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reMARQable

nMARQ™ Pulmonary Vein Isolation System for the Treatment of Paroxysmal Atrial Fibrillation

Sponsor: BIOSENSE WEBSTER, INC.
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Version: 5.2
 September 19, 2016

Protocol Agreement Form

Study Title: reMARQable, nMARQ™ PVI Ablation System IDE

I, the undersigned, have read and understand this clinical study, including the appendices. I will implement and conduct the clinical study in strict compliance with the study protocol and in accordance with good clinical practices (GCP) and all applicable laws and regulations. I will ensure that all persons assisting in this study are adequately informed about the protocol, study product(s), and their clinical study-related duties and functions.

I agree to maintain all study related information supplied by Biosense Webster, Inc. in strictest confidence. When information regarding this study is submitted to an institutional review board (IRB)/Independent Ethics Committee (IEC), it will be forwarded with a requirement that all study related material is to be held strictly confidential.

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Table of Contents

1.0 Protocol Summary	10
2.0 Abbreviations	16
3.0 Introduction.....	18
3.1 Background	18
3.1.1 Clinical Outcomes and Published Guidelines.....	18
3.1.2 Overview of General and Vascular Risks Associated with Catheter Ablation...	19
3.1.3 Study Population.....	21
3.2 Study Rationale.....	21
3.3 Previous Experience with nMARQ™ PVI Ablation System	22
3.3.1 Bench and Animal Studies.....	22
3.3.2 Circular Ablation Catheter and Crescent Ablation Catheter for the Radiofrequency Ablation of Atrial Fibrillation (AFCC-126) Feasibility Study.	23
3.3.3 REVOLUTION clinical study	23
3.4 Device Description	25
3.4.1 Description of Currently Marketed Devices	25
4.0 Detailed Risk Analysis	27
4.1 Description and Analysis of Risks	27
4.1.1 Minimization of Risks.....	30
5.0 Study Objectives.....	32
5.1 Primary Study Objectives	32
5.2 Secondary Study Objective: Subpopulation Neurological Assessment (SNA).	32
6.0 Study Design	33
6.1 Calibration Roll-in Phase: up to 250 Subjects	33
6.2 Main Study: up to 500 Subjects.....	33
6.3 Subpopulation Neurological Assessment (SNA): 60 Subjects.....	35
6.4 Total Enrollment.....	36
6.5 Study Duration, Completion, and Termination	36
6.6 Recruitment and Screening Procedures	36
6.7 Informed Consent and Enrollment Procedures	37
6.8 Subject Selection	37
6.8.1 Study Inclusion Criteria	37
6.8.2 Study Exclusion Criteria	37
6.9 Subject Status and Disposition Definitions.....	38

6.10	Subject Withdrawal	39
7.0	Definitions	40
8.0	Study Endpoints	41
8.1	Primary Safety Endpoint	41
8.2	Primary Effectiveness Endpoint	41
8.3	Secondary Endpoints	42
9.0	Schedule of Procedures and Examinations (Description of Treatment)	43
9.1	Patient Screening	43
9.2	Randomization	43
9.3	Study Medication	43
9.3.1	Anticoagulation Medications.....	43
9.3.2	Antiarrhythmic Drug Management.....	44
9.3.3	Use of Additional Medications.....	46
9.4	Pre-Procedure (Baseline) Assessments	46
9.5	Treatment Description	48
9.5.1	TEST - Required Devices.....	48
9.5.2	CONTROL – Required Devices.....	50
9.6	General AF Procedure Guidelines	51
9.6.1	Electrophysiology study and pre-ablation procedures:.....	51
9.6.2	TEST Group.....	52
9.6.3	CONTROL Group.....	53
9.6.4	Procedural data to be collected.....	54
9.6.5	Optional ablation procedure(s) based on clinical findings:.....	55
9.7	Post Procedure (pre-discharge) Assessment	55
9.8	Follow-up Visit Assessment	55
9.9	Summary of Subject Assessment	56
9.10	Descriptions of Procedures	57
9.11	Unscheduled Visits	59
9.12	Repeat Ablation Procedures	59
9.13	Core Laboratory for Evaluation Tests	60
10.0	Adverse Events	61
10.1	Definitions / Classifications	61
10.1.1	Adverse Event (AE).....	61
10.1.2	Serious Adverse Event (SAE).....	61
10.1.3	Primary Adverse Event.....	62
10.1.4	Adverse Device Effect / Serious Adverse Device Effect.....	63
10.1.5	Anticipated Adverse Events.....	63

10.1.6	Unanticipated Adverse Device Effect.....	66
10.1.7	Non-Serious Adverse Events.....	66
10.1.8	Study Device Failure or Malfunction.....	66
10.2	Causality.....	67
10.3	Intensity / Severity.....	67
10.4	Outcome.....	68
10.5	Adverse Event Reporting and Documentation Requirements.....	68
10.5.1	Adverse Event Reporting Requirements.....	68
10.5.2	Complaint Reporting.....	69
10.5.3	Adverse Event Documentation.....	69
10.6	Global Safety Monitoring Committee.....	70
11.0	Statistical Analysis.....	71
11.1	Overview of Study Design.....	71
11.2	General Considerations.....	71
11.3	Sample Size and Power Calculation.....	72
11.3.1	Main Study.....	72
11.3.2	Adaptive Sample Size.....	72
11.3.3	SNA Population Sample Size.....	73
11.3.4	Total Sample Size.....	73
11.4	Analysis Populations.....	73
11.5	Statistical Analyses for the Primary Endpoints.....	74
11.5.1	Primary Safety Endpoint.....	74
11.5.2	Primary Effectiveness Endpoint.....	74
11.5.3	Site Heterogeneity.....	75
11.5.4	Handling of Missing Data.....	76
11.5.5	Additional Analyses for Primary Effectiveness and Safety Endpoints.....	79
11.6	Adaptive Design Interim Analyses.....	80
11.6.1	Adaptive Sample Size.....	80
11.6.2	Sample Size Interim Analyses.....	80
11.6.3	Early Success Claim Interim Analyses.....	80
11.7	Secondary Effectiveness Endpoints Analyses.....	81
11.7.1	Acute Effectiveness (PVI Confirmation).....	81
11.7.2	One-Year Effectiveness.....	81
11.7.3	Long-Term Effectiveness.....	81
11.7.4	Secondary Effectiveness Endpoint Analyses.....	82
11.8	Secondary Safety Endpoints Analyses.....	82
11.8.1	Incidence of AEs and SAEs during 12 Month Follow-up.....	82
11.8.2	PV Stenosis at 3 Months Post Ablation.....	82
11.8.3	Incidence of AEs and SAEs during 2nd and 3rd Year Follow-up.....	82

11.9	Analyses for Additional Endpoints.....	82
12.0	Administrative Responsibilities	84
12.1	Institutional Review Board (IRB; or Equivalent) Review	84
12.2	Informed Consent	84
12.3	Subject Confidentiality.....	85
12.4	Data Monitoring.....	85
12.5	Labeling	85
12.6	Management of Protocol Deviations	86
13.0	Study Management	87
13.1	Study Timelines.....	87
13.2	Study Advisory Committee (SAC)	87
13.3	Interim Monitoring Committee.....	87
13.4	Investigator Responsibilities	88
13.5	Sponsor Responsibilities.....	89
13.6	Training	89
13.7	Sponsor Contact Information	90
13.8	Investigator Selection.....	90
13.9	Initiation of the Investigation.....	90
13.10	Data Reporting and Monitoring.....	90
13.11	Termination of the Study	91
13.12	Device Accountability	91
13.13	Device Returns	91
13.14	Annual Requirements.....	92
13.15	Electronic CRFs	92
13.16	Source Documentation.....	92
13.17	Subject Confidentiality/Record	93
13.18	Records.....	93
13.19	Record Retention and Archiving.....	94
13.20	Reports	94
13.21	Investigator’s Annual and Final Report.....	95
13.22	Publication Policy.....	95
13.23	Data Management.....	95

14.0 Regulatory / Ethical Considerations96
 14.1 Role of Sponsor96
 14.2 General Duties (21 CFR 812. 40).....96
 14.3 Selection of Investigators (21 CFR 812. 43).....96
 14.4 Supplemental Applications (21 CFR 812. 335 [A] and [B])96
 14.5 Maintaining Records (21 CFR 812. 140 [B])96
 14.6 Submitting Reports (21 CFR 812. 150 [B]).....97
15.0 References98

List of Figures and Tables

Table 2.0A: List of Acronyms/Abbreviations and Study Terms/Definitions	16
Table 3.4.1A: Marketed Devices to be Used with the nMARQ™ PVI System	26
Figure 6.2A: Study Design	34
Table 7.0A: AF and Ablation Terms.....	40
Table 9.3.2A: AAD Usage and Impact on Primary Effectiveness Classification	46
Table 9.4A: Baseline (Pre-Ablation) Evaluations and Completion Timeframe.....	47
Table 9.5.1A: TEST (nMARQ) Required Investigational Study Devices.....	48
Table 9.5.1B: TEST (nMARQ™) Required Non-Investigational Devices.	49
Table 9.5.1C: nMARQ™ Circular and Crescent** Irrigated Catheter – Maximum Settings for RF Power, Temperature and Duration	49
Table 9.5.1D: NAVISTAR® THERMOCOOL® Catheter - Recommended RF Energy Delivery Parameters when connected to the nMARQ™ Generator AND used for Atrial Ablation	50
Table 9.5.2A: CONTROL (THERMOCOOL® Navigational) Required Non-Investigational Devices	51
Table 9.9A: Summary of Subject Assessments	56
Table 10.1.3A: Primary Adverse Events.....	62
Table 10.1.5.A: Anticipated Adverse Events	63
Table 10.2A: Adverse Event Causality Classifications.....	67
Table 10.3A: Adverse Event Intensity / Severity Definitions.....	67
Table 10.4A: Adverse Event Outcome Classifications	68
Table 10.5.1A: AE Reporting Requirements.....	69
Table 13.20A: Responsibilities for Preparing and Submitting Reports	94

1.0 Protocol Summary

Title: reMARQable

Design: The Main Study will consist of a prospective, multi-center, randomized (1:1 concurrent nMARQ™ Catheter System [nMARQ] vs THERMOCOOL® Navigational Family of catheters [TC]), controlled, two-arm, single-blind design. Embedded within the Main Study will be a Subpopulation Neurological Assessment (SNA) with a prospective, controlled design, with consecutive enrollment.

Objective: The objective of this study will be to demonstrate safety and effectiveness of nMARQ compared to TC in treating subjects with drug-refractory symptomatic paroxysmal atrial fibrillation (PAF).

