SHINE

Multi-electrode Radiofrequency Balloon Catheter use for the Isolation of the Pulmonary Veins.

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The Biosense Webster Multi-electrode RF Balloon Catheter (D-1389-02-SI) and Multi-Electrode Circular Diagnostic Catheter (D-1390-01-SI, D-1390-02-SI, D-1390-03-SI) are for investigational device use only and are not commercially available anywhere in the world. "Balloon Catheter/Balloon Ablation Catheter" for RF balloon catheter and 'Frontera' for Circular Diagnostic catheter are internal Biosense Webster project names and other than as used in the present clinical investigation, are not intended for any other external use. The final commercial or trade name of the Multi-electrode RF Balloon and Circular Diagnostic Catheter may be different.

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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
ACL	Advanced Catheter Location
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
AMI	Acute Myocardial Infarction
ARB	Angiotensin II Receptor Blockers
AT	Atrial Tachycardia
ATP	Adenosine triphosphate
BID	Bis In Die (twice a day)
CA	Competent Authority
CABG	Coronary Artery Bypass Graft
CB	Cryoballoon
CHF	Congestive Heart Failure
CK	Creatine Kinase
COPD	Chronic Obstructive Pulmonary Disease
CNS	Central Nervous System
CPK	Creatinine Phosphokinase
CRF	Case Report Form
CRO	Clinical Research Organization
CS	Coronary Sinus
CSR	Clinical Study Report
CT	Computed Tomography
CVA	Cerebrovascular Accident or Stroke
DMC	Data Monitoring Committee
DM	Diabetes Mellitus
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

Acronym/ Abbreviation	Expanded Term
EMEA	Europe, Middle East and Africa
EP	Electrophysiology
ESC	European Society of Cardiology
FAM	Fast Anatomical Mapping
FDA	Food and Drug Administration
Fr	French
FU	Follow-Up
GCP	Good Clinical Practices
GSMC	Global Safety Monitoring Committee
HB	Hot Balloon
HM	Holter Monitoring
HRS/EHRA/ECAS	Heart Rhythm Society / European Heart Rhythm Association / European Cardiac Arrhythmia Society
ICE	Intracardiac Echocardiography
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Inner Diameter
IFU	Instruction for Use
ILR	Implantable Loop Recorder
ITT	Intention to treat
LA	Left Atrium
LB	Laser Balloon
LBBB	Left Bundle Branch Block
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
ME	Micro Electrode
MEDDEV	Medical Device Directive
MI	Myocardial Infarction
mITT	Modified Intent to Treat
MoCA	Montreal Cognitive Assessment
MoH	Ministry of Health
MRA	Magnetic Resonance angiogram
MRI	Magnetic Resonance Imaging
mRS	Modified Ranking Scale
NAE	Neurological Assessment Evaluable
NIHSS	National Institute of Health Stroke Scale
NSR	Normal Sinus Rhythm
NYHA	New York Heart Association
OD	Outer Diameter

Acronym/ Abbreviation	Expanded Term
PAF	Paroxysmal Atrial Fibrillation
PFO	Patent foramen ovale
PI	Principal Investigator
PN	Phrenic Nerve
PNP	Phrenic Nerve Paralysis
PP	Per Protocol
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QA	Quality Assurance
QC	Quality Control
QoL	Quality of Life
RA	Right Atrium
RF	Radiofrequency
RFCA	Radiofrequency Catheter Ablation
RV	Right Ventricle
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SP	Safety Population
SDV	Source Data Verification
SVC	Superior Vena Cava
TAS	Tri-Axial Sensor
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TS	Transseptal
TTE	Transthoracic Echocardiography
TTM	Transtelephonic Monitoring
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

Key roles and Responsible Parties

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

The sponsor maintains an updated list of principal investigators, sites, institutions and Contract Research Organizations (if applicable). The definitive list shall be integrated into the study report.

Protocol Summary

Study Name:	SHINE
Study Title:	Multi-electrode Radiofrequency Balloon Catheter use for the isolation of the pulmonary veins.
Study Number:	BWI_2017_01
Summary:	This clinical investigation is a prospective, multicenter, single arm clinical evaluation utilizing the Biosense Webster multi-electrode radiofrequency balloon catheter and the Biosense Webster multi-electrode circular diagnostic catheter. The objective of this clinical investigation is to assess the safety and acute effectiveness of the multi-electrode radiofrequency balloon catheter and multi-electrode circular diagnostic catheter (Frontera) when used for the isolation of the pulmonary veins in the treatment of Paroxysmal Atrial Fibrillation (PAF). A maximum of 230 evaluable subjects with symptomatic PAF who are candidates for atrial fibrillation ablation will be enrolled in this study, excluding roll-in subjects. Subjects will be evaluated at 7 days, 1, 3, 6 and 12 months following procedure. 40 subjects will be included in the Neurological Assessment Evaluable (NAE) subgroup.
Objective:	The objective of this study is to assess the safety and acute effectiveness of the multi-electrode radiofrequency balloon catheter and multi-electrode circular diagnostic catheter in the isolation of the atrial pulmonary veins in treatment of subjects with PAF.
Endpoint:	**Primary Endpoints:** <u>ACUTE SAFETY</u> Incidence of early onset Primary Adverse Events (PAE) (within 7 days of the mapping and ablation procedure). PAEs include the following AEs: • Death* • Atrio-Esophageal Fistula* • Myocardial Infarction • Cardiac Tamponade/perforation • Thromboembolism • Stroke/CVA • TIA • Phrenic Nerve Paralysis • Pulmonary Vein Stenosis* • Major Vascular Access Complication/Bleeding *Device or procedure related death, pulmonary vein stenosis and atrio-esophageal fistula, that occur greater than one week (7 days) and (≤) less or equal to 90 days post-procedure are considered and analyzed as primary AEs.

	ACUTE EFFECTIVENESS • Acute procedural success defined as confirmation of entrance block in treated PVs after adenosine and/or isoproterenol challenge (with or without the use of a focal catheter). **Main Secondary Endpoints:** • Incidence of individual PAE from the primary composite • Incidence of Serious Adverse Device Effects (SADEs) • Incidence of Serious Adverse Events (SAEs) within 7 days (early-onset), >7-30 days (peri-procedural) and >30 days (late onset) of initial ablation procedure • Incidence of non-serious adverse events • Incidence of pre-and post-ablation asymptomatic and symptomatic cerebral emboli as determined by MRI evaluations. • Frequency, anatomic location, and size (diameter and volume) of cerebral emboli by MRI evaluations at baseline, post-ablation and during follow-up. • Incidence of new or worsening neurologic deficits post-ablation and follow-up, compared to baseline. • Summary of NIHSS scores at baseline, post-ablation and during follow-up. • Summary of MoCA and mRS scores at baseline, 1 month and during further follow-up. • Hospitalization for cardiovascular events • Percentage (%) of PVI touch-up by focal catheter among all targeted veins and by subject. • Percentage (%) of subjects with use of focal catheter ablations for non-PV triggers. • Percentage (%) of subjects with freedom from documented symptomatic atrial fibrillation (AF), atrial tachycardia (AT), or atypical (left side) atrial flutter (AFL) episodes (episodes >30 seconds on arrhythmia monitoring device from day 91 to 180). • Percentage (%) of subjects with freedom from documented atrial fibrillation (AF), atrial tachycardia (AT), or atypical (left side) atrial flutter (AFL) episodes (episodes >30 seconds on arrhythmia monitoring device from day 91 to 180). • Percentage (%) of subjects with freedom from documented symptomatic atrial fibrillation (AF), atrial tachycardia (AT), or atypical (left side) atrial flutter (AFL) episodes (episodes >30 seconds on arrhythmia monitoring device from day 91 to 365). • Percentage (%) of subjects with freedom from documented atrial fibrillation (AF), atrial tachycardia (AT), or atypical (left side) atrial flutter (AFL) episodes (episodes >30 seconds on arrhythmia monitoring device from day 91 to 365). • Procedural parameters including but not limited to: total procedure and ablation time, balloon dwell time, RF application time, time to effect (PVI measured by Frontera), number of RF applications, fluoroscopy time and dose. • Health economic data, including but not limited to index procedural workflow costs, QoL and hospital costs.

	Roll-in subjects will not be included in the main study analyses, and will be analyzed separately
Population	Subjects diagnosed with symptomatic paroxysmal AF and candidate for RF ablation treatment through pulmonary vein isolation.
Study Design	Interventional, Pivotal, Prospective, multicenter, Single Arm Clinical Evaluation Roll-in Subjects: -1 roll-in subject will be included for ablating physicians that participated in the RADIANCE Study -2 roll-in subjects will be included by ablating physicians that didn't participate in the RADIANCE study and have extensive balloon experience (>15 cases/year) -3 roll-in subjects will be included by ablating physicians that didn't participate in the RADIANCE study and don't have extensive balloon experience (<15 cases/year) These subjects will not be analyzed for the main study endpoints. .
Clinical Sites	Up to 20 sites within Europe
Sample Size	Sample size calculations were performed using performance goals of 15% and 80% respectively for the safety and effectiveness endpoint rates. The primary safety and effectiveness endpoints will be evaluated using exact tests for binomial proportions at a one-sided 5% significance level. The sample size for the study is primarily driven by the safety endpoint. An adaptive Bayesian design[76] will be used to determine the sample size based on the safety endpoint alone. Sample size selection interim analyses will be performed after inclusion of 80, 130, 180, and 230 evaluable patients (includes all subjects who had the study catheter inserted, except roll-ins). Safety outcomes at 30 days will be used as a proxy for the primary safety endpoint at each interim analysis. The final safety analysis will be based on complete follow-up for the primary safety endpoint for all evaluable patients. Predictive probabilities of success will be used to determine whether the sample size at each interim analysis will be sufficient or if the trial enrollment will continue. At the time of each interim analysis, predictive probabilities of success will be estimated using the available data from all evaluable subjects, assuming a non-informative uniform prior distribution for the primary safety rate. Enrollment will be stopped if the predictive probability of trial success at any interim is greater than 90%, or if the predictive probability of trial success with the maximum sample size is less than a futility bound of 6.5%. Otherwise, enrollment will continue until the next interim or the final sample size. Analysis of the effectiveness endpoint will be performed at the final sample size determined for the safety endpoint. Power for the effectiveness endpoint assessment is >80% at all sample sizes ≥80 subjects. Operating characteristics of the adaptive design were simulated and the Type-I error for safety was shown to be less than 5%. In addition, the safety endpoint will be adequately powered for a range of safety rates. The simulation results will be provided in the Statistical Analysis Plan.

	Since Type-I errors for both safety and effectiveness are controlled at a 5% level, and the study will be successful if both safety and effectiveness objectives are met, the overall study Type-I error rate will be controlled at 5%. Based on a maximum amount of 20 sites, assuming an average of 2 ablating physicians per site, an estimated amount of up to 60 roll-ins will be included in the study.
Description of Investigational Devices	The **Multi-Electrode Radiofrequency (RF) Balloon catheter** is intended for use for cardiac electrophysiological ablation of pulmonary veins of the atria when used with the nMARQ™ Multi-Channel RF Generator, version 2.3.1. [redacted] The **Multi-Electrode Circular Diagnostic Catheter** is indicated for electrophysiological recording and stimulation of the atrial region of the heart and is used in conjunction with the Multi-Electrode Radiofrequency Balloon Catheter and ancillary equipment. [redacted]
Study Duration	Approximately 27 Months (enrollment and follow-up)
Participant Duration	Subjects will be followed till 12 months post-procedure
Study Inclusion Criteria	1. Diagnosed with Symptomatic Paroxysmal AF. 2. Selected for AF ablation procedure for pulmonary vein isolation. 3. Able and willing to comply with uninterrupted per-protocol anticoagulation requirements 4. Age 18-75 years. 5. Able and willing to comply with all pre-, post- and follow-up testing and requirements. 6. Signed Patient Informed Consent Form.
Study Exclusion criteria	1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause. 2. Previous surgical or catheter ablation for AF. 3. Anticipated to receive ablation outside the PV ostia and CTI region 4. Previously diagnosed with persistent, longstanding AF and/or continuous AF > 7 days, or > 48 hrs terminated by cardioversion. 5. Any percutaneous coronary intervention (PCI) within the past 2 months. 6. Valve repair or replacement and presence of a prosthetic valve. 7. Any carotid stenting or endarterectomy.

