atrial fibrillations (paroxysmal or persistent)	The VISITAG SURPOINT Module of the CARTO™ 3 System is a multiple-use medical device provided non-sterile, and as such it has no therapeutic use lifetime.	This study was conducted to evaluate the application during RF ablation.
InspIRE	NCT04524364 CIV-20-04032584	Biosense Webster, Inc.	TRUPULSE™ GeneratorVARIPULSE™ Bi-Directional Catheter	D-1417-01-I (TRUPULSE™ Generator) D-1412-01-SI (VARIPULSE™ Bi-Directional Catheter)	The VARIPULSE™ Catheter is indicated for use in catheter based cardiac electrophysiological mapping (stimulating and recording) and, when used with a TRUPULSE™ Generator, for cardiac ablation. The catheter provides location information when used with the CARTO™ 3 System.TRUPULSE™ Generator is indicated for use in conjunction with compatible cardiac ablation catheters to deliver pulsed field (PF) and radiofrequency (RF) energy during cardiac ablation procedures.	Adult patients with symptomatic paroxysmal atrial fibrillation	The VARIPULSE™ Catheter is non-implanted sterile catheter intended for single-patient, single-use only. There is no specific limitation in duration of use. The therapeutic device lifetime is the length of the procedure. Traditional point-by-point cardiac RF ablation typically last 2 to 4 hours.The TRUPULSE™ Generator s a reusable non-patient contacting device. There is no specific limitation in duration of use. The therapeutic device lifetime is the length of the procedure.	This study consists of two sequential waves. The WAVE I was the safety characterization phase, with intention to delineate safety and provide preliminary estimates for safety and acute effectiveness of the IRE system. The WAVE II phase was to evaluate safety and long-term effectiveness.

Name of the previous Clinical Investigation (CI)	NCT# (CIV-ID, if applicable)	Manufacturer	Investigational Medical Device (IMD)	Model of IMD	Indication	Target population in the study	Duration of use	Any other important differences between the previous CIs and the current CI
AdmIRE	NCT05293639	Biosense Webster, Inc.	TRUPULSE™ Generator VARIPULSE™ Bi-Directional Catheter	D-1417-01-I (TRUPULSE™ Generator) D-1412-01-SI (VARIPULSE™ Bi-Directional Catheter)	The VARIPULSE™ Catheter is indicated for use in catheter based cardiac electrophysiological mapping (stimulating and recording) and, when used with a TRUPULSE™ Generator, for cardiac ablation. The catheter provides location information when used with the CARTO™ 3 System. TRUPULSE™ Generator is indicated for use in conjunction with compatible cardiac ablation catheters to deliver pulsed field (PF) and radiofrequency (RF) energy during cardiac ablation procedures.	Adult patients with symptomatic paroxysmal atrial fibrillations	The VARIPULSE™ Catheter is non-implanted sterile catheter intended for single-patient, single-use only. There is no specific limitation in duration of use. The therapeutic device lifetime is the length of the procedure. Traditional point-by-point cardiac RF ablation typically last 2 to 4 hours. The TRUPULSE™ Generator s a reusable non-patient contacting device. There is no specific limitation in duration of use. The therapeutic device lifetime is the length of the procedure.	The study was conducted at 30 US sites with the total enrollment of 362 subjects.

30 Appendix 2

Definitions on 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 post-ablation 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 arrhythmia'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

31 Appendix 3

Table 11: 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.

32 Appendix 4

Country	Name of Competent Authority	Contact Information
Austria	Austrian Federal Office for Safety in Health Care (BASG)	clinicaltrials@ages.at
Belgium	The Federal Agency for Medicines and Health Products (FAMHP)	In Belgium the completed SAE Reporting Form may be sent to the R&D division of the FAMHP by e-mail at ct.rd@fagg-afmps.be or through CESP. If you send it directly by email to ct.rd@fagg-afmps.be, please mention the following in the subject line: "SAE notification – Clinical investigation Eudamed number" (use the Eudamed number provided on the approval letter).
Denmark	Danish Medicines Agency Medical Devices	Med-udstyr@dkma.dk
Lithuania	State Health Care Accreditation Agency under the Ministry of Health	vaspvt@vaspvt.gov.lt