The objective of the Subpopulation Neurological Assessment (SNA) is to evaluate the comparative incidence of symptomatic and asymptomatic cerebral emboli, and any associated neurological deficits, both pre- and post-ablation by treatment group, among a subset of Main Study subjects.

Clinical Sites: Up to 50 sites in the United States (U.S.) and other regions may be included in the study.

Subject Population: Subjects with symptomatic PAF who have had at least one AF episode documented within one (1) year prior to enrollment and who have failed at least one antiarrhythmic drug (AAD [class I or III, or AV nodal blocking agents such as beta blockers and calcium channel blockers] as evidenced by recurrent symptomatic AF, or intolerance to the AAD).

Term	Study Definition
AF episode*	AF documented by ECG monitoring and has a duration of at least 30 seconds or, if <30 seconds, is present continuously throughout the ECG monitoring tracing. The presence of subsequent episodes of AF requires that sinus rhythm be documented by ECG monitoring between AF episodes. [Atrial fibrillation and atrial flutter (including atypical flutter) are considered episodes of AF. Atrial flutter alone is not considered an episode of AF.]
Paroxysmal AF*	Recurrent AF (≥ 2 episodes that terminate spontaneously within 7 days. (Episodes of AF of ≤ 48 h duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.)

Term	Study Definition
Persistent AF*	Continuous AF that is sustained beyond 7 days. (Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after ≥ 48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.)
Symptomatic AF	AF where symptom(s) exhibited by the subject are concurrent with a documented episode by ILR, ECG, TTM, Holter monitor, or telemetry recording. Symptoms may include but are not limited to: palpitations, irregular pulse (e.g., rapid, racing, pounding, fluttering, bradycardia), dizziness, weakness, chest discomfort, and breathlessness.
Documented AF episode	An AF episode documented by an electrocardiographic monitoring tool. This may include ILR, ECG, TTM, HM, or telemetry strip. <i>Reporting of a symptomatic episode by a patient or in a referral letter is not considered a documented AF episode.</i>

* The HRS/EHRA/ECAS 2012 Consensus Statement recognizes that patients may have both paroxysmal and persistent AF episodes and that the AF classification should be defined as the most frequent type of AF experienced within 6 months of an ablation procedure.

Inclusion Criteria: Candidates must meet **ALL** of the following criteria:

1. Patients with symptomatic paroxysmal AF who have had at least one AF episode documented within one (1) year prior to enrollment. Documentation may include ECG, transtelephonic monitor (TTM), Holter monitor (HM), or telemetry strip.
2. Patients who have failed at least one antiarrhythmic drug (AAD; class I or III, or AV nodal blocking agents such as beta blockers and calcium channel blockers) as evidenced by recurrent symptomatic AF, or intolerance to the AAD.
3. Pre-procedure anticoagulation on warfarin, rivaroxaban, or apixaban.
 - If receiving warfarin therapy, patients must agree to take warfarin for at least 4 weeks prior to the scheduled ablation procedure.
4. Age 18 years or older.
5. Signed Patient Informed Consent Form (ICF).
6. Able and willing to comply with all pre-, post-, and follow-up testing and requirements.

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 ablation for atrial fibrillation.
3. Patients on amiodarone at any time during the past 3 months prior to enrollment.

4. AF episodes lasting > 7 days.
5. Any cardiac surgery within the past 60 days (2 months).
6. Any valvular cardiac surgical procedure (i.e., ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve).
7. CABG procedure within the last 180 days (6 months).
8. Awaiting cardiac transplantation or other cardiac surgery within the next 365 days (12 months).
9. Documented left atrial thrombus on imaging.
10. History of a documented thromboembolic event within the past one (1) year.
11. Diagnosed atrial myxoma.
12. Presence of implanted ICD.
13. 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.
14. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study.
15. Women who are pregnant (as evidenced by pregnancy test if subject is of child-bearing age and potential), breast feeding, or planning to become pregnant.
16. Acute illness or active systemic infection or sepsis.
17. Unstable angina.
18. Myocardial infarction within the previous 60 days (2 months).
19. Left ventricular ejection fraction <40%.
20. History of blood clotting or bleeding abnormalities.
21. Contraindication to anticoagulation (i.e., heparin, dabigatran, Vitamin K Antagonists such as warfarin).
22. Life expectancy less than 365 days (12 months).
23. Enrollment in an investigational study evaluating another device or drug.
24. Uncontrolled heart Failure or NYHA Class III or IV heart failure.
25. Presence of intramural thrombus, tumor or other abnormality that precludes catheter introduction or manipulation.
26. Presence of a condition that precludes vascular access.
27. Left atrial size >50 mm.

Roll-in Phase:

Roll-in nMARQ™ Catheter System: The first 3 subjects at each investigational site will be considered an nMARQ roll-in subject. An additional 1-2 (prospectively designated) roll-in subjects will be allowed per site to minimize the learning curve effect of using the new nMARQ system. Therefore, up to 5 roll-in subjects will be allowed per site. These subjects will be analyzed only as part of the Safety Population. For OUS

investigational sites with prior experience of at least 5 nMARQ cases, the minimum number of roll-in subjects will be 1.

Main Study:

Treatment Groups: Eligible subjects who sign the informed consent form (ICF) will be randomized into one of two study arms:

- **nMARQ™ Catheter System* (Test) Group:** up to 250 subjects will undergo catheter ablation with the nMARQ™ System.
 - * The nMARQ™ Catheter System consists of 2 investigational catheters (a circular and a crescent catheter; the crescent catheter was discontinued in January 2015) and an investigational multi-channel RF generator. Additionally, and as part of the system toolkit, a NAVISTAR® THERMOCOOL® Catheter may be utilized for necessary focal touch-up.
- **TC (Control) Group:** up to 250 subjects will undergo TC ablation.

Primary Endpoints:

Primary Safety:

The primary safety endpoint will be the incidence of early-onset primary adverse events within 7 days of the AF ablation procedure (pulmonary vein stenosis and atrio-esophageal fistula that occur beyond one week (7 Days) post-procedure shall be deemed primary AEs) in the as treated population.

Primary Effectiveness:

The primary effectiveness endpoint is freedom from documented, symptomatic atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL) episodes based on electrocardiographic data through the effectiveness evaluation period (3-12 months follow-up post ablation procedure) in the intention to treat (ITT) population as randomized.

Sample Size and Power Calculation:

Main Study:

Trial simulation was carried out to evaluate the performance characteristics of the trial. Under the assumptions of equivalent effectiveness success rate at 55% and equivalent safety event rate at 8.6% in both groups, at an experiment-wise error rate of 0.05, an adaptive sample size of 250-500 (mean sample size of 417) will provide 80% power for trial success, meeting both effectiveness and safety endpoints, and 82.8 and 87.4% power for meeting effectiveness and safety endpoints respectively. The probability of early trial success is 36.8%.

Total Sample Size:

- Includes up to 5 nMARQ roll-in cases per investigational site for a total of up to 250 Roll-in cases.
- An adaptive sample size of 250-500 subjects will be enrolled and randomized to nMARQ or TC in the Main Study.

Subpopulation Neurological Assessment (SNA):

The purpose of this neurological assessment is to evaluate the comparative incidence of symptomatic and asymptomatic cerebral emboli, with or without emboli-associated neurological deficits, at pre- and post-ablation time points and by treatment group.

SNA Endpoint:

The SNA primary endpoint is the comparative incidence of pre- and post-ablation symptomatic and asymptomatic cerebral emboli, as determined by MRI evaluations. The presence of emboli-associated neurological deficits was also evaluated, using the National Institute of Health Stroke Scale (NIHSS) and general neurological assessments.

SNA Clinical Sites

Up to 15 sites will be included in the assessment.

Number of SNA Subjects:

At least 60 subjects (30 from each treatment group in the Main Study) were selected for the SNA. The Roll-in subjects at each participating site were not included in the SNA. All other subjects consecutively enrolled in the Main Study at SNA sites were asked to also enroll in the SNA (until sufficient SNA subjects are accrued). This approach helped to mitigate the confounding effects of an nMARQ system learning curve, which is associated with early experience using a new and complex ablation catheter system.

Summary of Subject Assessments

Assessments	BL	D/C	D7	M1 D7-42	M3 D70-110	M6 D150-210 M9 D235-315	M12 D316-405	UNS	Y2 ±45D Y3 ±45D
Clinic visit	●			●	●	●	●	●	
Patient Information (Demographics) and Consent	●								
Medical history	●								
Pregnancy Test ¹	●								
TTE ²	●	●							
Imaging for detection of LA thrombus (e.g., TEE, ICE, CT, MRI) ³	●								
ECG ⁴	●	●		●	●	●	●	●	
TTM ⁵					●	●	●	●	
CT/MRA nMARQ GROUP ONLY	● ⁶				●				
Cardiac medication	●			●	●	●	●	●	
Adverse events	●	●	● ⁷	●	●	●	●	●	● ⁷
AFL/AT/AF recurrence and repeat ablation				●	●	●	●	●	● ⁷
CCS-SAF Scale	●				●	●	●	●	
Cerebral MRI ⁸	● ⁹	● ¹⁰		● ¹¹	● ¹¹	● ¹¹	● ¹¹	● ¹²	
Neurological Exam ⁸	● ⁹	● ¹⁰		● ¹¹	● ¹¹	● ¹¹	● ¹¹	● ¹²	
NIH Stroke Scale ⁸	● ⁹	● ¹⁰		● ¹¹	● ¹¹	● ¹¹	● ¹¹	● ¹²	
mRS	● ⁹				●				
MoCA	● ⁹			●	● ¹¹	● ¹¹	● ¹¹	● ¹²	

1. In all women of child-bearing age and potential. To be completed within 24 hours prior to ablation procedure.
2. Completed within 30 days prior to ablation period.
3. To be completed the day before or the day of the ablation procedure.
4. To be collected if completed as standard of care.
5. Dispensation of TTM device at Month 3.
6. Within 30 days prior to ablation procedure.
7. To be assessed via phone follow-up.
8. Only for SNA subjects.
9. To be performed within 72 hours prior to ablation procedure.
10. To be completed within 72 hours post-ablation procedure.
11. To be undertaken if neurologic symptoms and/or cerebral ischemic lesions identified in a prior evaluation.
12. To be completed only if: (i) a previously mandated test was missed; or, (ii) subject reports neurologic difficulties between scheduled follow-up visits and unscheduled assessment per investigator approval.