	8. Coronary artery bypass grafting (CABG), cardiac surgery (e.g. ventriculotomy, atriotomy), or valvular cardiac surgical or percutaneous procedure within the past 6 months. 9. Documented left atrium (LA) thrombus on baseline/pre-procedure imaging. 10. LA antero posterior diameter > 50 mm 11. Any PV with a diameter ≥ 26 mm 12. Left Ventricular Ejection Fraction (LVEF) < 40%. 13. Contraindication to anticoagulation (e.g. heparin). 14. History of blood clotting or bleeding abnormalities. 15. Myocardial infarction within the past 2 months. 16. Documented thromboembolic event (including transient ischemic attack [TIA]) within the past 12 months. 17. Rheumatic Heart Disease. 18. Uncontrolled heart failure or New York Heart Association (NYHA) function class III or IV. 19. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months. 20. Unstable angina. 21. Acute illness or active systemic infection or sepsis. 22. Diagnosed atrial myxoma or interatrial baffle or patch. 23. Presence of implanted pacemaker or implantable cardioverter defibrillator (ICD). 24. 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 chronic symptoms. 25. Significant congenital anomaly or medical problem that, in the opinion of the investigator, would preclude enrollment in this study. 26. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of child bearing age and plan on becoming pregnant during the course of the clinical investigation. 27. Enrollment in an investigational study evaluating another device, biologic, or drug. 28. Has known pulmonary vein stenosis. 29. Presence of intramural thrombus, tumor or other abnormality that precludes vascular access, or manipulation of the catheter. 30. Presence of an IVC filter 31. Presence of a condition that precludes vascular access. 32. Life expectancy or other disease processes likely to limit survival to less than 12 months. 33. Presenting contra-indication for the devices (e.g. TTE, CT, Holter, etc.) used in the study, as indicated in the respective instructions for use. 34. Categorized as a vulnerable population and requires special treatment with respect to safeguards of well-being Additional exclusion criteria for Neurological Assessment Evaluable (NAE) subjects: 35. Contraindication to use of contrast agents for MRI such as advanced renal disease, etc. (at PI discretion) 36. Presence of iron-containing metal fragments in the body 37. Unresolved pre-existing neurological deficit.

1 Background Information and Scientific Rationale

1.1 Background Information

Atrial Fibrillation (AF) is the most common sustained arrhythmia in humans. It affects anywhere from 0.4% to 1% of the general population, and increases in prevalence with age to approximately 8% in patients over 80 years of age.[1, 2] The primary clinical benefit of AF ablation is improvement in quality of life (QoL) resulting from the elimination of arrhythmia-related symptoms such as palpitations, fatigue, or effort intolerance.[3] In recognition of this, the elimination of symptomatic atrial arrhythmias was recommended by the 2017 HRS/EHRA/ECAS Consensus on Catheter and Surgical Ablation of Atrial Fibrillation.[3] The opinion of the ECC as expressed in their 2016 AF Management Guidelines is that "Catheter ablation of symptomatic paroxysmal AF is recommended to improve AF symptoms in patients who have symptomatic recurrences of AF on antiarrhythmic drug therapy and who prefer further rhythm control therapy, when performed by an electrophysiologist who has received appropriate training and is performing the procedure in an experienced center."[2, 4]

The 2017 HRS/EHRA/ECAS consensus statement states that electrical isolation of the pulmonary veins (PVs) from the left atrium 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 RF catheters has provided positive results for treating many types of supraventricular arrhythmias,[5, 6] including PAF.[5-11] However, the procedure is technically complex and has a long learning curve. Radiofrequency (RF) ablation success is highly dependent on operator skill and is associated with a high degree of PV reconnection.[12-14] Additionally, RF ablation carries a major complication rate of roughly 4.5%.[15]

In order to reduce technical complexity and potentially decrease major complications, balloon ablation catheters were developed. Balloon catheters use tissue cooling (cryoballoon), heating (hot balloon) or selective destruction with a laser (laser balloon) to create lesions and isolate PVs.

The second-generation cryoballoon (CB-2), so-called because of design improvements over the original first-generation cryoballoon, uses injected refrigerant to ablate tissue that comes in contact with the distal hemisphere of the balloon (cooling zone). Advantages of this technology over point-by-point RF ablation are that it is less complex, has shorter procedure times, short operator learning curve[16], durable PVI/low rate of AF recurrence,[17-20] minimal risk of atrioesophageal fistula or PV stenosis, successful ablation even in cases of complicated anatomy[16,21] and no requirement for 3D mapping.[22,23] While the CB-2 often allows single-shot PVI,[23-25] there is still some operator skill involved and various investigators have developed a pull-back technique (incomplete occlusion at the beginning of freezing) to minimize phrenic nerve (PN) injury.[25-28] In addition, PN pacing is required throughout the procedure on the right side so freezing can be immediately aborted if PN palsy (PNP) is observed.[19,22,26,27,29] Because of this, there is a greater rate of reconduction in the right superior pulmonary vein (RSPV).[18] Investigators who use the CB-2 differ in their recommendation of a "bonus freeze",[18,20,30,31] optimal dosing of cryoenergy (240 sec[22,24] vs. 180 sec[25,32] or even less,[29,30]), minimum temperature[21], the need for an endoluminal esophageal temperature cutoff[29,33,34], and

whether both sizes (23 mm and 28 mm[16]) should be used versus using the larger balloon exclusively.[19,23,31,34,35] Further disadvantages of this technique are that it is not appropriate for focal touch-ups or repeat ablation of conduction gaps,[18,20] and that the larger balloon, which most investigators seem to prefer[16], may not fit an especially narrow PV ostium.

The hot balloon (HB) is a compliant balloon that uses a heated saline/contrast mixture to heat the surrounding tissue and generate thermal lesions. Advantages of the HB system over conventional RF ablation are the possibility of single-shot PVI[36] and reduced risk of perforation/mechanical injury to endocardium.[37] In addition, the HB can be withdrawn immediately if phrenic nerve (PN) capture is lost, in contrast to the CB-2 which can adhere to the tissue and make withdrawal difficult.[38,39] A disadvantage to this system is that it still requires a fair amount of operator skill and finesse,[38,39] and the balloon position should be checked often by fluoroscopy and repositioned if indentation is noted.[39,40] The need for esophageal temperature monitoring and, when applicable, cooling[40] also increases procedural complexity. The need for PN pacing and/or fluoroscopic monitoring of the diaphragm is still paramount with this system in order to prevent PNP.[39,40] Because central balloon temperature, RF time, and the diameter to which the balloon is inflated are all dependent upon the thickness of the target ablation tissue (each PV, e.g.),[39,40] extensive pre-procedure imaging (intracardiac echocardiography [ICE] or 3-D Computed Tomography [CT]) is required.[39,40] Like the CB-2, HB is not useful for focal touchups or repeat ablation of gaps/ sites of reconduction. To ablate such areas, a conventional irrigated tip RF catheter is still needed.[39]

The laser balloon (LB) is a compliant balloon that can be inflated to a broad range of diameters and contains a central catheter shaft with a fiberoptic endoscope and a second fiber for laser energy delivery. Applications of laser energy last 20-30 seconds and cover a 30^{o} arc with the aim of overlapping lesions by 30-50% to achieve transmurality.[41,42] Esophageal temperature monitoring and PN pacing are still necessary. An advantage of this technology is that all endoscopic images are instantaneously displayed on a separate screen so that any potential gaps can be detected in real time.[41] The aiming and laser beams can be rotated, advanced, or retracted for flexibility in lesion pattern based on PV anatomy. The operator also has the ability to titrate laser energy.[41] Ablation in or near the blood source requires decreased energy output;[43] however, the threat of thermocoagulation exists.[44] A common finding with LB ablation is that long procedure times are required for conventional RF ablation.[41,43,45-52] It takes anywhere from 25-50 lesions to successfully isolate one PV.[45-48,53] Higher energy output is associated with decreased procedure time, but at the expense of greater risk of steam pop and balloon damage due to overheating.[45] A disadvantage inherent to this system is that the catheter shaft itself obscures about one fifth of the circumference of the PV ostium, so rotation of the catheter is required to complete ablation of the PV.[41,48] The same problem of obscuring the view occurs with a spiral mapping catheter, so it must be inserted after the balloon is deflated; therefore electrical mapping and ablation cannot be performed simultaneously.[41,52] Furthermore, the endoscopic images are 2-dimensional and therefore do not show the level of the ablation line in relationship to the PV ostium.[41] The possibility of misalignment increases each time the LB is repositioned.[52] Finally, since the LB is not designed as an over-the-wire device, there may be an increased risk of pericardial tamponade.[47,51]

A common advantage to all of these balloon ablation systems is good contact with the target tissue regardless of individual anatomy. A disadvantage is the difficulty of avoiding healthy or already-ablated tissue.

1.2 Previous Experience with the multi-electrode RF balloon catheter

1.2.1 Multi-Electrode RF Balloon Catheter In-Vivo Porcine Beating Heart Model

Refer to IB for detailed section.

The purpose of the study was to verify the safety and performance of the following devices in a porcine beating heart model, when simulating a clinical electrophysiology procedure (pulmonary vein isolation):

- Multi-electrode RF balloon catheter
- 13.5 F compatible deflectable sheath (Oscor®)
- CARTO® 3 software compatible with RF ablation balloon catheter

The study evaluated the Multi-electrode RF Balloon Catheter and its ability to work in conjunction with the nMARQ™ multi-channel RF generator and the CARTO® 3 system, COOLFLOW™ irrigation pump, catheter interface cable and standard pacing and recording system in a beating heart animal study to demonstrate safety and performance.

Based on the passing results under the study, the safety and performance of the multi-electrode RF balloon catheter simulating a clinical EP procedure in a porcine beating heart model is verified safe for clinical use.

1.2.2 Multi-Electrode Circular Diagnostic Catheter In-Vivo Porcine Beating Heart Model

Refer to IB for detailed section.

The purpose of the study was to verify the performance and safety of the Multi-Electrode Circular Diagnostic Catheter in a porcine beating heart model, when simulating a clinical electrophysiology procedure with use of following devices:

- nMARQ™ RF generator
- CARTO® 3 system, with software compatible with RF ablation balloon catheter
- Catheter Interface Cable
- Standard Pacing and recording system
- COOLFLOW® Irrigation Pump

The study evaluated the Multi-Electrode Circular Diagnostic Catheter and its ability to work in conjunction with the nMARQ™ multi-channel RF generator and the CARTO® 3 system, in a beating heart animal study to demonstrate safety and performance.

Gross pathology examination was performed and cardiac tissue was found to be normal. There was no evidence of thrombus, dissection, perforation, or other cardiac injury in left atrium of both animals where the multi-electrode circular diagnostic catheter was manipulated in the pulmonary veins.

Based on the results of safety and performance of multi-electrode circular diagnostic catheter in conjunction with multi-electrode RF balloon catheter and ancillary equipment, all characteristics passed the acceptance criteria. Multi-electrode circular diagnostic catheter is verified safe for clinical use and equivalent to the LASSO® catheter in all characteristics.

1.2.3 The RADIANCE Clinical Investigation

A first in human 'RADIANCE' study with the Multi-electrode RF Balloon Catheter enrolled subjects between December 2, 2016 and March 8, 2017 in Europe. In this feasibility study 40 subjects with paroxysmal atrial fibrillation were enrolled. One subject (7.1%) was excluded prior to RF ablation procedure. In total 39 subjects were treated with the investigational Biosense Webster multi-electrode RF balloon catheter. Four different centers with 9 different operators participated in the study.

Of the 40 enrolled subjects, 23 (57.5%) were male and 17 (42.5%) were female. The mean age for the 40 subjects was 60.7 ± 10.02 years. The most prevalent medical condition reported at baseline was (systemic) hypertension (22/40 (55.0%)). Subjects suffered from symptomatic AF for an average of 51.7 ± 49.71 months at baseline.

The primary endpoint was the incidence of primary procedure-related adverse events occurring within seven days of the procedure. From the primary safety endpoint, one subject (2.5%) experienced an early-onset (<7 days) primary adverse event, Diaphragmatic Paralysis. No subject deaths, atrio-esophagael fistula, myocardial infarction, cardiac tamponade/perforation, heart block, thromboembolism, CVA, TIA, pneumothorax, pulmonary edema, pericarditis, major vascular access complication/bleeding, moderate or severe pulmonary vein stenosis were reported.

Apart from the primary adverse events, there were 4 serious adverse events (SAE) reported as not being related to the investigational device and study procedure. One SAE (prolonged hospital stay for esophageal erythema) has been reported as possibly device and definitely (causal relationship) procedure related.

Among 39 subjects that underwent post-ablation cerebral MRI examination and 1 or more neurological assessment, 9 subjects (23.1%) were observed with new asymptomatic Cerebral Embolic (ACE) lesions. For one of these subjects, an air embolism on sheath insertion was noted during the procedure. 2/9 subjects had interrupted warfarin treatment. All ACE lesions were resolved during follow-up cerebral examination.

All 39 treated subjects underwent a post procedural esophageal endoscopy. No ulceration was observed in any of the cases. Only esophageal erythema was observed in 5 subjects (12.8%).

The procedural performance with the device was favorable, with 100 percent of the treated pulmonary veins electrically isolated without the need for a focal ablation catheter.

As a conclusion, results showed the RF balloon catheter was able to achieve facile, efficient and safe electrical isolation of all pulmonary veins with a high rate of first-pass isolation and infrequent evidence of latent pulmonary vein re-conduction.

1.3 Rationale for design of the clinical investigation

The theoretical advantages to the use of the multi-electrode Radiofrequency Balloon Catheter in conjunction with multi-electrode Circular Diagnostic Catheter includes the benefits of other balloon-based ablation systems, such as high probability of single-shot PVI with minimal collateral damage to non-PV structures, but without the drawbacks of excessive heating or cooling of the surrounding tissue. The existing limitation of other existing balloon catheters is in the fact that these are single ablative elements that deliver identical amounts of energy along the full pulmonary vein ostium circumference, which can lead to over-ablation of thin tissue, under-ablation of thick tissue, and unnecessary complications.

The Multi-electrode RF balloon catheter has the potential to deliver directionally-tailored energy using multiple electrodes and hereby optimizing both safety and efficacy. The current study is a pivotal study that utilizes this new technology in human subjects with PAF. This study will evaluate the safety and acute effectiveness of the Multi-electrode RF Balloon catheter, with the multi-electrode Circular Diagnostic Catheter when being used for PV isolation in treatment of atrial fibrillation. The data of the study will be used for CE-mark registration of the device.

1.4 Potential Risk and Benefit

1.4.1 Known Potential Risks

Pericarditis: With any balloon-based ablation, pericarditis can occur due to mechanical or thermal irritation of the myocardium.[48] This tends to be underreported[46] as it is usually transient and resolves without intervention.

Phrenic nerve palsy (PNP): Injury to the PN may occur as a result of RF application in the region of the right pulmonary veins. The reported incidence of PNP varies from 0% to 0.48% when RF energy is used for point-by-point ablation.[65,66] While the reported incidence of PNP following HB ablation (<4%)[38-40,54] or LB ablation (≤6%)[41-49,51,52,55] is low, the incidence of PNP with CB-2 ablation was reported to range from <5%[16,18,20,24,30,31,34,35] to 27%, [19,21,23,25-28,30,55-57] even with continuous phrenic nerve pacing during right-sided ablation and abortion of freezing upon loss of capture. In most cases, PNP with CB-2 is a transient complication,[22] recovering before the end of the procedure,[19,21,27,35] or, if not, by the time of discharge.[16,23,26,29,30,57] However, in a few cases it has been observed to persist for 10[20,23,31] to 20[25,28] months, suggesting that the injury is permanent.

Atrioesophageal fistula (AEF): The application of RF energy along the posterior left atrium can result in thermal injury to the esophagus and the formation of an AEF. AEF is a rare but

catastrophic complication of AF ablation that can occur due to the anatomical proximity of the esophagus to the posterior wall of the LA and that is associated with a high mortality rate.[58] AEF has not been observed in clinical experience with the HB or LB. Only one patient (1.8% of 55 patients) presented with AEF in one prospective observational study with the CB-2[19] and this was the only case found in 18 series of consecutive procedures totaling over 2000 patients.[16,19-21,23-31,34,35,55-57]

While AEF is uncommon with balloon-based ablation systems, damage to the esophagus is fairly common. One study found that superficial thermal lesions developed in 2% of patients and thermal ulcerations in 10% of patients following CB-2 ablation.[34] Another study showed an incidence of esophageal lesions of 3.19% with CB-2.[29] Esophageal lesions were reported in 1-10% of patients following ablation with the HB.[39,40,54] Cooling saline is sometimes infused into the esophagus during HB ablation,[39,40,54] but this carries with it the further risk of aspiration.[40] Esophageal injury is most often found after LB ablation, with mild thermal lesions found in 7%[41] to 8%[50] of patients and more severe ulcerations found in 5% to 15%.[41,50,55] The severity of esophageal lesions was greater with LB compared to RF catheter ablation in a head-to-head study.[50] Moreover, esophageal temperatures in excess of 38.5°-39° C necessitating cessation of energy delivery and/or repositioning of the balloon occur more than half of the time with LB ablation.[41,42,45] The clinical significance of esophageal lesions, if any, is not known.[25,33,34]

Many investigators attempt to mitigate esophageal damage by monitoring endoluminal temperature during the ablation procedure. A cutoff temperature of 3° C has 100% sensitivity and 100% specificity for predicting esophageal thermal lesions following CB-2 ablation.[20] However, esophageal temperature during LB ablation has poor specificity for esophageal injury, with no significant correlation between maximal esophageal temperature and incidence and severity of esophageal thermal lesions.[50]

Pulmonary vein stenosis: The risk of pulmonary adverse events (e.g. PV stenosis, thrombus and hypertension) associated with an RF ablation procedure targeting the pulmonary veins is considered small (<4%).[9,10,61-64] PV stenosis has not been reported following CB-2 ablation. In clinical experience with HB ablation, PV stenosis was reported in <2-5% of patients,[38-40] and was usually asymptomatic.[40] Similarly, with LB ablation, PV stenosis is rarely reported. In one study, mild stenosis (up to 25% narrowing of the PVs) was found in 44% of patients and moderate stenosis (26-50% narrowing) in 6%; there were no cases of severe stenosis (>50% narrowing).[47]

Thrombus formation: A thrombus may form on the ablation electrode during the application of RF current that could become dislodged and embolize to produce stroke, myocardial infarction, or other ischemic injury. The risk of thrombus is minimal with CB-2, but microthrombi were found in preclinical studies following HB ablation.[36] In the clinical setting with HB, 5 patients of 238 (2.1%) developed a cerebral infarction. However, in each case, this was attributed to arrhythmia recurrence and insufficient anticoagulation.[39] With LB, data suggest that more energy applications and higher energy output facilitate thermocoagulation.[44,53] Thrombus formation following ablation may also occur on the endocardium and may produce arterial or pulmonary embolus.

Pericardial effusion/ cardiac tamponade: Cardiac perforation may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. Pericardial effusion was reported in 0.6% - 7.3% of patients ablated with CB-2,[16,27,35,56] and cardiac tamponade in 0.2% - 3%.[21,24,25,28] Pericardial effusion may occur at a rate of 15% in patients treated with the HB.[37] With the LB, LA perforation has occurred from mechanical trauma due to a whipping motion of the sheath toward the LA roof after balloon retraction.[41,51] Aside from these reports, the incidence of pericardial effusion has been <2%[47,48] and cardiac tamponade ≤5%[46-48,51] with the LB. Significant hemodynamic compromise can result in neurologic injury or death. This risk is greatest in a thin-walled chamber (ie, RA, LA, or RV). However, the risk of perforation due to steam pop is reduced when the minimum amount of energy output required to achieve transmurality is used.[45]

Cerebral ischemic lesions: The incidence of transient ischemic attack (TIA) is <3% following CB-2 ablation;[25,30,35] however, in most studies imaging for silent ischemic brain lesions was not performed. In one study in which post procedural imaging was obtained, 13.6% of LB-treated patients were observed to have new embolic brain lesions, and another 2.3% had diplopia secondary to an ischemic lesion.[44] There were similar findings of diplopia due to a suspected ischemic event (1.4%) in another LB study.[46] The incidence of asymptomatic cerebral lesions seen on MRI 1-2 days post-procedure in a randomized controlled study was 24% for LB, which was not significantly different from RF catheter ablation or first-generation CB.[53]
According to HRS guidelines, 2017, Asymptomatic cerebral emboli (ACE) incidence is varying from 2%-15% as a complication to AF ablation. It is defined as an occlusion of a blood vessel in the brain due to an embolus that does not result in any acute clinical symptoms and is therefore 'silent'. Emboli can result from a thrombus, gas, air, tissue or fat. Source of micro-emboli include thrombi, which can develop on sheaths, materials, air introduction through sheath or during catheter exchange.

Coronary artery occlusion: RF current may cause occlusion of a coronary artery, either by direct thermal damage, spasm, or thrombosis. Research suggests that the risk of coronary occlusion is less than 0.5%.[59,60] Because coronary arterial occlusion could produce myocardial infarction, angina or death, the physician will attempt to restore coronary blood flow through pharmacological, catheter and/or surgical intervention as medically indicated.

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

Cardiac perforation: Cardiac perforation may result from catheter manipulation or application of RF current (risk is <1%).[59,60] This may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. However, the risk of perforation related to a deep steam pop is reduced if RF energy is not delivered perpendicular to the wall at power above 35 or 40 watts. If the lesion is deeper, the risk of steam pop is higher above 35-40 watts.

Cardiac valve injury: Injury to a cardiac valve may result from catheter manipulation or the application of RF current (risk <1%).[59,60] This may produce valvular insufficiency and possibly require surgical valve replacement.

Vascular access / bleeding complication: Vascular access complication, femoral

arteriovenous fistula, hematoma, and pseudoaneurysm are commonly reported following CB-2 (typically <4%),[16,19,21,23-27,30,35,55-57] or LB ablation (<6%).[46,49] Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels (risk <1%).[59,60] 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.[59,60]

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%).[67-69]

Infection: The percutaneous procedure carries risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%).[59,60] This risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.

Additional contraindications: Additional contraindications for RF ablation include: hemodynamic instability, bacteremia, coagulopathy, prosthetic tricuspid valve, intra-atrial or venous thrombosis, and pregnancy. A patient could develop an allergic reaction to the local anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure (risk <1%).[70-75]

1.4.2 Minimization of Risk

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

Patient selection: Subjects will be prescreened 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 adverse events (refer to Section 4.2 for the Exclusion Criteria).[22]

Pre-procedure imaging: Subjects must have a pre-procedure Transesophageal Echocardiogram (TEE) or Intracardiac Echocardiography (ICE) 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 RF ablation catheters will be selected for participation in the study. AF ablation procedures will be performed in electrophysiology laboratories with the assistance of skilled nurses and technicians. Ablating investigators will undergo device training, including a combination of didactic and hands-on training using the multi-electrode RF balloon catheter in a simulation model, prior to enrolling subjects.

The risk of PNP will be minimized by monitoring the PN with pacing maneuvers before the ablation. Ablation will be stopped immediately if evidence of PN impairment is observed, and the balloon will be repositioned.

The risk of PV stenosis will be minimized by not positioning the balloon within the tubular portion of the target PV. The balloon should not be inflated while the catheter is positioned inside the pulmonary vein; rather, it is always to be inflated in the atrium, then positioned at the PV ostium.

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

In order to help prevent esophageal injury, intraluminal esophageal temperature monitoring is required for the study.

Post-procedural management: In accordance with the 2016 ESC AF Management Guidelines[2], all subjects will be recommended to be maintained on systemic oral anticoagulation therapy for at least two months post-procedure, beginning within 6 hours post-procedure. After two-months post-procedure, a decision regarding continuation of systemic anti-coagulation agents will be based on the patient risk for thromboembolism. Systemic oral anticoagulation will be recommended to be continued beyond two-months post-ablation in patients with CHA_2DS_2-VASc score ≥2.

Safety data during enrollment and follow-up will be closely monitored and evaluated per the specific safety management plan for the study. Also, refer to safety section (9) for more information on safety management.

1.4.3 Known Potential Benefits

In patients with atrial fibrillation, elimination of or a reduction in symptoms is a major driving force for therapy. The primary clinical benefit of ablation of AF is an improvement in QoL resulting from the elimination of arrhythmia-related symptoms such as palpitations, fatigue, or effort intolerance.[3] The Balloon Type catheter is intended to allow for the ablation of larger areas of tissue compared to traditional single tip catheters. Thus, the multi-electrode RF balloon catheter should possess the benefit of reduced procedure time, the possibility of single-shot-PVI, and fewer catheter exchanges.

Moreover, ablation procedures using Balloon catheters are typically less complex than point-by-point ablation procedures. By implementing a compliant balloon design, the RF balloon Catheter can mold to varied PV anatomy and achieve very good contact with the tissue. This allows for easier positioning of the catheter, shorter operator learning curves, faster total procedure times, and potentially reduces the amount of power required to create a circumferential contiguous lesion in the ostium of the pulmonary vein.

2 Objectives and Purpose

2.1 Objective

The primary objective of this clinical investigation is to demonstrate the safety and acute effectiveness of the Multi-Electrode Radiofrequency Balloon Catheter in conjunction with the multi-electrode circular diagnostic catheter, in the isolation of the atrial pulmonary veins in treatment of subjects with paroxysmal atrial fibrillation. Specifically:

- To demonstrate the safety based on the proportion of early-onset (within 7 days of ablation procedure) primary adverse events.
- To demonstrate the acute effectiveness based on the proportion of acute procedural success defined as confirmation of entrance block in treated PVs after adenosine and/or isoproterenol challenge (with or without the use of a focal ablation catheter).

The major secondary objective of this study is to evaluate the incidence of (serious) adverse events during and after procedure up to 12 months following procedure. The need for the use of a focal catheter (touch-up) to get to PV isolation will also be evaluated.

2.2 Purpose

The purpose of this study is to prove that the use of the Multi-Electrode Radiofrequency Balloon Catheter, in conjunction with the multi-electrode circular diagnostic catheter, for the isolation of the atrial pulmonary veins in treatment of subjects with paroxysmal atrial fibrillation is safe and effective. The results of this study will be used for CE-mark registration of the Multi-Electrode Radiofrequency Balloon Catheter.

3 Study Design and Endpoints

3.1 Description of the Study Design

A roll-in phase of up to 3 subjects per ablating physician with the multi-electrode RF balloon catheter will be implemented. The design of the main study will be carried out as an interventional, pivotal, prospective, multicenter, single-arm clinical study.

3.1.1 Roll-In Subjects

One key purpose of this study will be to demonstrate the acute effectiveness of the multi-electrode RF balloon catheter in the absence of confounding evidence that reflects early stages of a medical device learning curve. In addition to a requirement for multi-electrode RF balloon catheter training prior to each ablating physician's participation in this study, additional experience of the multi-electrode RF balloon use, in the context of this clinical investigational plan, would serve to generate a clearer perspective of the multi-electrode RF

catheter acute effectiveness in treating PAF subjects. Therefore, to minimize the learning curve effect of using the multi-electrode RF balloon catheter, roll-in subjects will be prospectively assigned to each ablating physician per the training plan specifically designed for this study.