2.0 Abbreviations

Table 2.0A: List of Acronyms/Abbreviations and Study Terms/Definitions

Acronym/ Abbreviation	Expanded Term
AAD	Antiarrhythmic Drug
ACC/AHA	American College of Cardiology/American Heart Association
ACL	Advanced Catheter Location
ACT	Activated clotting time
AE	Adverse Event
AF	Atrial Fibrillation
AMI	Acute Myocardial Infarction
ARB	Angiotensin II Receptor Blockers
AT	Atrial Tachycardia
CABG	Coronary Artery Bypass Graft
CHF	Congestive Heart Failure
CK	Creatine Kinase
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CS	Coronary sinus
CT	Computed tomography
CVA	Cerebrovascular Accident or Stroke
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
EMEA	Europe, Middle East and Africa
EP	Electrophysiology
FAM	Fast Anatomical Mapping
FDA	Food and Drug Administration
Fr	French
FU	Follow-Up
GCP	Good Clinical Practices
GSMC	Global Safety Monitoring Committee
HM	Holter Monitoring
HRS/EHRA/ECAS	Heart Rhythm Society / European Heart Rhythm Association / European Cardiac Arrhythmia Society
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instruction For Use
ILR	Implantable Loop Recorder
ITT	Intention to treat
LA	Left Atrium

Acronym/ Abbreviation	Expanded Term
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
NSR	Normal Sinus Rhythm
PAF	Paroxysmal Atrial Fibrillation
PFO	Patent foramen ovale
PI	Principal Investigator
PV	Pulmonary Vein
PVAC [®]	Pulmonary Vein Ablation Catheter [®]
PVI	Pulmonary Vein Isolation
QoL	Quality Of Life
RA	Right Atrium
RF	Radiofrequency
RFCA	Radiofrequency Catheter Ablation
RV	Right Ventricle
SAE	Serious Adverse Event
SDV	Source Data Verification
SNA	Subpopulation Neurological Assessment
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TS	Transseptal
TTE	Transthoracic Echocardiography
TTM	Transtelephonic Monitoring
UADE	Unanticipated Adverse Device Effect

3.0 Introduction

3.1 Background

3.1.1 Clinical Outcomes and Published Guidelines

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the developed world.¹ Most recently published studies, which discuss prevalence of AF, continue to cite pivotal studies that were published prior to 2005.²⁻⁵ AF prevalence increases with age, ranging from 0.1% to 9%, in adults under 55 and over 80 years old, respectively.⁶ In fact, the ATRIA Study revealed that 5.3% of adults over 60 had a diagnosis of nonvalvular AF, with rates higher in non-Hispanic whites than in other races and ethnicities.⁷ The number of Americans with AF has been estimated at 2.66 million and is expected to surpass 5.6 million by 2050.^{6,8} An alternate estimate of US prevalence is even higher, based upon data from a Minnesota community, with 15.9 million cases projected in 2050.⁹ Another recent community-based study noted that the 10-year risk of AF ranged from less than 1% to over 24% depending on risk strata.¹⁰ A European study reported lifetime risk of developing AF as 25%.¹¹

Prevalence and/or incidence studies of AF have also been conducted in other regions of the world including: Japan (overall annual prevalence rate of 9.3/1000 patient-years and overall prevalence rate of 4.4% for men and 2.2% for women \geq age 80); France (prevalence estimated to be between 600,000-1 million people and incidence estimated to be between 110,000-230,000 new cases per year); Brazil (age-adjusted prevalence of AF of 3.9% for men and 2.0% for women); and, China (age-adjusted prevalence of 0.65% for persons \geq 30 years of age)¹²⁻¹⁶. The percentage of AF patients with paroxysmal AF, at first detection, was 76% in the previously-mentioned Minnesota community study and 53% in a French study that contained a higher proportion of patients with permanent AF.^{9,17}

Atrial fibrillation is a supraventricular arrhythmia that is characterized by chaotic and uncoordinated contractions of the atria. Episodes of AF are initiated by ectopic sites which derive from the pulmonary veins, in more than 90% of cases. One or several pulmonary veins may be implicated and often multiple initiation sites (foci) originate from a single vein. The foci originate in the muscular cardiac bundles that line the pulmonary veins. These muscular extensions occupy various proportions within the vein perimeter, ranging from a single quadrant to the entire circumference. AF is most often diagnosed from an electrocardiogram (ECG) when an irregular ventricular rate is present. Characteristic ECG findings include the absence of P-waves, which are replaced with irregular atrial complexes (fibrillatory waves) that vary in amplitude, shape, and timing. In subjects with intact atrio-ventricular (AV) conduction, the R-R interval will almost always vary due to the irregular conduction of impulses from the atria to the ventricles.¹⁸ The frequency and duration of AF episodes varies, with current guidelines dividing the condition into paroxysmal, persistent, longstanding persistent, and permanent types.¹⁸

Briefly, paroxysmal AF is defined as recurrent AF that terminates spontaneously within 7 days. Persistent AF is defined as AF sustained beyond 7 days, or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion. Permanent AF is long-standing AF in

which cardioversion has failed or is no longer attempted. The most recently published HRS/EHRA/ECAS Consensus Statement included similar definitions for paroxysmal and persistent AF; current diagnostic terms now include ‘long standing persistent AF’, which is defined as continuous AF of greater than 1 year duration.¹⁹

Cardiopulmonary co-morbidities, such as heart failure (HF) and hypertension, have been associated with the occurrence of AF.¹⁸ Patients suffering from episodes of AF have an increased long-term risk of stroke, HF, and all cause mortality.²⁰ This is especially true among women, where AF is an independent predictor of adverse cardiovascular events such as stroke and HF.²⁰ The risk of ischemic stroke in AF patients is anywhere from 2 to 7 times greater than in individuals without AF, and exceeds a rate of 7% per year when pathological changes are detected by brain imaging. In one study, the 3-year incidence of development of AF in patients with HF was 9%.^{18,21} AF also has been associated with a 40-90% increased mortality rate.^{3,22}

The impact of undesirable symptoms associated with AF cannot be underestimated. Patients describe a considerably impaired quality of life that is independent of disease severity.^{23,24} Improvement in patients’ quality of life following treatment of AF is directly correlated with the restoration and maintenance of normal sinus rhythm.²³⁻²⁶ The treatment of AF and its consequences make this disease a costly public health burden. Total annual US expenditure for the treatment of AF patients has been estimated at \$6.65 billion, and approximately \$15.7 billion USD in the European Union.^{18,27}

Radiofrequency (RF) catheter ablation has provided excellent results for treating many types of supraventricular arrhythmias.²⁸⁻³³ The prevalent use of catheter ablation techniques, targeting the isolation of the pulmonary veins (PVs), was reflected in the 2007 and 2012 HRS/EHRA/ECAS Consensus Statements, emphasizing that electrical isolation of the PVs from the left atrium is “the cornerstone for most AF ablation procedures” and is widely considered the best method to treat AF in the paroxysmal AF population.^{19,34} In the prevention of recurrent AF, recent clinical guidelines have evolved from a point of considering catheter ablation as a reasonable alternative to pharmacological therapy to a recognition that it may be appropriate as a first-line therapy in rare clinical situations or for selected symptomatic patients with HF and/or reduced ejection fraction.^{18,34,35} A key contributor to the current perspective is that, since the 2007 and 2012 Consensus Statements, “a large body of literature, including multiple prospective randomized clinical trials, has confirmed the safety and efficacy of catheter ablation of AF”.¹⁹

Systematic reviews and meta-analyses of multiple AF studies have demonstrated clear advantages of catheter ablation in preventing disease recurrence.³⁷⁻³⁹ There have been multiple randomized clinical trials that have measured outcomes of catheter ablation versus AAD alone, in patients with paroxysmal AF. Among these trials, while the definitions of success varied, reported catheter ablation efficacy rates ranged from 66 to 89%.⁴¹

3.1.2 Overview of General and Vascular Risks Associated with Catheter Ablation

In general, rare but serious complications of catheter ablation occur in the range of 2-3% of cases, with approximately 1 in 1000 (0.1%) having a fatal outcome.^{39,40} A global survey, published in 2005, reported a 6% incidence of major complications among 8,745 AF ablation

procedures. More than 1 procedure was performed on 27% of these patients.³⁵ However, a more recent global survey, published in 2010, reported a post-ablation complication rate of 4.5%, from among more than 16,000 catheter ablation procedures. These results reflected treatments of patients with paroxysmal, persistent and longstanding persistent AF, within which one would expect a much higher rate of complications in the latter two patient groups versus paroxysmal AF patients.⁴¹

There are a variety of possible vascular complications, with a reported incidence of assorted events ranging from 0-13%. More definitive occurrence rates, among 8,745 ablation procedures, have included 0.53% for pseudoaneurysm and 0.43% arteriovenous fistulae.³⁵ Other critical vascular complications included intracerebral microembolic events, caused by air or thrombus, which manifest as stroke, TIA, or silent microemboli. Intracerebral thromboembolism has been reported in electrophysiology literature for AF up to a 7% incidence and the majority of published studies report at least one cerebrovascular event. Most embolic events occur within a 24-hour period following an ablation procedure. However, these data derive from varied measurement techniques, with inconsistencies in reporting cerebrovascular events. As a result, catheter ablation for AF has yet to clearly demonstrate a reduced risk of stroke, an important consideration in the management of AF patients.⁴²

Post-ablation silent (asymptomatic) intracerebral microembolic lesions have a major impact on therapeutic approaches to AF. Though general causes of microembolic lesions may be well understood, what remains unclear is the precise influence of individual and combined factors, such as patient health status, selected catheter ablation technology, overall patient management, control of RF energy during ablation, and peri- and intraprocedural anticoagulation regimens. To better understand some or all of these factors, in the context of using the nMARQ™ Circular- and nMARQ™ Crescent-shaped Irrigated RF ablation Catheters to achieve pulmonary vein isolation (PVI), when used in conjunction with the nMARQ™ Multi-channel RF Generator, this study will include an assessment of the frequency, size and anatomic location of post-ablation, intracerebral, microembolic lesions and any measurable, associated neurological deficits.

Recent studies have included analyses of cerebral ischemia following AF ablation, using magnetic resonance imaging (MRI). MRI has been used to assess symptomatic cerebrovascular accidents after RF ablation and is a very valuable tool in identifying post-ablation asymptomatic cerebral ischemia.⁴³⁻⁵⁰ Two non-randomized, comparative studies, using MRI analysis, found that new cerebral lesions were much more common among patients treated with a Pulmonary Vein Ablation Catheter (PVAC, Medtronic Ablation Frontiers), as compared to those patients treated with either a cryoballoon or a conventional irrigated RF ablation catheter. Cerebral microembolic lesions for PVAC occurred in approximately 38% of patients. There was a 6% combined incidence of cerebral microembolic lesions for cryoballoon and conventional RF ablation. Though the number of subjects was small in each of the 3 published studies (N = 108, 74, & 89, respectively), the marked differences of incidence of microembolic lesions, between PVAC and the other two devices, were statistically significant (p<0.001 on multivariate analysis⁴⁵ and p = 0.003).^{45,46,48} In all 3 studies, no significant differences were found between cryoablation and conventional irrigated RF ablation for this endpoint.