-1 roll-in subject will be included for ablating physicians that participated in the RADIANCE Study

-2 roll-in subjects will be included by ablating physicians that didn't participate in the RADIANCE study and have extensive balloon experience (>15 cases/year)

-3 roll-in subjects will be included by ablating physicians that didn't participate in the RADIANCE study and don't have extensive balloon experience (<15 cases/year), to minimize the learning curve effect of

A subject who is excluded or discontinued will not count toward the roll-in subjects. All roll-in subjects will be followed for 12 months post-procedure. The roll-in subjects will be excluded from the main study analyses and will be analyzed separately.

3.1.2 Main Study

This will be an interventional, pivotal, prospective, multicenter, single-arm safety and acute effectiveness clinical evaluation utilizing the Biosense Webster Multi-electrode RF Balloon Catheter in combination with the Biosense Webster Multi-Electrode Circular Diagnostic Catheter.

Eligible subjects who sign the informed consent form and who comply with all inclusion and exclusion criteria will be enrolled and treated with the Multi-Electrode RF balloon catheter in conjunction with the multi-electrode circular diagnostic catheter. An adaptive sample size of up to 230 evaluable subjects (non roll-in) be included in the main study phase. All study subjects (including roll-ins) will be followed-up for 12 months after study procedure.

Planned statistical analyses of these endpoints are described in the Statistical Analysis section (section 14) of this clinical investigational plan.

3.1.3 Neurological Assessment Study

A focused neuropathological evaluation will be integrated within the Main Study. This subset of subjects will be included in the neurological assessment evaluable subgroup (NAE). Subjects will be assessed for incidences of symptomatic and asymptomatic pre-and post-ablation cerebral emboli with either an absence of CNS deficits (asymptomatic) or with emboli-associated neurological symptoms (symptomatic).

A prospective evaluation of 40 subjects at participating sites will be included in this assessment. The mandatory roll-in subjects will not be eligible for the NAE assessment to minimize the confounding influence of a learning curve during early use of a complex medical device. Enrollment in the NAE population may be terminated prior to achieving the target 40 subjects if study enrollment ends early after a planned interim look.

At participating sites and considering the above caveats, all subjects (non roll-in) who are enrolled in the main study will be considered for participation in the NAE, per specific eligibility requirements:

1. IF a subject satisfies any one of the 3 following conditions he/she will be excluded from the NAE:
   - Presence of iron-containing metal fragments in the body
   - Subject has a contraindication to use of contrast agents for MRI such as advanced renal disease etc. (at PI discretion)
   - Subject has an unresolved pre-existing neurological deficit.
2. Subject must provide written informed consent for MRI, NIHSS, MoCA, mRS, and general neurological assessments.

3.2 Study Endpoints

3.2.1 Primary Endpoints

- **Acute Safety**

The primary safety endpoint is the incidence of early onset Primary Adverse Events (PAEs) (within seven (7) days of the initial mapping and ablation procedure). PAEs include the following AEs (refer to Section 9.1.3 for a complete list and definitions):

Death*	Stroke/CVA
Atrio-Esophageal Fistula*	TIA
Myocardial Infarction	Phrenic Nerve Paralysis
Cardiac Tamponade/perforation	Pulmonary Vein Stenosis*
Thromboembolism	Major Vascular Access Complication/Bleeding

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

- **Acute Effectiveness**

Acute procedural success defined as confirmation of entrance block in treated PVs after adenosine and/or isoproterenol challenge (with or without the use of a focal catheter)

3.2.2 Secondary Endpoints

- **Safety:**
  - incidence of individual PAE from the primary composite
  - Incidence of Serious Adverse Device Effects (SADEs)
  - Incidence of Serious Adverse Events (SAEs) within 7 days (early onset), >7-30 days (peri-procedural) and >30 days (late onset) of initial ablation procedure
  - Incidence of non- serious adverse events
  - Incidence of pre-and post-ablation asymptomatic and symptomatic cerebral emboli as determined by MRI evaluations.
  - Frequency, anatomic location, and size (diameter and volume) of cerebral emboli by MRI evaluations at baseline, post-ablation and during follow-up.
  - Incidence of new or worsening neurologic deficits, post-ablation and at follow-up, compared to baseline.
  - Summary of NIHSS scores at baseline, post-ablation and during follow-up.

  - Summary of MoCA scores at baseline, 1 month follow-up and during further follow-up.
  - Hospitalization for cardiovascular events (with hospitalization defined as prolonged stay ≥2 nights post index procedure or in-patient stay not concurrent with index procedure ≥ 1 calendar day)
- **Effectiveness:**
  - Percentage (%) of PVI touch-up by focal catheter among all targeted veins and by subject.
  - Percentage (%) of subjects with use of focal catheter ablation for non-PV triggers
  - Percentage (%) of subjects with freedom from documented, symptomatic atrial fibrillation (AF), atrial tachycardia (AT), or atypical (left side) atrial flutter (AFL) episodes (episodes >30 seconds on arrhythmia monitoring device from day 91 to 180).
  - Percentage (%) of subjects with freedom from documented, atrial fibrillation (AF), atrial tachycardia (AT), or atypical (left side) atrial flutter (AFL) episodes (episodes >30 seconds on arrhythmia monitoring device from day 91 to 180).
  - Percentage (%) of subjects with freedom from documented, symptomatic atrial fibrillation (AF), atrial tachycardia (AT), or atypical (left side) atrial flutter (AFL) episodes (episodes >30 seconds on arrhythmia monitoring device from day 91 to 365).
  - Percentage (%) of subjects with freedom from documented, atrial fibrillation (AF), atrial tachycardia (AT), or atypical (left side) atrial flutter (AFL) episodes (episodes >30 seconds on arrhythmia monitoring device from day 91 to 365).

- **Additional analyses on procedural characteristics, including but not limited to:**
  - Total procedure time, ablation time, RF application time, balloon dwell time, time to effect (PVI)
  - Number and time of RF applications per PV location
  - Fluoroscopy time and dose

- **Health economic assessments, including but not limited to:**
  - Index procedural workflow costs
  - Hospital costs
  - Quality of Life (AFEQT questionnaire)

Roll-in subjects will not be included in the main study analyses and will be analyzed separately.

4 Study Population

4.1 Participant Inclusion Criteria

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

1. Diagnosed with Symptomatic Paroxysmal AF.
2. Selected for AF ablation procedure for pulmonary vein isolation.

3. Able and willing to comply with uninterrupted per-protocol anticoagulation requirements
4. Age 18-75 years
5. Able and willing to comply with all pre-, post- and follow-up testing and requirements.
6. Signed Patient Informed Consent Form.

4.2 Participant Exclusion Criteria

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

1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
2. Previous surgical or catheter ablation for AF.
3. Anticipated to receive ablation outside the PV ostia and CTI region
4. Previously diagnosed with persistent, longstanding AF and/or continuous AF > 7 days, or > 48 hrs terminated by cardioversion.
5. Any percutaneous coronary intervention (PCI) within the past 2 months.
6. Valve repair or replacement and presence of a prosthetic valve.
7. Any carotid stenting or endarterectomy.
8. Coronary artery bypass grafting (CABG), cardiac surgery (e.g. ventriculotomy, atriotomy), or valvular cardiac surgical or percutaneous procedure within the past 6 months.
9. Documented left atrium (LA) thrombus on baseline/pre-procedure imaging.
10. LA antero posterior diameter > 50 mm
11. Any PV with a diameter ≥ 26 mm
12. Left Ventricular Ejection Fraction (LVEF) < 40%.
13. Contraindication to anticoagulation (e.g. heparin).
14. History of blood clotting or bleeding abnormalities.
15. Myocardial infarction within the past 2 months.
16. Documented thromboembolic event (including transient ischemic attack [TIA]) within the past 12 months.
17. Rheumatic Heart Disease.
18. Uncontrolled heart failure or New York Heart Association (NYHA) function class III or IV.
19. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months.
20. Unstable angina.
21. Acute illness or active systemic infection or sepsis.
22. Diagnosed atrial myxoma or interatrial baffle or patch.
23. Presence of implanted pacemaker or, implantable cardioverter defibrillator (ICD), or tissue-embedded, iron-containing metal fragments.
24. 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 chronic symptoms.
25. Significant congenital anomaly or medical problem that, in the opinion of the investigator, would preclude enrollment in this study.

26. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal), lactating, or who are of child bearing age and plan on becoming pregnant during the course of the clinical investigation.
27. Enrollment in an investigational study evaluating another device, biologic, or drug.
28. Has known pulmonary vein stenosis.
29. Presence of intramural thrombus, tumor or other abnormality that precludes vascular access, or manipulation of the catheter.
30. Presence of an IVC filter
31. Presence of a condition that precludes vascular access.
32. Life expectancy or other disease processes likely to limit survival to less than 12 months.
33. Presenting contra-indication for the devices (e.g. TTE, CT, Holter, etc.) used in the study, as indicated in the respective instructions for use.
34. Categorized as a vulnerable population and requires special treatment with respect to safeguards of well-being

Additional exclusion criteria for Neurological Assessment Evaluable (NAE) subjects:

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

4.3 Participant Withdrawal or Termination

4.3.1 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 adverse event (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
- The participant no longer meets eligibility criteria or meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation.
- Subject withdraws consent
- Subject is lost to follow up

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

4.3.2 Handling of Participant Withdrawals or Termination

If a subject is removed or withdraws from the study, the date and reason for withdrawal will be recorded on the appropriate electronic case report form (eCRF). If the subject is withdrawn due to an adverse event (AE) or serious adverse event (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.

4.4 Subject Enrollment Disposition

- **Enrolled Subjects:** Patients who sign the informed consent form.
- **Evaluable Subjects**: All enrolled subjects who have the study catheter inserted.
- **Excluded Subjects:** Subjects who are enrolled but never undergo insertion of the study catheter. Excluded subjects will only be followed between ICF signature and exclusion for event reporting.
- **Roll-In Subjects:** Enrolled Subjects who have the study catheter inserted and RF delivered during the roll-In phase of the ablating investigator. These subjects will not be included in the main study analyses and will be analyzed separately.
- **Discontinued Subjects**: Enrolled subjects who have the study catheter inserted but do not undergo ablation (i.e., no RF energy is delivered with the study catheter). Discontinued subjects will remain in follow-up for 30 days.
- **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.

5 Responsibilities

5.1 Investigator Responsibilities

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

- Assuring compliance by site personnel with the provisions of the protocol
- Providing the Sponsor with:
  - Signed, dated Investigator Agreement
  - Written EC approval letters and EC-approved consent forms
  - Signed, dated Financial Disclosure form for each participating investigator
  - Curriculum vitae for each investigator
- Maintain an accurate and current Delegation of Authority log which identifies individuals authorized to perform work for the study and assuring compliance by site personnel with the provisions of the protocol
- Completing the appropriate training on the device (ablating investigators only) and the study protocol prior to enrolling and treating subjects
- Maintain accurate and current logs for the study such as:
  - Subject log, Device Accountability Log
- Obtain initial and amendment (if applicable) EC approval and annual review/approval thereafter for the study protocol and informed consent as applicable
- Obtain informed consent form and enroll patients
- Perform medical procedures
- Order tests required by the study protocol
- Review pre-procedure imaging pertaining to the pulmonary vein size prior to treatment
- Follow subjects until the end of the study protocol
- Accurately complete and sign eCRFs in a timely manner
- Maintain relevant source documentation and allow Sponsor direct access to perform monitoring or auditing duties
- Maintain records and provide reports according to prevailing regulatory requirements
- Share relevant study-related information with delegated study staff
- Inform the appropriate entities (e.g., Sponsor, CA, EC) in a timely manner regarding the occurrence of AEs and/or product malfunctions.
- Making sufficient effort to maintain contact with treated subjects who fail to comply with the follow-up requirements
- Maintain study records for at least 5 years or as specified per country specific record retention requirements after the study is completed and or terminated. The Sponsor will notify the Investigator of either of these events.
- Complying with EC and Sponsor annual report requirements, including the final report.

5.2 Sponsor Responsibilities

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

- Conduct of pre-study site assessment and approval
- Preparation and modification (if applicable) of study documents including but not limited to the protocol, CRFs and informed consent
- Selection of appropriately qualified and trained individuals, including monitors, to conduct the study
- Conduct protocol and device training for investigators and research personnel as applicable
- Set-up of study-specific committees.
- Obtain signed study contracts from investigators/hospitals, 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 Principal Investigator at each site.
- Update Report of Priors, IFU, IB, and Risk Analyses, as applicable
- Update investigators on safety issues, if needed
- Report to study investigators and regulatory agencies, as required
- Have AEs reviewed by the study-specific committees, as required
- Communications with the competent authority
- Submission of any amendments to the Clinical Study Protocol/Investigational Plan to the competent authority.

6 Study Device Description

6.1 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.

6.2 Device Storage and Stability

Devices are to be stored in a secure/locked location and in accordance with the IFU. Do not use this device after the "Use By" date.