A fourth publication also included MRI analyses for cerebral microemboli. Among PVAC, cryoballoon, and conventional RF ablation catheters, the authors reported a high number of post-ablation intracerebral ischemic events.⁴⁴ In post-ablation MRI analyses, asymptomatic cerebral lesions were found in 33/86 (38%) patients. Of the 33 patients, 30 were ablated with phased RF (PVAC) technology. Fourteen of the 33 patients underwent follow up MRI assessments for up to one year post-ablation. MRI analyses identified 50 new lesions (average of 3-6/patient); however, none were associated with neurological symptoms. The predominant anatomic locations of microemboli were: left hemisphere (60%) or cerebellum (26%). Overall, half (52%) were ≤ 3 mm diameter, 42% were from 4-10 mm diameter, and 3 (6%) were more than 10 mm in diameter. Only the 3 largest lesions were present beyond 3 months post-ablation. Among all microembolic lesions identified, 94% resolved without residual scarring at follow-up >2 weeks to <1 year after ablation.

3.1.3 Study Population

Current practice guidelines reflect extensive expert reviews of published risks and benefits among various treatment modalities and patient populations. Calkins *et al.* have indicated that the highest ratio of benefits over risks (Class I) and the strongest level of clinical evidence (Level A) support the use of catheter ablation among symptomatic, paroxysmal AF patients, who are refractory or intolerant of at least one Class I or III antiarrhythmic medication.¹⁹ Other experts have recommended catheter ablation for symptomatic PAF in patients failing a single AAD either strongly or under certain conditions.^{18,40,51,52} All key published guidelines agree that the primary clinical benefit of catheter ablation for PAF is an improvement in quality of life, following abatement of arrhythmia-related symptoms.

According to the HRS/EHRA/ECAS 2012 Consensus Statement, stand alone catheter ablation, prior to the initiation of an antiarrhythmic drug, is a reasonable approach for symptomatic patients with paroxysmal AF.¹⁹ In this circumstance, the benefits of catheter ablation outweigh the risks (Class IIa); however, the strength of evidence/data supporting this therapeutic modality (Level B) reflects a limited number of clinical studies. Not all expert bodies are in line with the aforementioned expert opinion. In a 2010 publication, the ESC-published guidelines and recommendations for the management of AF recommended first-line use of ablation for patients with paroxysmal AF and minimal or no heart disease.⁵¹ The authors conceded that data comparing the use of AADs versus ablation are limited but add that ablation may be a reasonable first-line therapy for some patients with AF. As more robust and consistent clinical research data are made public, ablation as first-line therapy may well be widely supported among medical communities and regulatory authorities, in the future.

3.2 Study Rationale

Catheter ablation has been used for over a decade to treat AF patients to achieve PVI. The primary intent of this study is to generate clear and sufficient safety and effectiveness data for PMA approval on the use of the nMARQ™ Circular-shaped Irrigated RF ablation Catheter, in achieving PVI, when used in conjunction with the nMARQ™ Multi-channel RF Generator.

The 2012 HRS/EHRA/ECAS Expert Consensus Statement points out that the “concordance of the clinical trial data revealing the superiority of ablation over drugs for symptomatic paroxysmal AF recurrences” and the difficulties of subject enrollment and study management in conducting drug versus ablation studies, have led to widespread support of more relevant study designs, which compare a “novel device” to one that is already approved for use.¹⁹ The design of this protocol, a comparison of the nMARQ™ Catheter System [nMARQ™] versus the already marketed THERMOCOOL® Navigational Family of catheters [TC], reflects the same approach as supported by global experts for industry-sponsored clinical trials that assess new technology for catheter ablation.

Anticoagulation leading up to, during, and following ablation treatment, can influence subject outcomes, particularly stroke. Therefore, this protocol will require a specific regimen for anticoagulation (Section 9.3.1) throughout the study period based on current recommendations and standards of practice. These requirements will include (i) a warfarin, rivaroxaban, or apixaban treatment regimen; (ii) a need to keep the pre-ablation International Normalized Ratio (INR) ≥ 2.0 (for patients receiving warfarin treatment); (iii) appropriate use of heparin during the procedure to maintain an Activated Clotting Time (ACT) ≥ 325 seconds; (iv) giving heightened attention to continuous flushing of sheaths; and, (v) maintaining a vigilant awareness of risks of air embolism.

Efforts to achieve PVI with current catheter designs may present technical challenges for some operators in creating long contiguous ablation lines. Currently available RF catheters are used to ablate single targets (areas of potential) at a time in patients with AF; however, long contiguous lesions, which are formed by making multiple, consecutive single lesions, are often required to achieve PVI. Placement of additional RF lesions in the left and right atria has been investigated by a number of research centers^{34, 31, 53, 54} (e.g., a line of block between the left inferior PV and the mitral annulus); however, there is no consensus on the necessity, quantity, or anatomical placement of these extra RF lesions. Given that the nMARQ™ irrigated RF ablation catheters were designed specifically to create long continuous lesions, this trial will evaluate the relative ability of physicians to achieve PVI with confirmed entrance block.

The primary purpose of this randomized, controlled study is to establish the overall safety and effectiveness of the nMARQ™ PVI System for the radiofrequency catheter ablation treatment of symptomatic, drug refractory, paroxysmal atrial fibrillation. A key focus within the full safety assessment of the nMARQ™ System will be the frequency of occurrence, clinical sequelae, and duration of effect of cerebroembolic lesions associated with stroke, TIA, or silent microemboli. Other key measurements will address the duration and manner in which treated subjects remain asymptomatic.

3.3 Previous Experience with nMARQ™ PVI Ablation System

3.3.1 Bench and Animal Studies

Bench and animal testing has been performed using the nMARQ™ Circular and Crescent Irrigated Catheters and the nMARQ™ Multi-channel RF Generator. Please refer to the Report of Prior Investigations for detailed summaries of the test protocols and corresponding reports.

3.3.2 Circular Ablation Catheter and Crescent Ablation Catheter for the Radiofrequency Ablation of Atrial Fibrillation (AFCC-126) Feasibility Study

A total of 9 subjects were enrolled in this study from December 2009 through July 2010. One subject was excluded (after signing the informed consent form) for not meeting the inclusion criteria to have a documented AF episode in the 6 months prior to enrollment. Therefore, 8 subjects are considered evaluable, 5 PAF subjects (62.5%, 5/8) and 3 Persistent AF subjects (37.5%, 3/8). The mean age at date of procedure was 59.9 ± 7.2 years and ranged from 26.7 to 70.9. Three (3) of the enrolled subjects (33.3%) were female and six (6) (66.7%) were male.

Excluding the protocol-specific arrhythmias, the most prevalent medical condition reported at baseline was atrial flutter (55.6%) followed by hypertension (33.3%).

No subject deaths, early-onset primary AEs, serious adverse events or device or procedure related adverse events were reported. Four non-serious adverse events were reported; all were unrelated to the device or procedure. Two (2) subjects required a repeat ablation procedure, both >6 months post index ablation.

No pulmonary vein stenosis ($\geq 70\%$ narrowing) was reported for any of the subjects treated with the investigational catheters.

All investigators responded that the catheter/tissue contact interface was ‘excellent.’ On a scale of 1 to 5, the mean rating for effectiveness of mapping and ablation for both catheters was 4 or greater. Acute success, defined as isolation of a targeted pulmonary vein using the nMARQ™ Circular or nMARQ™ Crescent Irrigated Catheter, was greater than 60% for each targeted vein (LIPV: 62.5%, LSPV: 75%, RIPV: 62.5%, RSPV: 75%).

The Circular and Crescent Irrigated Catheters, when used with the RF Generator System for the treatment of paroxysmal and persistent atrial fibrillation, performed as expected.

3.3.3 REVOLUTION clinical study

The REVOLUTION study is a prospective, multi-center, non-randomized clinical evaluation of subjects undergoing RF catheter ablation for the treatment of drug refractory symptomatic PAF. Following a successful 20 subject Workflow phase, the study continued with Roll-in (the first 3 enrolled) subjects at each site, followed by the enrollment of subjects into the Effectiveness Cohort. A total of 186 subjects were enrolled in this study across 8 sites in Europe. Of these 186 subjects, five (5) were excluded (4 nMARQ and 1 ThermoCool), leaving 181 subjects planned for ablation procedures. Eighteen (18) of the 181 subjects underwent ablation with the THERMOCOOL® catheter while the remaining 163 subjects (Safety Cohort) were scheduled for ablation with the nMARQ™ System. Three (3) nMARQ subjects were discontinued from the study since no RF energy was delivered with the nMARQ™ Catheter so the Evaluable Cohort consists of 160 subjects undergoing ablation with the nMARQ™ Catheter. Excluding the workflow and roll-in subjects, 118 subjects comprise the Effectiveness Cohort.

All except 2 of the subjects in the Evaluable Cohort completed the 12 month follow up of the study, representing a high compliance rate of 98.8% (158/160). Overall TTM compliance within the Effectiveness Cohort was 87.0%, demonstrating rigorous AF recurrence monitoring throughout the study follow up period.

Of the 163 subjects in the Safety Cohort, 112 (68.7%) were male and 51 (31.3%) were female. The mean age for the 163 subjects was 58.7 ± 10.24 years, representative of PAF population. The most prevalent medical condition reported at baseline was hypertension (62/163, 38.0%), followed by atrial flutter (32/163; 19.6%) and dyslipidemia (20/163, 12.3%). Subjects suffered from symptomatic AF for an average of 5.5 years at baseline and the majority of subjects (64.8%) were classified as NYHA Class I.

No subject deaths, strokes, MI, PV stenosis, esophageal fistula, thromboembolism or unanticipated adverse device effects were reported in the trial. For the primary safety endpoint, 9 (5.5%) subjects experienced an early-onset (≤ 7 days) primary AEs, with only 4 (2.5%) subjects assessed with some level of device-relatedness. The primary safety endpoint was met since the observed rate of primary adverse events at 5.5%, and the corresponding upper bound of the 95% CI at 10.2% were less than the pre-specified performance goal of 16%.

Apart from the primary adverse events, there were no other subjects observed with device-related SAEs throughout the 12 month follow-up period. However, 2 subjects exhibited SAEs deemed as possibly related to procedure for dyspnea and TIA. In both cases, the condition completely resolved. No pulmonary vein stenosis ($> 70\%$ narrowing), as evaluated by baseline and post ablation CT/MRA imaging, was observed in any of the study subjects.