6.3 Device Preparation

Information related to device preparation can be found in the Instruction for Use.

6.4 Instructions for Use

A comprehensive set of IFU for the Study Devices, Generator, and all accessory cables/interface cables is contained in each product package and is also available upon request.

6.5 Device Description and Specific Considerations

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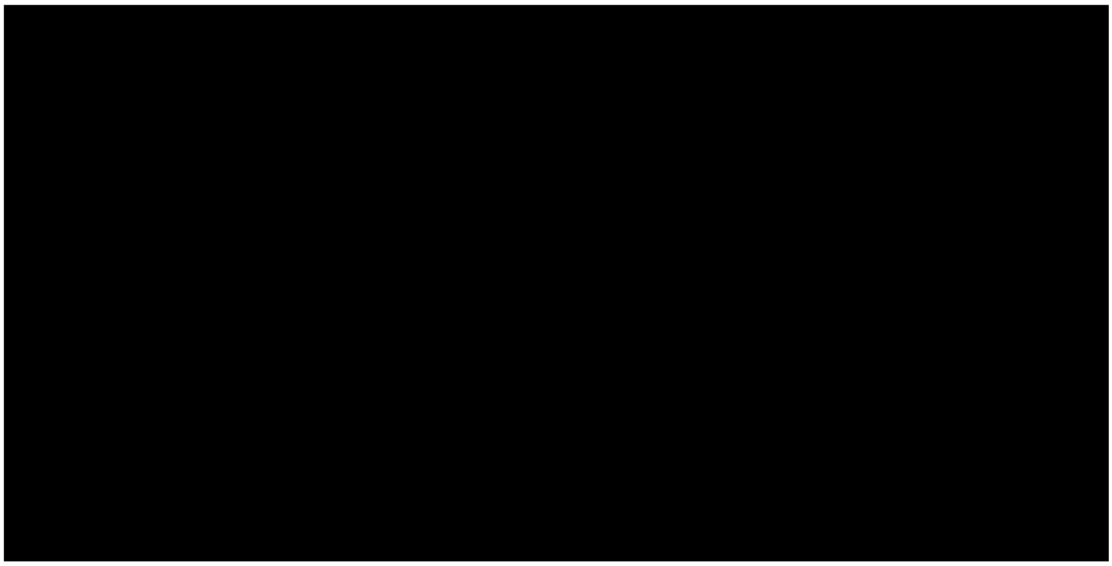
[redacted]



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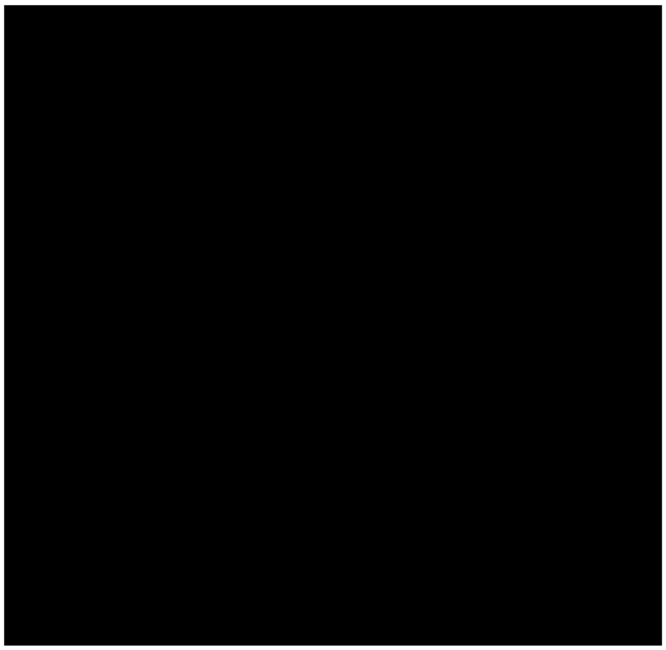

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7 Study Medication

The following medications are applicable for this protocol:

- PRIOR to the procedure
  - Uninterrupted anticoagulation therapy should be in place at least 1 month prior to ablation procedure
  - If receiving warfarin/coumadin therapy, subjects must be maintained on warfarin/coumadin for at least 3 weeks prior to treatment with an INR ≥ 2 (to be confirmed maximum 48h hours pre-procedure). Any INR <2 within 3 weeks prior to ablation will lead to exclusion of the patient or postponement of the study procedure.
  - 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.
  - AAD therapy should be managed as per the institution's standard of care

- DURING the procedure
  - Administer a heparin bolus PRIOR to transseptal puncture.
  - Target an ACT of 350-400 seconds prior to inserting the balloon and throughout the procedure.
    - ACT levels **MUST** be checked every ± **15-30 minutes** during the procedure to ensure an ACT target of 350-400. All recordings (ACT level, timing of heparin administration and dose) must be documented in the medical records as source documentation.
  - Flush all tubing and sheath continuously with heparinized saline.

- FOLLOWING the procedure
  - Anticoagulation therapy is strongly recommended for at least 2 months following ablation.
  - Additional medications needed to treat clinical indications are at the discretion of the clinical investigation physician.
  - AAD management during the study will be at the discretion of the investigator

8 Study Schedule

8.1 Screening and Informed Consent

Subjects presenting to the institution with symptomatic PAF and considered for an RF ablation procedure should be screened by the investigator or designated member of the research team for study eligibility per the protocol inclusion and exclusion criteria. Sites will be instructed to screen all subjects who require a documented RF 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 regulatory authorities and study site's Ethics Committee. 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 ICH-GCP and with applicable local and federal 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 informed consent form will be enrolled into the study. Each eligible subject who signs the informed consent on the additional neurological assessments and has post-MRI completed will be included in the NAE subgroup. No subject should undergo any clinical investigation specific tests or examinations that fall outside the standard of care without first signing the patient informed consent form for this clinical investigation.

8.2 Baseline Evaluation and Procedures

8.2.1 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.
- **Medication history**: Medication history (cardiac medication, AAD medication, anticoagulation regimen and any other clinically significant medication history) shall be gathered by interview or from medical records following enrolment but prior to the ablation procedure and should be recorded in the eCRF.
- **Anticoagulation therapy**: Uninterrupted anticoagulation management is mandatory for each study subject. For subjects on warfarin/coumadin therapy, subjects shall be maintained on Warfarin/Coumadin for at least 3 weeks prior to treatment with an INR ≥ 2 (to be confirmed maximum 48h hours pre-procedure). Any INR <2 within 3 weeks prior to ablation will lead to exclusion of the patient or postponement of the study procedure. The results must be available prior to start of procedure.
- **Electrocardiogram** (12-Lead ECG). Data from 12-lead ECG recordings will be collected if available.
- **Transthoracic Echo (TTE)** to determine the atrial size and LVEF% should be completed within 60 days prior to the study ablation procedure.
- **Cardiac multi slice CT/MRA image** to evaluate the number, size and anatomy of the pulmonary veins and the left atrial anatomy within 30- days pre-procedure is mandatory. For each PV, the following measurements are to be done:
    - Major axis (mm)
    - Minor axis (mm)
    - Average diameter (mm)
- Subjects with a PV with average diameter of ≥ 26mm will be excluded from the study.
- **For subjects included in the neurological assessment subgroup, Cerebral MRI, Neurological Exam and Neurological Evaluation using the Montreal Cognitive Assessment (MoCA), NIH Stroke Scale and Modified Rankin Scale (mRS)** are required to be performed within 72- hours pre-procedure to evaluate the neurological condition and presence of neurological deficits of the subjects before undergoing study ablation procedure. A certified/qualified neurologist 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.
- Imaging for **detection of left atrial thrombus** or other structural contraindications to an ablation procedure is mandatory the day before or the day of the ablation procedure. Presence of a thrombus will require postponement of the ablation procedure or may even lead to exclusion of the subject from further study involvement. The imaging method to be used for atrial thrombus detection is transesophageal echocardiography (TEE) or intracardiac Echocardiography (ICE)

- **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.
- **Quality Of Life questionnaire AFEQT** to be collected prior to procedure
- **Adverse Events** must be collected from the time the subject signs the informed consent onwards

8.2.2 Study Ablation Procedure Guidelines

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8.2.2.2 Study Ablation Procedure Sequence

Subjects will arrive to the electrophysiology 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** for this study should follow the below sequence:

- Review CT/MRA to evaluate the number and size of the PV and the left atrial anatomy prior to the ablation procedure
- Transseptal puncture
- Mapping and recording with Lasso® or PentaRay®. Lasso® or PentaRay® to be withdrawn from the left atrium after mapping and recording, prior to insertion of any of the study catheters
- Placement of multi-electrode esophageal temperature monitoring device

- Confirmation of target ACT 350-400 PRIOR to insertion of the Balloon Catheter into the left atrium and maintain throughout the procedure
- Introduction of the RF Balloon Catheter
- Introduction of the Multi-Electrode Circular Diagnostic Catheter (Frontera)
- PV ablation with RF Balloon Catheter and confirmation of isolation by the Frontera
- Confirmation of PV isolation in all targeted PVs using the Frontera
- ROLL-IN SUBJECTS ONLY: Confirmation of PV isolation using Lasso®. Note that use of Lasso® is not allowed for non roll-in subjects.
- ROLL-IN SUBJECTS ONLY: Voltage map creation
- Isoproterenol/Adenosine challenge
- Confirmation of entrance block in all targeted PVs

8.2.2.3 Study Ablation Procedure Guidelines

Electrophysiology Study, Mapping and Ablation Procedure

- Anesthesia or sedation should be delivered per standard EP lab procedure.
- Placement of diagnostic catheters:
  - Coronary sinus catheter in the CS for pacing purposes
  - Other catheters may be placed at the discretion of the investigator
- Mandatory use of a multi-electrode esophageal monitoring device to minimize risk of esophageal injury.
- (Optional: Introduce an Intracardiac Echo (ICE) probe to review LA anatomy and PVs)
- Administration of heparin bolus PRIOR to transseptal puncture.
- A single transseptal puncture should be performed per standard EP lab. Aim for an anterior, inferior puncture.
- Following successful transseptal puncture, a FAM map can be performed utilizing Lasso® or PentaRay® (at investigator discretion).
- Confirm target ACT 350-400 sec. Systematic anticoagulation with heparin should be administrated with ACT level checked every ± 15-30 minutes to target ACT of 350-400 seconds throughout the procedure.
- Introduction of the 13.5 F sheath. Before inserting the sheath into the patient, flush the sheath with heparinized normal saline to remove air bubbles. In order to achieve a smooth introduction of the sheath a 10 or 11 F dilator to upsize the femoral vein access before introducing the sheath is recommended.
- Introduce the Balloon Catheter and Frontera Catheter as per instructions for use. To facilitate insertion, the Y-connector (Copilot, Abbot, 0.096 inch) should be used. The choice of loop diameter (15mm, 20mm and 25mm) of the Frontera Catheter is at investigator's discretion. Prior to extending the balloon outside the sheath, advance the Frontera Catheter under fluoroscopy to access the vein
- Use the steerable sheath to drive the Frontera Catheter to the first target vein under fluoroscopy.
- Advance and position the Balloon Catheter at the pulmonary vein ostium.
- Start saline flow rate at 35 mL/min to fully expand balloon.
- Check for occlusion using Radiopaque Contrast (use contrast & saline mixture of 50/50).

- Perform and record angiography to confirm occlusion of the PV (mandatory). Ensure that the catheter is not inside the pulmonary vein before starting ablation.
- Identify the posterior electrodes via the fluoroscopic markers (optional) and on the CARTO image, prior to each ablation.
- When position is satisfactory, commence energy delivery with the Balloon Catheter.
- Prior to ablation in the region of the right sided veins, precautionary measures to evaluate the proximity to the phrenic nerve are mandatory.
    - Pace out of the superior vena cava (SVC) for phrenic nerve pacing.
    - Assure diaphragmatic capture PRIOR to RF delivery.
    - Stop RF delivery if phrenic nerve capturing is lost or attenuated.
- Ensure continuous monitoring of ablation parameters, PV recordings and esophageal temperature during RF energy delivery.
    - Stop RF ablation posteriorly if esophageal temperature rises more than 2 degrees from baseline temperature.
    - Record time to Pulmonary Vein Isolation. Bonus lesions are not permitted once acute PVI has been confirmed
    - Turn off RF energy delivery to posterior electrodes after maximum 20 seconds
- All subjects will undergo PV ablation with the Balloon Catheter until PVI is achieved and isolation confirmed by Frontera Catheter
- Confirmation of entrance block of all targeted PV by Frontera Catheter
- Additionally, in case of roll-in subjects, confirm entrance block of all targeted PV with Lasso® and perform voltage mapping
- Administer adenosine or isoproterenol for each targeted PV to rule out dormant conduction.
- (If necessary and at the investigator's discretion, a commercially available ThermoCool® family catheter may be inserted to complete PVI or other identified targets.)
- Confirmation of entrance block of all targeted PVs

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

- Prophylactic ablation outside the PV or CTI region, empirical sites and CFAE ablation is not allowed per protocol.
- If an arrhythmia requiring ablation outside the PV or CTI region (investigator discretion) is identified, the subject will be excluded from the study before any of the study catheters (Balloon or Frontera) has been inserted.
- If linear lesions for CTI AFL are placed, bidirectional block should be confirmed as demonstrated by mapping and/or pacing maneuvers.