Acute effectiveness, defined as the confirmation of entrance block in the targeted PVs, was achieved in 100% (117/117; entrance block data not available for 1 subject) of Effectiveness Cohort subjects. The use of a focal catheter for PV isolation was based on investigator's choice and preference. This leads to a wide variability of touch-up use between the different participating investigational centers and resulted into an average touch-up rate of 16.1% of the targeted PVs. Three (3) of the 8 investigational centers did not use any touch up for any of the nMARQ subjects. This represents a low rate of touch up use that is acceptable for achieving PV isolation.

The primary effectiveness endpoint was freedom from documented symptomatic AF through 8 months (day 240) post-index ablation. The primary effectiveness endpoint was met with 71.6% (83/116) of subjects achieving freedom from documented symptomatic AF recurrence at 8 months post ablation. At the 12 month follow-up visit, freedom from documented symptomatic AF in the Effectiveness Cohort was 60.3% (70/116), still exceeding the performance goal of 49%. Further analysis demonstrated a positive association between investigator experience and freedom from recurrent AF. The predicted probability of success after approximately 15 procedures was 70%.

Since the initiation of the REVOLUTION Study, published literature has generated an increased awareness of post-ablation asymptomatic cerebral emboli (ACE). Although there was no incidence of stroke or other thromboembolic events in REVOLUTION study subjects, to better

understand the performance of the nMARQ™ System in light of the recently published literature on ACE, Biosense Webster added an amendment to the REVOLUTION study protocol that included the Subpopulation Neurological Assessment (SNA). The SNA focused on generating pre- and post-ablation cerebral MRI assessments to evaluate intracerebral microemboli and neurological assessments in a subset of the overall study population.

The SNA Cohort consisted of 19 evaluable Test (nMARQ) and 17 evaluable Control (ThermoCool) subjects. Among the 36 subjects part of the SNA Cohort, 5 (13.9%) subjects were observed with asymptomatic cerebral embolic (ACE) lesions post ablation. One subject (1/17; 5.9%) was part of the 17 subjects in the control group and 4/19 (21.1%) occurred within the test group. No new neurological deficits were observed in the 5 subjects with ACE. None of the 5 subjects with ACE had pre- or post-ablation NIHSS Scores above zero. None of the subjects exhibited any new neurological abnormalities post-ablation. Of the 5 subjects that developed ACE 1 nMARQ subject exhibited ACE associated with suboptimal irrigation. Except for this one subject, observations of ACE were isolated to one site in the study and detected in both arms of the SNA assessment. No incidence of ACE was observed in subjects exclusively treated with warfarin and $INR \geq 2.0$ at the time of ablation.

As a conclusion, operational and procedural variables such as anticoagulation management may have influenced the development of ACE in the REVOLUTION study. The % of ACE reported in REVOLUTION may possibly be further reduced by strict anticoagulation management and optimal procedural operation.

When combined with evidence of high acute procedural success, favorable procedural, quality of life, and secondary effectiveness measures, these results demonstrate an acceptable safety and effectiveness profile that supports the safe use of the nMARQ™ Catheters along with the RF generator for the treatment of PAF.

3.4 Device Description

3.4.1 Description of Currently Marketed Devices

Table 3.4.1A lists the marketed devices that are used in conjunction with the nMARQ™ PVI System.

Table 3.4.1A: Marketed Devices to be Used with the nMARQ™ PVI System

Device	Description
NAVISTAR® THERMOCOOL® Catheter	Marketed in the US, EMEA, and other regions.
Catheter Interface Cable (various model #s)	Marketed in the US, EMEA, and other regions.
COOLFLOW® Irrigation Pump (CFP002) and Tubing Set (CFT001)	The COOLFLOW Saline Irrigation Pump (CFP001) is marketed in EMEA but is investigational in the US. The Tubing Set (CFT001) is marketed in the US, EMEA, and other regions.
CARTO® 3 EP Navigation System (Various Versions other than V 2.5 or later approved C3 version)	Marketed in the US, EMEA, and other regions

4.0 Detailed Risk Analysis

The risks posed are expected to be comparable to those anticipated during routine use of catheter ablation systems for intracardiac radiofrequency (RF) ablation procedures and use of AAD therapy according to current AF management guidelines.^{1,18,34} Appropriate measures have been outlined in this protocol to minimize the risk to subjects, while still providing the possible benefits of the treatment options to be studied.

RF catheter ablation has been used for nearly two decades, and the risks and complications are well understood. The uses of non-irrigated and saline-irrigated ablation catheters are routine for many PAF ablation procedures. Section 3.1.2 provides a summary of some general risks associated with RF catheter ablation. When compared to the usual standards of practice and published literature few, if any, additional risks are anticipated for subjects enrolled in this study, during and following RF ablation of symptomatic PAF. A summary of risks associated with catheter ablation, including analysis of and plans to minimize these risks, is provided below:

4.1 Description and Analysis of Risks

The most common complications associated with catheter ablation of AF include: cardiac tamponade, with a reported incidence of >1.0%, pulmonary vein stenosis, with a 2003 publication reporting a 3.4% incidence of serious PV stenosis (21/608 procedures) and more recently reported occurrences, among 8,745 AF ablation procedures, of 0.32% acute PV stenosis and 1.3% persistent PV stenosis.^{35,55} Complication rates for esophageal injury are quite varied, depending upon energy source used, lesion location, or type of lesion found (erythema, necrotic ulceration, perforation, or fistula formation). Phrenic nerve injury, related to the application of RF energy, has a <1% reported incidence.^{56,57}

A 2010-published global survey has provided a comprehensive understanding of complications associated with RF catheter ablation. Reported serious complications, among more than 16,000 procedures, included 25 procedure-related deaths (0.15%), 213 episodes of cardiac tamponade (1.31%), 115 transient ischemic attacks (0.71%) and, 37 strokes (0.23%). An overall mortality rate of 0.1% was reported, among 45,115 AF procedures (32/32,569 patients). Among the most frequent causes of death were cardiac tamponade (25% of deaths), stroke (16%), atrio-esophageal fistula (16%) and massive pneumonia (6%).³⁹

Radiofrequency current may cause occlusion of a coronary artery, either by direct thermal damage, spasm, or thrombus formation. Experience at numerous centers suggests that the risk of coronary occlusion is less than 0.5%.^{49,50} Coronary arterial occlusion could produce myocardial infarction (MI), angina or death. Should occlusion of a coronary artery occur for any reason, the investigator will attempt to restore coronary blood flow through pharmacological, catheter and/or surgical intervention as medically indicated.

The application of radiofrequency 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.

As discussed in Section 3.1.2, thrombus generation during the procedure may pose a serious and even life-threatening risk to the patient. Thrombus may form on the ablation electrode during the application of radiofrequency current with or without any change in impedance. The thrombus might become dislodged and embolize to produce an ischemic stroke, MI, or other occlusive injury. The risk of thromboembolism is reduced by quickly terminating the application of current after an impedance rise, which limits the size of the coagulum on the electrode. The use of open irrigation catheters, such as the THERMOCOOL[®] Catheters, provide cooling of the electrode-tissue interface, allowing the use of higher power while reducing the risk of thrombus formation. Probably the most important aspect of TC is the near absence or very low likelihood of thrombus formation during RF.⁵⁸ In an analysis of 6 clinical studies utilizing the NAVISTAR[®] THERMOCOOL[®] Catheter there was no reported incidence of stroke or TIAs within 7 days postprocedure.⁵⁸

Thrombus formation on the endocardium following ablation may produce an arterial or pulmonary embolus. This risk may be reduced by the use of aspirin or anticoagulation therapy, at the discretion of the physician.

Cardiac perforation may result from catheter manipulation or application of radiofrequency current. Published risks of cardiac perforation range from <1% to 2.4%.^{35,41,49,50} This potentially life-threatening injury may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. In a recent study representing early experience using the nMARQ[™] PVI Ablation System, there were 2 (2/138, 1.4%) reported incidents of tamponade. Significant hemodynamic compromise can result in neurologic injury or death. An increased risk of cardiac perforation may be associated with the use of a saline-irrigated electrode catheter due to its ability to create a larger, deeper RF lesion. This risk is greatest in a thin walled chamber (i.e., RA, LA, appendage, or RV); 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 levels above 35 or 40 watts. If the lesion is deeper, the risk of steam pop is higher at power levels above 35-40 watts.

There is an incrementally small risk associated with use of a saline-irrigated electrode catheter rather than a standard electrode catheter. The larger RF lesion size produced with an irrigated catheter may cause moderate intra-procedural pain associated with RF applications and also may slightly increase the risk of cardiac perforation³³. Pain can be managed with intravenous analgesics. Additionally, use of the cooled electrode tip catheter may reduce procedural and fluoroscopy times and increase procedural success by increasing lesion depth and by minimizing coagulum formation, which necessitates removal and re-deployment of the ablation catheter. While the ability to cool the electrode-tissue interface allows the use of higher power (up to 50 watts) than a conventional 4 mm electrode, RF power in the range of 30-40 watts is often adequate. For any given power setting, the power delivered to the tissue is similar to that used with a 4 mm electrode.

Injury to a cardiac valve may result from catheter manipulation or the application of radiofrequency current (risk <1%).^{43,49,50} This may produce valvular insufficiency and possibly require valve replacement surgery.

The application of RF current along the posterior left atrium can result in thermal injury to the esophagus and the formation of an atrio-esophageal fistula. This is a very rare (0.04%) but severe complication of RF ablation that may require surgical intervention and may result in permanent impairment or death.⁴³ Reducing power at sites in close proximity to and/or avoiding sites directly over the esophagus may reduce the risk of thermal injury. Additionally, using esophageal monitoring techniques may minimize risk of injury¹⁹. Four cases of esophageal fistula associated with European commercial use of the product have been reported: two cases occurred soon after launch in 2013 and two occurred in early 2015. All four cases occurred outside of the reMARQable clinical study.

Investigations have determined that workflow was a key contributing factor in all four events. Based on the investigation of the two cases in early 2015 it was concluded that the absence of esophageal protection coupled with extensive RF ablation on the left posterior atrial wall that included near-continuous ablation lasting up to 8 minutes. Mitigations for this risk are provided in sections 9.5.1 and 9.6.1.

Injury to the phrenic nerve may occur as a result of RF application in the region of the right pulmonary veins. The reported incidence of phrenic nerve injury varies from 0% to 0.48% when RF energy is used for catheter ablation. Prior to ablation in the region of the RSPV, investigators are encouraged to perform precautionary measures such as evaluation of proximity to the phrenic nerve and pacing maneuvers. In a recent study representing early experience using the nMARQ™ PVI Ablation System, there was 1 (1/138, 0.7%) reported incident of diaphragmatic paralysis.