<u>Verification of ablation procedure</u>

- Verification of isolation of the targeted PVs by demonstrating entrance block into each targeted PV is required.

- To verify entrance block, analyze electrograms in sinus and/or atrial paced rhythm to confirm that no PV potentials are present.
- Administration of adenosine (ATP) and/or isoproterenol for each targeted PV prior to verification of entrance block is required.
- Demonstration of entrance block MUST be confirmed and documented by the Frontera Catheter. (Followed by Lasso® validation for roll-in subjects)
- The ablation procedure is considered complete when confirmation of entrance block in targeted PVs is confirmed.

8.2.3 Collection of Ablation Procedure data for post-analysis

At the completion of the study ablation procedure, two back-up copies of the CARTO® and generator 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 provided to/ collected by the Sponsor.
A copy of the fully anonymized angiography images (preferable with contrast), confirming position of the balloon and occlusion of the PVs will be provided to / collected by the Sponsor.

8.2.3.1 Data collection during study ablation procedure

The following information will be collected during the procedure:

RF ablation parameters per PV

- Number of RF application(s) per target PV
- Number of RF application(s) required with a focal catheter
- Total RF duration per target PV
- Total time of RF application with the balloon catheter until PV isolation of targeted vein was achieved (TTI = time to isolate)
- Total time of RF application with the focal catheter (if applicable)
- PVI confirmed with Frontera Catheter
- PVI confirmed with Lasso® (roll-in subjects only)
- PV acute reconnection yes/no

RF ablation parameters per application

- Targeted veins (location)
- Ablation number of the generator
- Total Duration of RF energy per application
- Balloon Inflation Index prior to target PV application
- Identification of posterior pacing electrodes
- Ablation parameters (impedance, temperature, power, number of active electrodes per application, total duration of RF application, RF duration of posterior/anterior electrode, etc.) will be collected during the ablation procedure via the generator log files.
- Ablation lesion information will be collected in the CARTO3 system.

Ablation parameters, including but not limited to

- Percentage of targeted PV isolated on first shot

- Percentage of targeted PV with acute reconnections

Procedural parameters, including but not limited to

- Duration of time in mapping (LA and PVs)
- Total RF duration (consecutive time of RF energy delivered by multi-electrode RF balloon catheter and focal catheter (if applicable)
- Total PVI time with balloon catheter (Duration of time from 1st PV application to final PV application)
- Total PVI time with focal catheter (if applicable)
- Total procedure time (from first femoral puncture to catheter removal)
- Total fluoroscopy time and dose
- Total Balloon dwell time (from first RF balloon insertion until RF balloon removal)
- ECG data
- Total fluid delivered via ablation catheter
- Total fluid delivered via intravenous line (if captured)
- Fluid output (if captured)
- Net Fluid input
- ACT level and timepoint of heparin administration
- Strategy to evaluate the proximity to the phrenic nerve
- Strategy used to minimize risk of esophageal injury
- Type of temperature probe, cut-off temperature and any abnormal increases in temperature observed.

8.2.4 Pre-Discharge Assessments

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

- Cardiac and Anti-Coagulation Medication Regimen.
- TTE
- Adverse Events
- ECG in case standard of care
- For subjects in the neurological assessment subgroup: Cerebral MRI, Neurological exam and Neurological Evaluation using the NIH stroke Scale within 48- hours post procedure, prior to discharge. A certified/qualified neurologist must perform neurologic exams at pre-and post-ablation and possibly at other follow-up visits, pending previous findings of micro-emboli/neurologic deficits.

8.2.5 Repeat Ablation Procedures

Repeat procedures may be performed at the discretion of the investigator. Repeat procedures during follow up may be managed per investigator discretion using an commercially available ablation catheter. The follow-up schedule will remain based on the initial ablation procedure.

8.3 Post-Ablation Follow-up Schedule

The subject will be required to complete follow-up visits through 12 months post initial ablation procedure. Follow-up will be done at 7 days (phone call or clinic visit), 1, 3, 6 and 12 months (clinic visit).

Discharged subjects will receive a telephone call or have a clinic visit at 7 days (7D, day 6-8) post ablation procedure to assess any occurrence of Primary Adverse Events; otherwise, in-hospital surveillance will capture any Primary Adverse Events.

Follow-up visits should be scheduled according to the following timeframes: 1 month (1M, day 23-37), 3 month (3M, day 76-104), 6 month (6M, day 150 - 210) and 12 month (12M, day 315-405). Follow-up visit schedule should be based on the date of the index study ablation procedure and will not reset if subject undergoes a repeat AF ablation procedure.

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

- Adverse events (1M through 12M)
- Cardiac and Anti-coagulation medication regimen (1M through 12M)
- Atypical (left side) AFL/AT/AF recurrences and repeat ablations (1M through 12M)
- NYHA Functional Class Scale (3M)
- 12 Lead-ECG (if completed per standard of care)
- Quality of Life questionnaire AFEQT (3, 6 and 12M)
- Cardiac CT/MRA (3M): 3M follow-up CT/MRA should be performed for subjects presenting with symptoms on PV stenosis, using the same imaging technique as pre-ablation. Pre-ablation and post-ablation CT/MRAs of symptomatic subjects will be analyzed by a core lab to evaluate the level of PV stenosis.
- Transtelephonic monitoring (TTM) (1M through 12M)
  Subjects will be provided with a TTM device at the 1M follow-up visit and asked to record and transmit a minimum of 1 transmission (60 seconds) every week through the end of month 5 of follow-up. Starting at month 6 of follow-up, subjects will be asked to record and transmit a minimum of 1 transmission (60 seconds) every month until the effectiveness evaluation period is completed (12 months post index procedure). Subjects will also be asked to transmit any symptom-triggered episode that occurs from the time they receive the TTM device through the 12M follow-up visit. A core lab will be used to evaluate and assess the TTM tracings.

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

- 24 Hour Holter (6M and 12M)
  Holter monitor will be used at 6M and 12M 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. A core lab will be utilized to evaluate and assess the 24-hour Holter recordings.

For subjects in the NAE subgroup:

- Cerebral MRI, neurological exam and NIH Stroke Scale assessments will be performed at 1M, 3M, 6M and 12M visit in case observations were noted during previous assessments.
- MoCA and mRS assessments are mandatory at 1M visit. Subjects with findings of micro-emboli/neurologic deficits will undergo additional MoCA/mRS through 12M follow-up
- A certified/qualified neurologist must perform neurologic exams at pre-and post-ablation and possibly at other follow-up visits, pending previous findings of micro-emboli/neurologic deficits

8.4 Early Termination Visit

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

8.5 Unscheduled visit

If a subject returns for a potential study related cardiovascular or neurological visit outside of the protocol-defined visit schedule provided in Table 8.7-A, the visit will be considered “unscheduled” (UNS). An investigator may request an unscheduled visit in the presence of a new or worsened cardiovascular condition or neurological deficit. If the unscheduled visit is for a repeat ablation procedure, the protocol follow-up schedule is based on the index ablation procedure. For all unscheduled visits, an unscheduled visit eCRF must be completed and the subject must also return for their next scheduled study visit per clinical investigational plan.

8.6 Core Laboratory for Evaluation

Independent central core laboratories or expert physician(s) will conduct objective evaluations of TTM, Holter, Cerebral MRI and will evaluate PV stenosis of symptomatic subjects.

8.7 Schedule of Events Table

Table 8.7 A displays the required schedule for subject treatments and evaluations.

Table 8.7 A: Summary of Subject Assessments

Assessments	Pre-ablation	Pre-discharge	7D (D6-8)	M1 (D23-37)	M3 (D76-104)	M6 (D150-210)	M12 (D315-405)	UNS
Clinic visit	●			●	●	●	●	●
Phone Call			●[1]					
Patient Informed Consent*/Demographics	●							
Medical/AF history	●							
Cardiac Medication Regimen	●	●	●	●	●	●	●	●
Anti-coagulation Regimen	●	●		●	●	●	●	●
CHA2DS2-Vasc Score	●							
NYHA functional Class Scale	●				●			
Pregnancy Test	●[2]							
QoL (AFEQT questionnaire)	●				●	●	●	
TTE	●[3]	●						
LA thrombus detection (TEE/ICE)	●[4]							
ECG	●[5]	●[5]		●[5]	●[5]	●[5]	●[5]	●[5]
Cardiac CT/MRA	●[6]				●[6]			
Adverse events	●	●	●	●	●	●	●	●
AFL/AT/AF recurrence and repeat ablation				●	●	●	●	●
Arrhythmia Monitoring[11]				●[11]	●[11]	●[11]	●[11]	●[11]
24-hour Holter/FUP call						●[12]	●[12]	
Cardiovascular hospitalization			●	●	●	●	●	●
Cerebral MRI (NAE subjects only)	●[7]	●[8]		●[9]	●[9]	●[9]	●[9]	●[10]
Neurological Exam (NAE subjects only)**	●[7]	●[8]		●[9]	●[9]	●[9]	●[9]	●[10]
NIH Stroke Scale (NAE subjects only)	●[7]	●[8]		●[9]	●[9]	●[9]	●[9]	●[10]
mRS (NAE subjects only)	●[7]			●	●[9]	●[9]	●[9]	●[10]
MoCA (NAE subjects only)	●[7]			●	●[9]	●[9]	●[9]	●[10]

1. May be substituted with a clinic visit.
2. In all women of childbearing age and potential. To be completed within 72-hours prior to ablation procedure.
3. To be completed within 60 days prior to ablation procedure
4. To be completed the day before or the day of the study ablation procedure. Imaging modality TEE or ICE.
5. To be collected if completed as standard of care.
6. To be completed within 30 days prior to ablation procedure. CT-MRA to be repeated at 3M FU in case the subjects presents with PV stenosis symptoms.
7. To be completed within 72-hours pre-procedure.
8. To be completed within 48-hours post-procedure.
9. To be undertaken if neurologic symptoms and/or cerebral ischemic lesions identified in a prior evaluation.
10. To be completed only if a previous mandated test was missed, or if subject reports neurologic difficulties between scheduled follow-up visits and unscheduled assessment per investigator approval.
11. Arrhythmia monitoring via TTM once per week as from 1M to the end of month 5 follow-up, once a month as from month 6 and whenever subject feels symptoms (day 30-365).
12. Arrhythmia monitoring via 24H Holter, site to contact subject and verify if any symptoms experienced during the Holter monitoring. Symptoms are to be reported in applicable CRF.

* Within 60 days prior to procedure

** A certified/qualified neurologist must perform neurologic exams at pre-and post-ablation and possibly at other follow-up visits, pending previous findings of micro-emboli/neurologic deficits.

9 Assessment of Safety

9.1 Specific Safety Parameters

9.1.1 Definition of Adverse Events (AE)

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

Specifically, an adverse event (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 device or procedure. Physical findings (including vital signs) observed at follow-up, or pre-existing physical findings that worsen compared to baseline are considered adverse events.

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.

AF recurrence by itself is considered a recurrence of disease (pre-existing condition), and, therefore, **does not meet the definition of an AE**. Recurrence of pre-existing AFL/ atrial tachycardia (AT) is also considered recurrence of disease, and does not meet the definition of an AE.

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

- Minor pericarditis attributable to the ablation procedure defined as pleuritic chest discomfort with or without pericardial rub and ECG changes.
- AF/AFL/AT recurrence requiring pharmacological or synchronized electrical cardioversion during the hospitalization for the index ablation procedure, or throughout the duration of the study. However, new onset of left atrial flutter occurring post-ablation is an AE. Re-ablation for AF or pre-existing AFL/AT itself is not an AE, however any procedural complication is considered an AE and shall be reported within the applicable timelines.

9.1.2 Definition of Serious Adverse Event (SAE)

A serious adverse event (SAE) is any event that meets one or more of the following criteria:

- Leads to a death
- Leads to a serious deterioration in the health of a subject that resulted in:
  - A life-threatening illness or injury

- An injury or permanent impairment of a body structure or a body function
- In-patient hospitalization or prolongation of an existing hospitalization*
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to body structure or a body function

- Leads to fetal distress, fetal death or a congenital abnormality or birth defect.

Planned hospitalization for a condition present prior to the participant's enrollment in the study will not meet the definition of an SAE. An AE would meet the criterion of "hospitalization" if the event necessitated an admission to a health care facility (e.g., an overnight stay). Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

9.1.3 Primary Adverse Event

A **Primary AEs** is an event listed in Table 9.1.3A which occurs within the first week (7 days) following an ablation procedure.