Radiation exposure during fluoroscopic imaging of 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%).^{52,54}

The risk of pulmonary AEs (e.g., pulmonary vein stenosis, thrombus and hypertension) associated with an AF ablation procedure targeting the pulmonary veins is <4%.^{42,59-65}

Other potential complications, which may result from catheter insertion and manipulation as part of a prerequisite electrophysiology study and mapping procedure, include:

- Allergic reaction to the local anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure (risk <1%).⁶⁶⁻⁷⁰
- Arterial or venous injury, including arterial dissection, thrombosis, occlusion, AV fistula, pseudoaneurysm, or hemorrhage at the catheter insertion sites or at other sites along the vessels (risk <1%).^{49,50} This may produce hemorrhage, hematoma or ischemic injury to an extremity or major organ.
- Hemorrhage as a result of anticoagulation (risk <0.5%), which may require transfusion.^{49,50}
- Infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%).^{43,49,50} This risk can be minimized by using standard aseptic technique and by the use of antibiotic agents when indicated.

Excessive heat generation during RF ablation is a known hazard for AF ablation procedures. In addition to thermal risk associated with overlapping electrodes and suboptimal thermocouple contact to cardiac tissue, a new risk has been identified that was the main cause of a voluntary field action. This risk was due to improper solder joint(s) resulting in thermocouple malfunction and has been resolved through process improvements and validated testing.

4.1.1 Minimization of Risks

The criteria for subject selection, methods, personnel, facilities, and training that have been specified for this study are intended to minimize the risk to subjects undergoing this procedure. Subjects will be screened carefully prior to enrollment in the study to ensure compliance with the inclusion and exclusion criteria. The exclusion criteria have been developed to eliminate confounding co-morbidities that might interfere with study interpretation; to furnish a more homogenous study population that allows a focused characterization of the nMARQ™ device for the treatment of PAF; and, to exclude subjects with a medical history or condition that increases their risk of adverse events.

Subjects meeting any of the following three criteria must have a pre-procedure TEE to screen for the presence of LA thrombus:

- Subjects with history of AF sustained beyond 7 days, or lasting less than 7 days and requiring pharmacological or electrical cardioversion, who are in AF at the time of ablation.
- Subjects with known risk factors such as structural heart disease, presence of risk factors for stroke (i.e., CHADS₂ score >1), and atrial enlargement.
- Subjects who have been in AF for 48 hours or longer or for an unknown duration unless systemic anticoagulation at a therapeutic level has been maintained for at least three weeks.

All other subjects who do not meet the criteria above must either undergo TEE or one of the following methods to screen for LA thrombus on the day before or the day of the ablation procedure. The imaging method used is at the discretion of the investigator based on the patient's medical history and the investigator's medical judgment:

- Computed Tomography (CT)
- Intracardiac Echocardiography (ICE)
- Magnetic Resonance Imaging (MRI)

Participating investigators will be experienced and highly skilled in performing electrophysiology studies, intracardiac mapping and ablation of AF with the use of RF ablation catheters. Each site's Principal Investigator will have satisfied the established training criteria. Procedures will be performed in electrophysiology laboratories with the assistance of skilled nurses and technicians. The laboratory will contain sufficient resuscitative equipment and facilities to manage any potential complication. Immediate access to cardiac surgical facilities, as well as a qualified cardiovascular surgeon, will be available during the ablation procedure in the event that surgical intervention becomes necessary.

Ablation procedures with TC will be performed according to the products' Instructions for Use, including but not limited to instructions regarding indications and contraindications for using

these devices.

The efforts to minimize the risk associated with the 3 identified excessive thermal hazards are described below. Risk analyses were performed in conformance with BWI design control procedures and it was concluded that these mitigations reduced the risk to an acceptable level.

The root cause analysis for the soldering issue has been identified and changes to manufacturing and validation process have been implemented to effectively address this issue. Further, when catheter positioning results in overlapping electrodes or catheter positioning results in an electrode thermocouple not being in juxtaposition with the atrial wall, there is a risk of excessive heat generation if the scenario is not readily recognized by the investigator. This protocol, investigator training, and Instructions for Use (IFU) have been revised to enhance investigator awareness.

5.0 Study Objectives

5.1 Primary Study Objectives

- To demonstrate the safety of the nMARQ (Test) Group compared to the TC (Control) Group based on difference in proportion of early-onset (within 7 days of ablation procedure) primary adverse events, using a non-inferiority margin of 8% for subjects with symptomatic PAF.
- To demonstrate the effectiveness of the nMARQ (Test) Group compared to the TC (Control) Group based on difference in proportion of freedom from documented, symptomatic AF/AT/AFL through 12 months post ablation follow-up using a non-inferiority margin of 15% for subjects with symptomatic PAF.

5.2 Secondary Study Objective: Subpopulation Neurological Assessment (SNA)

To evaluate, within a subset of the Main Study PAF population, the comparative incidence of pre- and post-ablation symptomatic and asymptomatic cerebral emboli, as determined by MRI evaluations. The presence of emboli-associated neurological deficits will also be evaluated, using the National Institute of Health Stroke Scale (NIHSS), the Montreal Cognitive Assessment (MoCA), modified Rankin Scale (mRS), and general neurological assessments.

6.0 Study Design

Following a Calibration Roll-In Phase of up to 5 nMARQ subjects per investigational site, the design of the Main Study will be carried out as a prospective, multi-center, randomized (1:1 concurrent nMARQ™ Catheter System [nMARQ] vs THERMOCOOL® Navigational Family of catheters [TC]), controlled, two-arm, single-blind, clinical study.

6.1 Calibration Roll-in Phase: up to 250 Subjects

One key purpose of this study will be to demonstrate the effectiveness of the nMARQ™ RF Catheter System in the absence of confounding evidence that reflects early stages of a complex medical device learning curve. In addition to a requirement for nMARQ™ System training prior to each Principal Investigator's participation in this study, additional experience of nMARQ™ use, in the context of this protocol, would serve to generate a clearer perspective of nMARQ™ System effectiveness in treating PAF patients. Therefore, the first 3 subjects enrolled at each site will be assigned to the nMARQ group as a calibration roll-in subject. An additional 1-2 roll-in subjects (prospectively designated) will be allowed at each site to minimize the learning curve effect of using the new nMARQ™ System. Up to 5 roll-in subjects will be allowed per site. A subject who is excluded prior to insertion of the nMARQ™ catheter, will not count toward the roll-in subjects. For OUS investigational sites with prior experience of at least 5 nMARQ cases, the minimum of roll-in subjects will be 1. All calibration roll-in subjects will be followed for 3 years post-ablation and be included in the Safety Population.

6.2 Main Study: up to 500 Subjects

This will be a prospective, multi-center, randomized (1:1 concurrent nMARQ™ Catheter System [nMARQ] vs. THERMOCOOL® Navigational Family of catheters [TC]), controlled, two-arm, single-blind, clinical study for subjects with symptomatic PAF who have had at least one AF episode documented within one (1) year prior to enrollment and who have failed at least one antiarrhythmic drug (AAD [class I or III, or AV nodal blocking agents such as beta blockers and calcium channel blockers]) as evidenced by recurrent symptomatic AF, or intolerance to the AAD.

Eligible subjects who sign the study informed consent form and who satisfy all Inclusion and Exclusion Criteria will be randomized into one of two treatment groups:

- **Test Group:** subjects who undergo catheter ablation with the nMARQ™ System.
- **Control Group:** subjects who undergo catheter ablation with a device from the approved THERMOCOOL® Navigational Family of catheters.

Randomized subjects will not be made aware of the treatment arm they have been assigned to throughout the effectiveness evaluation (through 12 months post-ablation).

The Test Group will be compared to the Control Group to assess non-inferiority with respect to the primary effectiveness and safety endpoints. An adaptive sample size of 250-500 subjects will be used for the Main Study. Planned statistical analyses of these endpoints are described in the Statistical Analysis section (Section 11.0) of this protocol.

For this study, it is the Sponsor's intention that the enrolled patient population be as representative as possible of the well-defined study population. Investigators will be strongly encouraged to evaluate all consecutive eligible patients for participation in the study and, if inclusion and exclusion criteria are met, to approach all eligible patients. Centers will be selected for participation in the study based on their capacity to screen and enroll a reasonable number of eligible patients and perform the required study procedures, according to this protocol. Sponsor will attempt to include a diversified group of investigational sites engaging a variety of academic and private institutions geographically located throughout the US and other regions. To ensure a widespread distribution of data and minimize site bias, no more than 20% of the total enrollment (including test and control) will be allowed at a single site.