Table 9.1.3-A: Primary Adverse Events

Primary Adverse Event	Description / Criteria
Death*	Subject death directly related to the device or procedure and occurs at any time during or after the procedure.
Atrio-Esophageal Fistula*	Defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophagus erosion combined with evidence of a fistulous connection to the atrium such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT or MRI scan is the most common method of documentation of an atrio-esophageal fistula.
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**/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

Primary Adverse Event	Description / Criteria
Thromboembolism	Formation of a clot (thrombus) inside a blood vessel causing obstruction to blood flow. The thrombus can migrate (embolus) and obstruct distal vascular sites. Diagnostic tests to help detect thromboembolisms may include but are not limited to angiography (pulmonary or distal), ventilation-perfusion (V/Q) scans, venography, Doppler ultrasonography, spiral CT, and echocardiography.
Stroke/Cerebrovascular Accident (CVA)	Diagnosis: -Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. -Duration of a focal or global neurological deficit ≥24 h; or <24 h, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death. -No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences).† -Confirmation of the diagnosis by at least one of the following: Neurology or neurosurgical specialist; Neuroimaging procedure (MR or CT scan or cerebral angiography); Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) Definition: Stroke: (diagnosis as above, preferably with positive neuroimaging study) Minor—Modified Rankin score <2 at 30 and 90 days†† Major—Modified Rankin score ≥2 at 30 and 90 days
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, associated with symptoms of dyspnea and orthopnea (diagnosed by chest x-ray). 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

Primary Adverse Event	Description / Criteria
Pulmonary Vein Stenosis*	A reduction of the diameter of a PV. Severe PV stenosis (≥70% reduction in the diameter of the PV) will be considered a primary adverse event and major complication of AF ablation.
Major Vascular Access Complication /Bleeding	Major Bleeding: Requires and/or treated with transfusion or results in a 20% or greater fall in hematocrit. Major Vascular Access Complication: Defined as 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.

* Device or procedure related death, atrio-esophageal fistula and pulmonary vein stenosis that occur greater than one week (7 days) **and (≤) less or equal to 90 days** post-procedure shall be deemed Primary AE.

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

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

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

9.1.4 Adverse Device Effect / Serious Adverse Device Effect

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

NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the 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 Serious Adverse Device Effects (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

9.1.5 Unanticipated (Serious) Adverse Device Effect

An unanticipated adverse device effect (UADE) or unanticipated serious adverse device effect (USADE) is any serious adverse effect on health, safety, any life-threatening problem, or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or risk analysis

report, or any other unanticipated serious problem associated with a device that relates to rights, safety, or welfare of subjects. Refer to Table 9.2.4A for a comprehensive list of foreseeable and anticipated adverse events.

9.1.6 Study Device Deficiency, Failure or Malfunction

A device has failed if it does not perform according to the IFU or fails to meet the expectations of the device and/or investigator (i.e., related to appearance of the device, performance, durability, safety, effectiveness, quality, reliability, labeling, etc.). 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 9.4.1 AE documentation and reporting requirements.

9.2 Classification of an Adverse Event

9.2.1 Severity of Event

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

Table 9.2.1-A: 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.

9.2.2 Relationship to Study Device

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's 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 MEDDEV 2.7/3 Rev3.

Table 9.2.2-A: Adverse Event Causality Classifications

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

9.2.3 Outcome

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

Table 9.2.3-A: 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)

9.2.4 Expectedness

An anticipated Adverse Event 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 adverse events that are reasonably anticipated to occur during the cardiac electrophysiology procedure are listed in Table 9.2.4A. These events should be reported via EDC as anticipated AEs. Anticipated adverse events are to be reported to the sponsor via EDC as indicated in section 9.4.

Table 9.2.4-A: provides a comprehensive list of anticipated AEs.

Anticipated Adverse Events	
Acute Respiratory Distress Syndrome (ARDS)	Air embolism
Allergic reaction	Allergic reaction to Anesthesia (e.g., hair loss)
Anaphylactic shock	Anemia
Anesthesia reaction	Apnea - sedation induced
Arrhythmia: bradycardia	Arrhythmia: pro-arrhythmias
Arrhythmia: tachycardia	(Aspiration) pneumonia
Asthmatic attack	
Atelectasis	Atrial fibrillation*
Atrio-Esophageal fistula	Atypical left atrial flutter
AV fistula	Bleeding complications
Bleeding requiring transfusion	Cardiac arrest
Cardiac perforation	Cardiac thrombo-embolism
Cerebro-vascular accident (CVA) / stroke	Chest pain/discomfort
Complete heart block, temporary or permanent	Conduction block: ongoing / resolved
Congestive Heart Failure	Coronary artery dissection
Coronary artery occlusion	Coronary artery spasm
Coronary artery Thrombosis	Damage to the vascular system
Death	Deep venous thrombosis
Diaphragmatic paralysis	Dislodgement of permanent pacing leads
Disseminated Intravascular Coagulation	Dyspnoea
Endocarditis	Epistaxis
Exacerbation of pre-existing arrhythmia*	Expressive aphasia
Fainting	Fatigue
Gastric reflux	Gastrointestinal diverticulosis
Gastro-intestinal NOS	Heart Failure
Hematoma (local) /ecchymosis	Hemorrhage
Hemothorax	High / increased creatine phosphokinase (CPK)
Hypotension	Hypoxia

Increase in frequency or duration of episodes of typical atrial flutter	Increased phosphokinase level
Infection, localized	Infection, systemic
Injury to skin, muscle, connective tissue due to body position, electrical cardioversion, etc.	Laceration
Leakage of air or blood into the lungs or other organs due to perforation	Liver toxicity
Local hematoma/ecchymosis	Mobile strands in Inferior Vena Cava
Myocardial Infarction	Nausea
Neurological disorders (headache)	Neurological disorders (poor coordination)
Neurological disorders (tremor)	Obstruction to the vascular system
Palpitations	Perforation to the vascular system
Pericardial effusion without tamponade	Pericardial effusion resulting in tamponade
Peripheral embolus	Pericarditis
Peripheral thromboembolism	Peripheral nerve injury
Phrenic nerve damage	Phlebitis
Pneumothorax	Pleural effusion
Pulmonary edema	Pseudoaneurysm
Pulmonary hypertension	Pulmonary embolism
Pulmonary vein dissection	Pulmonary toxicity, like acute pulmonary syndrome
Pulmonary vein thrombus	Pulmonary vein Stenosis
Renal failure	Pump failure
Respiratory failure	Respiratory depression
Rhabdomyolysis, including produced by body position or propofol	Retroperitoneal hematoma
Seizure	Sedation induced CO_2 retention with lethargy and cholecystitis
Skin burns (due to cardioversion, tape, etc)	Sepsis
Skin injury / muscle or connective tissue injury due to body position, electrical cardioversion	Skin discoloration
Tamponade	Skin rash
Thrombocytopenia	Temperature elevation
Thrombosis	Thromboembolism
Transient extremity numbness	Thyroid disorders
Unintended complete or incomplete AV, Sinus node, or other heart block or damage	Transient ischemic attack (TIA)
Urinary tract injury or infection related to the urinary catheter	Urinary retention
Vasovagal reactions	Valvular damage/insufficiency
Volume overload	Vision change
X-ray radiation injury of skin, muscle and/or organ	Worsening obstructive, restrictive, or other form of pulmonary disease

*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.]

9.3 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 AE/SAEs since the last visit.

All AEs need to be followed until the event is resolved (with or without sequelae). 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.

9.4 Reporting Procedures

9.4.1 Adverse Event Documentation and Reporting Requirements

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

Each AE must be reported to the sponsor regardless of classification, seriousness, intensity, outcome or causality. The investigator is responsible for ensuring that all AEs observed by the investigator, or reported by the subject, that occur from the time that the subject has signed the informed consent through the end of the study are properly assessed, recorded, and reported as defined and described in the AEs, Adverse Device Effects and Device Deficiencies section of this protocol. All adverse events 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 principal investigator(s), the sponsor shall communicate both opinions to the concerned parties.

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

In the case of serious device effects and device deficiencies that could have led to serious adverse device effects, 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 9.4.1-A.

Table 9.4.1-A: 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.

9.4.2 Serious Adverse Events Reporting

All SAEs, whether or not they are related to the device or procedure, **must be reported** to the Sponsor, via eCRF, **immediately upon awareness of event but no later than 72 hours** by the study site personnel.

The study investigator shall report the SAE and device deficiencies that could have led to SAE to the reviewing EC in accordance with the local EC requirements. 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 serious adverse device effects, the Sponsor will determine whether the risk analysis needs to be updated and whether corrective or preventative action is required.

The sponsor will submit as per site specific requirements to all participating clinical investigators, an update of all SAEs and all device deficiencies that could have led to a SAE occurring to all participating sites. Event reporting to relevant regulatory authorities for non CE-marked devices per MEDDEV 2.7/3 Rev3 guidelines will occur by the sponsor and if indicated per local country requirements by the investigator. Pursuant to EN ISO 14155: 2011 all SAEs will be fully recorded and reported by the sponsor to the regulating Ministry of Health (MOH) as well as the EC according to the deadlines in force.

9.4.3 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 unanticipated adverse device effect occurring during an investigation according to EC requirements.

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

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

9.5 Safety Oversight

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

10 Administrative Responsibilities

10.1 Ethics Committee and Competent Authority Application

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

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

10.2 Audits and Inspections

The sponsor and/or designee and/or Regulatory Authorities may contact the participating institution to inform the investigator of an upcoming audit/inspection. The investigator should immediately notify the sponsor of any Regulatory Authority 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.

11 Deviations from the Clinical Study Plan

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

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

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

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

All instructions described in this study protocol are to be followed. If an amendment is required, it must be made in written form and receive approval from all persons and authorities who approved the original protocol. Administrative changes (do not affect subject's benefits/risks ratio) may be inserted with abbreviated approval. All amendments will be distributed to all original protocol recipients.

12 Investigational Product

12.1 Use of the Investigational Device and Investigator Experience

In addition to the clinical protocol training (i.e. during the site initiation visit), all investigators who will be performing the ablation procedures for this study will be required to attend both a didactic session, which includes detailed reviews of the study catheter (specifications, parameters, etc.) and the results of the preclinical studies completed. Ablating physicians with no prior in human experience with multi-ablation catheter will also receive hands-on training using the Multi-electrode RF Balloon Catheter. The combination of the didactic and hands-on (in-vitro and/or in-vivo) portions of the documented device training will provide the investigator with the experience necessary to perform the protocol specified procedures for the study.

Investigators selected will be highly skilled in intracardiac mapping and AF ablation with RF ablation catheters.

12.2 Materials

Biosense Webster, Inc., Irwindale, CA USA, has manufactured the catheters to be used in this study. The investigational devices were built in a clean room environment, and sterilized using EtO gas, in a manner similar to standard, commercially approved Biosense Webster products.

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

12.3 Device Acquisition and Accountability

After obtaining a fully executed clinical trial agreement and appropriate competent authority (CA)/ethical committee (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 is 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 Sponsor will label all investigational devices as "Investigational device" in a prominent location.

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

12.4 Device Returns

All investigational devices (**used and unused**) will be returned to the Sponsor's attention at the below address. Any suspected malfunctioning device or device associated with an adverse event (device related or possibly device related) will undergo a thorough complaint analysis and must be properly documented on the electronic case report form (eCRF). All returned devices must be properly labeled with the subject identification number, date of issue, identified as a defective return, non-defective return, or adverse event (as applicable). All tracking information must be retained in the event the package has been lost and requires tracking. All investigational devices should be returned to:

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

13 Clinical Monitoring

Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with applicable regulatory requirement(s). Each site will undergo periodic monitoring of the study, which involves a visit from a Sponsor representative, qualified to perform such visit. Monitoring visits may include, but are not limited to, the following:

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

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

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

14 Statistical Methodology

14.1 Analysis Population

14.1.1 Main-Study

- **Modified Intent-To-Treat (mITT) Population**: The Modified Intent-To-Treat (mITT) population consists of enrolled subjects who meet eligibility criteria and have the study catheter inserted.
- **Safety Population (SP):** The Safety Population will consist of all enrolled subjects who have undergone insertion of the study catheter.
- **Per Protocol (PP) Population:** The PP population is a subset of the mITT population and will include subjects who comply with the following criteria:

- Are enrolled and meet all eligibility criteria
- Have undergone RF ablation with the study catheter
- Have been treated for the study-related arrhythmia

- **Neurological Assessment Evaluable (NAE) Population:** The NAE Population will include at least 40 subjects who are subset of the Per Protocol Population, consent and are eligible for the required neurological assessments, and have post-ablation MRI. Assessment of incidence of new lesions requires availability of pre-and post MRI. Assessment of incidence of new deficits requires availability of pre-and post-neurological evaluation. Enrollment in the NAE population may be terminated prior to achieving the target number of subjects if study enrollment ends early after a planned interim look.

14.1.2 Roll-In

- **Roll-In Population**: The Roll-In population will include all subjects from the roll-in phase of the ablating physician that have the study catheter inserted. All endpoints will be analyzed for the roll-in population separately.

14.2 Study Design

This clinical investigation is a prospective, multicenter, single arm clinical evaluation utilizing the Biosense Webster multi-electrode radiofrequency balloon catheter and the Biosense Webster multi-electrode circular diagnostic catheter. The sample size for the study is primarily driven by the safety endpoint. An adaptive Bayesian design[76] will be used to determine the sample size based on the safety endpoint alone. Sample size selection interim analyses will be performed when 80, 130, 180, and 230 evaluable subjects are enrolled in the main study (mITT Population). Safety outcome at 30 days will be used as a proxy for the primary safety endpoint at each interim. The final safety analysis will be based on complete follow-up for the primary safety endpoint for all evaluable patients in the main study. Predictive probabilities of success will be used to determine whether the sample size at each interim analysis will be sufficient or if the trial enrollment will continue. Sample size simulations were performed using performance goals of 15% and 80% respectively for the safety and effectiveness endpoint rates.