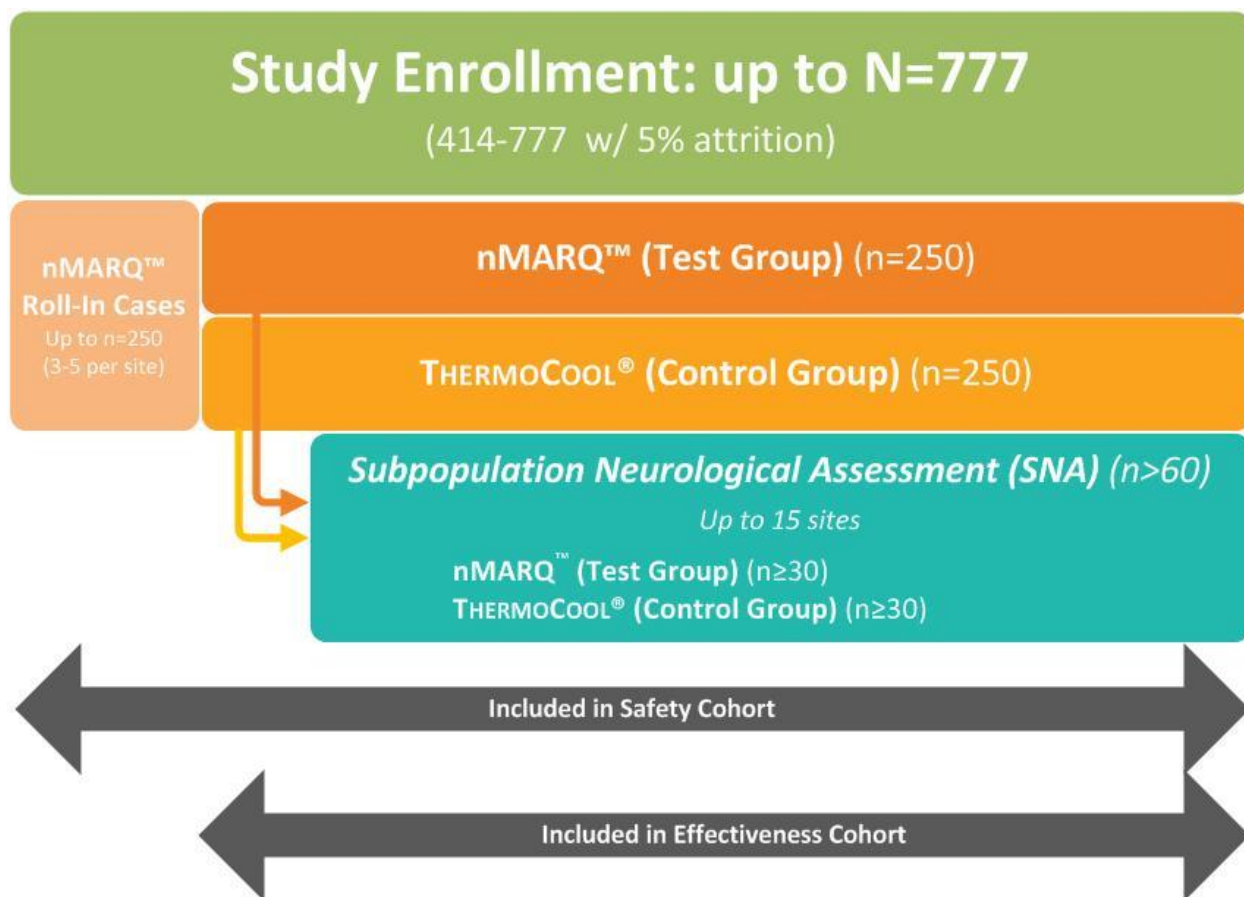


Figure 6.2A: Study Design

6.3 Subpopulation Neurological Assessment (SNA): 60 Subjects

A focused neuropathological evaluation was integrated within the Main Study. Subjects were 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). The SNA addressed some recently published reports of silent (asymptomatic) cerebral emboli, as documented by MRI, immediately following RF ablation and among multiple ablation catheter systems. The reported frequencies of these occurrences vary considerably according to the types of catheters used, study methods, and imaging methodology. Data from the SNA Final Analysis Report support the conclusion that the safety profile of the nMARQ irrigated catheter and its system is within acceptable limits based on previously reported data in literature where occurrence of ACE ranges from 6.8%⁴⁸ to 21.4%.⁴⁴

An evaluation of at least 60 subjects (included in 250-500 total) were included in this assessment and were performed at up to 15 of the participating sites. To assure that the minimum numbers of Test and Control subjects participated in the SNA, enrollment continued until reaching at least 30 Test and 30 Control subjects. The SNA was a prospective, controlled evaluation, with consecutive enrollment, comparing outcomes of Main Study Test and Control subjects treated with the nMARQ and TC, respectively. The mandatory 3-5 Roll-in nMARQ subjects was NOT be eligible for the SNA. This approach minimized the confounding influence of a learning curve during early use of a complex medical device.

Subjects who participated in the SNA were enrolled on a consecutive basis according to the randomization schedule. Ablation therapy was according to the randomization that took place upon entering the Main Study with a maximum of 25% of the total SNA subjects at each site. The associated SNA ICF was a supplement to the current Main Study ICF. Subjects who, for any reason, did not qualify or consent to undergo the additional tests as part of the SNA were continued as enrolled subjects in the Main Study.

At participating SNA sites and considering the above caveats, all remaining subjects (until SNA enrollment targets are met), who are enrolled in the Main Study and randomized to one of the two treatment groups, were sequentially considered for participation in the SNA, per specific eligibility requirements.

1. If a subject satisfies any one of the 3 following conditions he/she was **excluded** from the SNA :
 - Subject has a pacemaker, cardiac defibrillator, or tissue-embedded, iron-containing metal fragments.
 - Subject has a contraindication to use of contrast agents for MRI such as advanced renal disease.
 - Subject has an unresolved pre-existing neurological deficit.
2. Subject provided written informed consent for MRI, National Institute of Health Stroke Scale (NIHSS), Montreal Cognitive Assessment (MoCA), Modified Rankin Scale (mRS), and general neurological assessments.

Special cautionary measures were taken for SNA subjects with claustrophobia or obesity. Subjects with claustrophobia or obesity were cautioned about the confining tubular space of an MRI machine and the length of time to complete brain imaging. Subjects with either problem risk severe emotional stress were provided a detailed explanation of the procedure and allowed to see an MRI machine prior to their signing an ICF for SNA.

6.4 Total Enrollment

It is anticipated that 5% of potential subjects screened for eligibility will not participate in this study due to a failure to satisfy one or more inclusion/exclusion criteria; loss of contact by the study site; or, early subject withdrawal before or after randomization. To account for this attrition, between 414 (= 250 / 0.95 + 150 Roll-in) and 777 (= 500 / 0.95 + 250 Roll-in) subjects will need to be enrolled so that 250-500 subjects will participate in the Main Study. All subjects enrolled will be followed for 3 years following their index ablation procedure.

6.5 Study Duration, Completion, and Termination

Duration: The study duration is anticipated to be approximately 7.5 years; 4.5 years for enrollment phase (including the time in which enrollment was suspended), with an additional 3 years to complete follow-up.

Completion: The study will be considered complete when the 3 year post-ablation follow-up phone calls are complete for all subjects. At study completion, each site will undergo a monitoring visit to conclude any outstanding issues, collect all outstanding eCRF information, verify device accountability, and discuss any other items relevant to the conclusion of the study.

Termination: The study may be terminated prematurely at the discretion of the Sponsor or on statistical grounds (i.e., effectiveness or futility is determined). 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 IRB / EC / EB). If early termination of the study is required due to safety concerns or the occurrence of unanticipated SAEs, 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.

6.6 Recruitment and Screening Procedures

Patients with symptomatic PAF who have failed at least 1 AAD and are deemed eligible for RF ablation will be screened for this study. Eligible subjects must have at least one documented AF episode within 1 year prior to enrollment. An electronic screening log will be maintained by each study site and will be used to document patients considered for potential enrollment into the study. The screening log will be part of the electronic CRF database and should be completed for any patient considered for study enrollment, regardless of selection outcome, as this will allow a better management of site specific study enrollment issues and rates.

6.7 Informed Consent and Enrollment Procedures

If deemed eligible for and willing to participate in the study, a patient or legal representative must sign the study's informed consent form (ICF) prior to enrollment and collection of any study-related data. The ICF and any revisions must have prior approval of the Sponsor and study site's institutional review board (IRB), central IRB, or equivalent (e.g., ethics committee [EC] or ethics board [EB]). The signed ICF must be kept in the subject's files at the study site, with a signed copy of the ICF provided to each subject.

6.8 Subject Selection

All patients considered for a RF ablation procedure for drug refractory recurrent symptomatic PAF should be screened by the investigator or designated member of the research team for study eligibility.

6.8.1 Study Inclusion Criteria

Candidates must meet ALL of the following criteria:

1. Patients with symptomatic paroxysmal AF who have had at least one AF episode documented within one (1) year prior to enrollment. Documentation may include ECG, transtelephonic monitor (TTM), Holter monitor (HM), or telemetry strip. See Section 7.0 of the protocol for specific definitions of documented AF, symptomatic AF, and paroxysmal AF.
2. Patients who have failed at least one antiarrhythmic drug (AAD; class I or III, or AV nodal blocking agents such as beta blockers and calcium channel blockers) as evidenced by recurrent symptomatic AF, or intolerance to the AAD.
3. Pre-procedure anticoagulation on warfarin, rivaroxaban, or apixaban.
 - If receiving warfarin therapy, patients must agree to take warfarin for at least 4 weeks prior to the scheduled ablation procedure.
4. Age 18 years or older.
5. Signed Patient Informed Consent Form (ICF).
6. Able and willing to comply with all pre-, post-, and follow-up testing and requirements.

6.8.2 Study 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 ablation for atrial fibrillation.
3. Patients on amiodarone at any time during the past 3 months prior to enrollment.
4. AF episodes lasting > 7 days.
5. Any cardiac surgery within the past 60 days (2 months)
6. Any valvular cardiac surgical procedure (i.e., ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve).
7. CABG procedure within the last 180 days (6 months).

8. Awaiting cardiac transplantation or other cardiac surgery within the next 365 days (12 months).
9. Documented left atrial thrombus on imaging.
10. History of a documented thromboembolic event within the past one (1) year.
11. Diagnosed atrial myxoma.
12. Presence of implanted ICD.
13. 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.
14. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study.
15. Women who are pregnant (as evidenced by pregnancy test if subject is of child-bearing age and potential), breast feeding, or planning to become pregnant.
16. Acute illness or active systemic infection or sepsis.
17. Unstable angina.
18. Myocardial infarction within the previous 60 days (2 months).
19. Left ventricular ejection fraction <40%.
20. History of blood clotting or bleeding abnormalities.
21. Contraindication to anticoagulation (i.e., heparin, dabigatran, Vitamin K Antagonists such as warfarin).
22. Life expectancy less than 365 days (12 months).
23. Enrollment in an investigational study evaluating another device or drug.
24. Uncontrolled heart Failure or NYHA Class III or IV heart failure.
25. Presence of intramural thrombus, tumor or other abnormality that precludes catheter introduction or manipulation.
26. Presence of a condition that precludes vascular access.
27. Left atrial size >50 mm.

6.9 Subject Status and Disposition Definitions

All criteria listed below apply to both the Test and Control Groups.

Screen Failure: subjects that are screened, but do not meet eligibility criteria and have NOT signed an ICF. Screen failures should be captured in the electronic database. No data will be collected, only the date of screening and the reason for exclusion.

Enrolled Subjects: all subjects who sign the study ICF.

- **Excluded Subjects:** subjects who have signed the ICF, but are found to not meet the study eligibilities, PRIOR to insertion of the study catheter. Excluded subjects will not be included in either the effectiveness or safety analyses of the study catheters.
- **Evaluable Subjects:** all enrolled subjects who have the study catheter inserted. (Calibration Roll-in and randomized subjects.)
 - **Discontinued Subjects:** evaluable subjects who have the study catheter inserted but do not undergo ablation (i.e., no RF energy is delivered with the study catheter). Subjects

will be categorized as “discontinued” if ablation is not possible due to equipment failure or if their arrhythmia is determined at the time of electrophysiologic study to be a non-study arrhythmia; e.g., AFL instead of PAF (required for subject enrollment per study inclusion criteria). Discontinued subjects will remain in follow-up for 30 days as part of the safety cohort. If an SAE is reported for a discontinued subject, they will be followed until event resolution.