At the time of each interim analysis, predictive probabilities of success will be estimated using the available data from all evaluable subjects in the mITT population, assuming a non-informative uniform prior distribution for the primary safety rate. Enrollment will be stopped if the predictive probability of trial success at any interim is greater than 90%, or if the predictive probability of trial success with the maximum sample size is less than a futility bound of 6.5%. Otherwise, enrollment will continue until the next interim or the final sample size. Analysis of the effectiveness endpoint will be performed at the final sample size determined for the safety endpoint. Power for the effectiveness endpoint assessment is >80% at all sample sizes ≥80 subjects.

The primary safety and effectiveness endpoints will be evaluated using exact tests for binomial proportions at a one-sided 5% significance level.

In order to control for operational bias, the timing and results of the interim analyses will not be revealed to study investigators unless an interim analysis results in a decision to stop enrollment. The interim analyses will be conducted seamlessly with no interruption to study enrollment unless indicated by an interim analysis. An independent statistician will be responsible for conducting the interim analyses, and reviewing the results with the designated Data Monitoring Committee (DMC). The DMC charter will document the role and responsibilities of the committee and the independent statistician. The predicted probability of study success or summary results which are calculated at the time of the interim analysis will not be disseminated by the statistician performing the interim analysis until the time of the final database lock for the CSR.

14.3 Treatment Assignment

This is a single arm clinical study and all enrolled patients will be assigned to the study treatment.

14.4 Interval Windows

Please refer to Table 8.7 A.

14.5 Primary Endpoints and Associated Hypothesis

14.5.1 Analyses for Primary Effectiveness Endpoint

The null and alternative hypotheses are:

Hypothesis H_0: $P_E \leq 0.80$

H_a: $P_E > 0.80$

P_E: Proportion of patients with acute procedural success defined as confirmation of entrance block in treated PVs after adenosine and/or isoproterenol challenge (with or without the use of a focal catheter)

Analysis Population: The per-protocol population will be used as the primary analysis population. Subjects with missing effectiveness endpoints data will be excluded in the primary analysis. Sensitivity analyses for missing data will be performed using the PP and population to assess the impact of missing data on the primary effectiveness outcome and are described in the Statistical Analysis Plan (SAP).

14.5.2 Analyses for Primary Safety Endpoint

The null and alternative hypotheses are:

Hypothesis H_0: $P_S \geq 0.15$

H_a: $P_S < 0.15$

P_S: **The rate of early onset Primary Adverse Events**

Analysis Population:

The Modified Intent-To-Treat (mITT)will be used as the primary analysis population. Subjects with missing primary safety data will be excluded in the primary analysis. Sensitivity analyses for missing data will be performed in the mITT population and are described in the Statistical Analysis Plan (SAP).

14.6 Levels of Significance

A 1-sided alpha of 0.05 will be used for statistical testing and confidence intervals unless otherwise noted. The safety of this device was initially assessed in a feasibility study, and a safety event rate of 2.6% (1 in 39 patients) was observed. Given the available data on subjects from the feasibility study it was concluded that the proposed study could provide sufficient evidence for safety of the device using a type-I error of 5%, rather than requiring the conventional 2-sided 5%.

14.7 Sample Size Justification

A Bayesian adaptive design will be utilized to select the final sample size of the trial. Sample size selection interim analyses will be performed when the mITT Population reaches 80, 130, and 180 patients, and predictive probabilities for trial success will be used to determine whether the sample size at the time of the interim analysis will be sufficient or if the trial will continue to the full sample of 230. The final stopping sample size of 230 was determined by power calculations for the primary safety endpoint.

It is assumed that the attrition rate for the study will be negligible. Study enrollment will continue during each interim analysis until a decision is reached to stop enrollment based on the interim results. Due to the continued enrollment during this time, we expect additional subjects to be enrolled into the study. These additional subjects will be included in the primary analyses and should account for the potential subject attrition.

14.7.1 Adaptive Sample Size Determination

In this section, an incidence of any primary adverse events will be referred to as a failure for the primary safety endpoint. The methods described in Broglio et al.[76] will be used for adaptive determination of the sample size.

At the time of each interim analysis, predictive probabilities of success for safety will be calculated once using the current sample size and another time using the maximum sample size allowed. A uniform prior distribution will be assumed for the safety rate at the first interim analysis, and the distribution will be updated with the observed data at each subsequent interim analysis. The number of failures for the primary safety endpoint in subjects with incomplete information will be assumed to follow a beta-binomial distribution. The predicted number of failures for the primary safety endpoint will be estimated from these beta-binomial

distributions. The observed and predicted number of failures will provide estimates for the anticipated study outcomes with the sample size at the time of the interim analysis and the maximum sample size allowed. The Bayesian predictive probability of success for safety for each case will be calculated from these estimates.

Enrollment will be stopped if the predictive probability of success for safety with the current sample size is greater than 90% or if the predictive probability of success for safety using the maximum sample size allowed is less than 6.5%. Otherwise, enrollment will continue until the 230th subject is recruited. The Statistical Analysis Plan contains details on the timing of the interim analysis and estimation of the predictive probability of success at the interim looks. Regardless of whether enrollment stops at one of the interim analyses or continues to a sample size of 230 subjects, the primary safety and efficacy analyses will be conducted after all subjects have completed their 3-month post-procedure evaluation.

14.7.2 Power and Type-I Error Simulations

Trial simulations were performed to estimate the Type-I error rate and the power for the success of the safety endpoint under a range of assumptions for the true safety rate and the assumed enrollment schedule. For accrual rates of 1.7, 3.4, 5.1, 8.5, 11.9, 17, 20.4, 23.8, 25.5, 25.5, 25.5, 25.5, 25.5, 25.5, and 25.5 patients per month for months 1 to 15 respectively, and true safety rates of 0 to 9.0%, the power for showing success for the safety endpoint is estimated to be greater than or equal to 80.0%. For a safety rate of 9.5% this power decreases to approximately 73.0%. Based on the feasibility study results discussed in section 14.7, it is unlikely that the safety event rate is higher than 9.0%. The posterior probability of the safety rate being less than or equal to 9.0% is estimated to be 0.886. Therefore, we expect the study to be sufficiently powered for the primary safety endpoint. With a true effectiveness rate of 96.0% and a performance goal of 80.0%, a minimum of 80 patients will provide 99.9% power for meeting the primary effectiveness endpoint. As a result, the power estimates for the primary safety endpoint closely estimate the overall power of the study.

Since the primary analysis is performed at a 5.0% level Type-I error and the sample size is selected independent of the effectiveness endpoint, the Type-I error for the effectiveness hypothesis is controlled at 5.0%. To estimate the Type-I error for the primary safety endpoint, we considered the hypothetical scenario that the primary safety endpoint is on the decision boundary (i.e. equal to 15%). Based on 25,000 trial simulations, the estimated Type-I error for this scenario was 4.7%. As the primary safety rate moves away from the decision boundary under the null hypothesis, the Type-I error for the test decreases. Since our study success is defined as meeting both primary safety and effectiveness endpoints and because the Type-I error for each of these tests is controlled at 5.0%, the overall study Type-I error will be controlled at 5.0% (Please refer to the SAP for more details).

Based on the simulation results, we concluded that the study is adequately powered to meet the primary safety and effectiveness endpoints and that the Type-I error for the overall trial success is controlled at 5%.

14.8 Analyses to be Conducted

14.8.1 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, 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.

14.8.2 Disposition of Study Subjects

Subject disposition will be summarized for all enrolled subjects by summary tables, listings and flow diagrams.

14.8.3 Demographic and Baseline Characteristics

All demographic characteristics, procedural, and immediate post-operative details will be summarized overall in the safety and mITT populations. Descriptive statistics will also be presented for roll-in subjects.

14.8.4 Analysis for Primary Effectiveness Endpoint

The primary effectiveness endpoint will be evaluated using the exact test for a binomial proportion at a one-sided significance level of 5%. If the lower bound of the exact two-sided 90% confidence interval of the primary effectiveness endpoint rate is greater than the performance goal of 80%, the study will be considered to have demonstrated effectiveness.

14.8.5 Analysis for Primary Safety Endpoint

The primary safety endpoint will be evaluated using the exact test for a binomial proportion at a one-sided significance level of 5%. If the upper bound of the exact two-sided 90% confidence interval of the primary safety endpoint rate is less than the performance goal of 15%, the study will be considered to have demonstrated safety.

14.8.6 Analyses of Secondary and Additional Endpoints

Percentage (%) of subjects with freedom from documented symptomatic atrial fibrillation (AF), atrial tachycardia (AT), or atypical (left side) atrial flutter (AFL) episodes will be estimated in the mITT population at 180 and 365 days with the corresponding one-sided 95% exact binomial lower bound.

Descriptive statistics will be presented for the remaining secondary endpoints in the Safety and mITT Populations overall and by roll-in cases. The neurological assessment related endpoints will be analyzed in the NAE population. No formal statistical hypotheses and

inferential statistics will be formulated and performed for the remaining effectiveness and safety endpoints. Details of analyses methods for secondary and additional endpoints will be provided in SAP.

14.8.7 Handling of Missing Data

Patients with missing effectiveness data will be excluded from the primary effectiveness analysis. Sensitivity analyses for missing data will be performed in the PP populations to assess the impact of missing values on the primary effectiveness outcome and are described in the SAP. Subjects with missing primary safety data will also be excluded from the primary safety analysis. Sensitivity analyses for missing data will be performed in SP and mITT populations and are described in the Statistical Analysis Plan (SAP)

14.9 Interim Monitoring

An independent statistician will be responsible for conducting the interim analyses and reviewing the results with a designated Data Monitoring Committee (DMC). The DMC charter will document the role and responsibilities of the committee and the independent statistician.

15 Ethics and Protection of Human Subjects

15.1 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 and the MDD 93/42/EC and the local government. The Sponsor will also maintain compliance with Good Clinical Practice (ICH version 4 du 1 May 1996), the European standard EN ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects), the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Tokyo 2004), 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 adverse events and deviations from the protocol.

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

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

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

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

15.2 Informed Consent Process

15.2.1 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 (Brazil, 2013), ISO 14155:2011, and approved by the reviewing Regulatory Authority 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 Informed Consent Form (ICF), they are granting approval for study personnel to review their medical records and to collect/analyze personal medical information. Subjects should also be informed that study personnel will maintain confidentiality of the medical records at all times.

The ICF will be written in a native, non-technical, language that is understandable to the subject and is to be approved by the applicable EC prior to enrolling subjects. The subject or designee will be provided with ample time to read and understand the ICF and to consider participation in the study. Informed consent will be requested prior to enrollment and must

be personally signed and dated by the subject, or subject's legal representative, prior to performance of any study related activity or procedure. If a subject is unable to read or write, informed consent shall be obtained through the aid of an independent witness who will be present throughout the process. The written ICF and any other information shall be read aloud and explained to the prospective subject and, whenever possible, subject shall sign and date the ICF. The witness must also sign and date the ICF attesting that the information was accurately explained and that informed consent was freely given. The point of enrollment corresponds with the time that subjects signs the informed consent.

The investigator and/or designee must also clearly document the process of obtaining informed consent in the subject's source documents. The voluntary process of obtaining informed consent confirms the subject's willingness to participate in the study. It's the investigator's responsibility to ensure that the informed consent process is performed in accordance with ICH-GCP and, where applicable, local and federal regulations. Subjects should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the trial. Subjects or his/her legal representative must be given ample time and opportunity to inquire about details of the trial and all questions about the trial should be answered to the satisfaction of the patient or the representative. Failure to provide written informed consent renders the subject ineligible for the study. If new information becomes available that can significantly affect a subject's future health and/or medical care, this information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing informed consent in writing by dating and signing the amended ICF.

15.3 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 Competent Authorities 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.

15.3.1 Research use of Stored Data

- Intended Use: Data collected under this protocol may be used to study Atrial Fibrillation.
- 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.

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

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

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

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

17 Quality Assurance and Quality Control

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

Following written SOPs, monitors will verify that the clinical trial is conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. If noncompliance is identified, Sponsor is required by regulation to implement measures to secure compliance.

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

18 Data Handling and Record Keeping

18.1 Data Collection and Management Responsibility

The Sponsor will be responsible for all data management activities. These activities include development of an electronic data collection (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.

18.1.1 Data Collection

Electronic Case Report Forms (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.

18.1.2 Data Reporting

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

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

Table 18.1.2-A: Responsibilities for Preparing and Submitting Reports

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

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

18.1.3 Data Verification and Review

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

18.1.4 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.

18.2 Study Record Retention and Archiving

Records and reports for the study will remain on file at the site for a minimum of 5 years or per country specific record retention requirements following notification by the sponsor that all investigations have been terminated or completed. This documentation must be accessible upon request by the regulatory authorities, 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.

19 Study Suspension or Termination

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

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

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

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

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

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

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

20 Data and Publication Policy

Publications and/or presentation of clinical investigation results will be coordinated between Biosense Webster, Inc. and the clinical investigation author(s). 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.

21 Document Filing

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

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