- **Calibration Roll-in Subjects:** enrolled subjects who have the study catheter inserted and RF delivered during the Calibration Roll-in Phase. These subjects will be included as part of the analyses for secondary safety endpoints but not analyses for the primary endpoints. Roll-in cases are not randomized and will be limited to not more than 5 subjects enrolled and treated at each site.
- **Lost to Follow-up Subjects:** subjects who are enrolled and evaluable, but contact is lost after most recent follow-up 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 (as described in Section 6.10) or are terminated from the study prior to completion of all follow-up visits.
- **Completed Subjects:** enrolled subjects who have not been excluded, discontinued, withdrawn, early terminated or lost-to-follow-up from the study prior to the final study visit.

6.10 Subject Withdrawal

Subjects may withdraw consent for study participation at any time without penalty or loss of benefits to which they may otherwise be entitled. The investigator may also remove a subject from the study for any of the following reasons: no longer meets eligibility criteria, withdrawal is in the subject’s best interest, subject preference, concurrent illness, non-compliance, etc. Subjects 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.

If a subject is removed 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.

7.0 Definitions

Table 7.0A: AF and Ablation Terms

Term	Study Definition
AF episode	AF documented by ECG monitoring and has a duration of at least 30 seconds or, if <30 seconds, is present continuously throughout the ECG monitoring tracing. The presence of subsequent episodes of AF requires that sinus rhythm be document by ECG monitoring between AF episodes. [Atrial fibrillation and atrial flutter (including atypical flutter) are considered episodes of AF. Atrial flutter alone is not considered an episode of AF.]
Paroxysmal AF*	Recurrent AF (≥ 2 episodes that terminate spontaneously within 7 days. (Episodes of AF of ≤ 48 h duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.)
Persistent AF*	Continuous AF that is sustained beyond 7 days. (Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after ≥ 48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.)
Symptomatic AF	AF where symptom(s) exhibited by the subject are concurrent with a documented episode by ILR, ECG, TTM, Holter monitor, or telemetry recording. Symptoms may include but are not limited to: palpitations, irregular pulse (e.g., rapid, racing, pounding, fluttering, bradycardia), dizziness, weakness, chest discomfort, and breathlessness.
Documented AF episode	An AF episode documented by an electrocardiographic monitoring tool. This may include ILR, ECG, TTM, HM, or telemetry strip. <i>Reporting of a symptomatic episode by a patient or in a referral letter is not considered a documented AF episode.</i>
AF recurrence	Recurrence of an AF episode as defined.
Complete PVI	Entrance block confirmed for all targeted PVs.
Procedure time	Time from the introduction of the first catheter to withdrawal of last catheter.
RF time	Summation of RF delivery time during a procedure.
Pulmonary vein stenosis (PV stenosis)	PV stenosis is defined as a reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as: None: 0-20% Mild: >20%-49%, Moderate: ≥ 50 -69%, and Severe: ≥ 70 % <i>Severe PV stenosis is considered a primary adverse event for this study.</i>

* The HRS/EHRA/ECAS 2012 Consensus Statement recognizes that patients may have both paroxysmal and persistent AF episodes and that the AF classification should be defined as the most frequent type of AF experienced within 6 months of an ablation procedure.

8.0 Study Endpoints

8.1 Primary Safety Endpoint

The primary safety endpoint for this study is the incidence of early-onset (within 7 days of the ablation procedure) primary AEs.

Death	Pericarditis requiring intervention (major)
Myocardial infarction (MI)	Cardiac Tamponade/Perforation
Pulmonary vein (PV) stenosis [†]	Pneumothorax
Diaphragmatic paralysis	Vascular Access Complications
Atrio-esophageal fistula [†]	Pulmonary edema
Transient Ischemic Attack (TIA)	Hospitalization (initial and prolonged)*
Stroke/Cerebrovascular accident (CVA)	Heart block
Thromboembolism	

*Excludes hospitalization (initial & prolonged) solely due to arrhythmia (AF/AFL/AT) recurrence or due to non-urgent cardioversion (pharmacological or electrical). Refer to Table 10.1.3A for definitions of the Primary AEs.

[†]Pulmonary vein (PV) stenosis or atrio-esophageal fistula that occurs greater than one week (7 days) post-procedure shall be deemed a Primary AE.

Refer to Table 10.1.6A for a comprehensive list of anticipated adverse events.

8.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is defined as freedom from documented symptomatic AF/AT/AFL based on electrocardiographic data during the effectiveness evaluation period (Day 91-365). Additionally if a subject meets any one of the following criteria, then the subject will be considered as chronic effectiveness failure.

- Acute procedural failure (i.e., failure to confirm entrance block in all pulmonary veins post-procedure).
- A new AAD for AF during the effectiveness evaluation period (refer to Section 9.3.2 for details).
- A repeat ablation for AF beyond the 90 day blanking period (refer to Section 9.12 for details).
- A repeat ablation not conducted with the nMARQ system for Test Group subjects.
- >2 repeat ablation procedures in the blanking period (Day 0-90).
- A non-study ablation catheter (non nMARQ or TC) was used during the index ablation procedure.

Note: For repeat ablation within the blanking period for nMARQ subjects, use the nMARQ™ System only (e.g., NAVISTAR® THERMOCOOL® catheter or nMARQ™ catheters).

8.3 Secondary Endpoints

The secondary endpoints supporting the study objective are:

Acute Effectiveness:

- Acute effectiveness is defined as complete PVI confirmation as documented by confirmed entrance block (i.e., complete PVI with or without the use of the toolkit's focal catheter).

One-Year Effectiveness:

- Freedom from AF/AFL/AT off antiarrhythmic drug therapy as assessed from the end of the 3-month blanking period to 12 months following the ablation procedure.

Long-Term Effectiveness:

- Freedom from AF/AFL/AT off antiarrhythmic drug therapy as assessed from the end of the 3-month blanking period to 2 year following the ablation procedure.
- Freedom from AF/AFL/AT off antiarrhythmic drug therapy as assessed from the end of the 3-month blanking period to 3 year following the ablation procedure.

Long Term Safety:

- Incidence of AEs and serious adverse events (SAEs) during the 12 month follow-up period post ablation procedure.
- Assessment of PV stenosis at 3 months post-ablation.
- Incidence of AEs and serious adverse events (SAEs) during the 2nd and 3rd year follow-up period post ablation procedure.

Additional Endpoints:

- % PV isolation by study devices, by subject and by PV
- Repeat ablation rate (For AF/AFL/AT)
- Cardiac specific hospitalization rate
- Total fluoroscopy time
- Overall procedure time
- Ablation procedure related parameters
- Device use per targeted PV

Subpopulation Neurological Assessment (SNA) (subset of patients):

- Comparative incidence of symptomatic and asymptomatic cerebral emboli pre- and post-ablation.
- Frequency, anatomic location, and size (diameter and volume) of cerebral emboli by MRI testing at baseline, post-ablation and during follow-up (if lesions observed).
- Incidence of new or worsening neurologic deficits, post-ablation and during follow-up.
- Change from baseline in NIHSS score post-ablation and during follow-up (2 point change in either direction constitutes significant change). Change in baseline compared to post-ablation for Montreal Cognitive Assessment and modified Rankin scale.

9.0 Schedule of Procedures and Examinations (Description of Treatment)

9.1 Patient Screening

An electronic screening log that is maintained at the clinical site will be used to document all patients reviewed for potential inclusion into the study.

Patients who sign the patient informed consent form will be considered enrolled in the study. No patient should undergo any study-specific tests or exams that fall outside the standard of care without first signing the patient informed consent document for this study.

An informed consent document must be obtained for a patient that is a potential study candidate prior to collection of any study specific data collection or exams (excludes standard of care treatments).

9.2 Randomization

Following completion of the Calibration Roll-in Phase (up to 5 subjects) at each site, eligible subjects who have signed a Main Study Informed Consent Form will be randomized 1:1 to either the nMARQ™ Catheter system (Test) treatment arm or the TC (Control) treatment arm. Dynamic randomization will be defined and executed to balance the two treatment groups by site and gender via the Medidata Balance interactive web-based randomization system (IWRS). The designated personnel at each site will be required to access the electronic randomization system to obtain the randomization assignment after entering stratification factors. The randomization treatment assignment and related information (e.g., randomization date and stratification factors) will be passed on to the electronic data capture system and integrated with the subject's clinical study data.

9.3 Study Medication

During this study, current AF management guidelines and the Investigator's routine clinical practices are to be followed as closely as possible.^{1,18,34} These include the use of anticoagulants and AADs. AADs are defined as class I or class III, or AV nodal blocking agents such as beta blockers (BB) and calcium channel blockers (CCB). Previously ineffective AADs can be administered. A new AAD can be administered, however, if continued past Day 90 (blinking period) this will be considered a primary effectiveness failure. The choice of rate control versus rhythm control therapy and the specific drugs used will be left to the Investigator's discretion.

9.3.1 Anticoagulation Medications

The following anticoagulation regimen is required for all study subjects, Test and Control.

Pre-Ablation Regimen

Based on recommendations from the 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation pre-ablation anticoagulation (warfarin, rivaroxaban, or apixaban) therapy is REQUIRED for this study.

- If receiving warfarin therapy, subject must be maintained on warfarin for 4 weeks prior to the scheduled ablation procedure and **weekly INR measurement recorded in the medical records**. These periodic INR measurements should be documented in the medical records as source documentation. **Do NOT discontinue warfarin prior to the procedure.**
 - Subject INR should be recorded 4-5 days prior to the procedure, 1-2 days before the procedure, and on the day of the procedure.
 - INR **MUST** be ≥ 2.0 on the day of the ablation procedure. This must be documented in the medical records as source documentation.
- If receiving rivaroxaban or apixaban therapy, continuation of therapy throughout the procedure is recommended.^{73,74}

During Ablation Procedure

- Administer a heparin bolus prior to transseptal puncture. **Prior to commencing ablation, ensure that an activated clotting time (ACT) of ≥ 325 is achieved. Maintain an activated clotting time (ACT) of ≥ 325** , targeting 350 seconds throughout the ablation procedure.
- ACT levels **MUST** be checked every 15-30 minutes during the procedure to ensure ACT ≥ 325 seconds. All recordings must be documented in the medical records as source documentation.
- Flush the sheath continuously with heparinized saline.

Following Ablation Procedure

- If on warfarin, subjects **MUST** be maintained on warfarin anticoagulant for 2 months post-procedure. (Reinitiate warfarin within 4-6 hours post procedure.)
 - INR must be maintained at 2.0-3.0.
- If receiving rivaroxaban or apixaban therapy, continuation of therapy throughout the procedure is recommended with discontinuation at 2 months post-procedure depending on clinical judgment at the time.
- After 2 months post-procedure, decisions regarding continuation of systemic anti-coagulation agents should be based on subject's risk factors. It is recommended that physicians follow the relevant recommendations from the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of AF.

9.3.2 Antiarrhythmic Drug Management

Definitions:

Antiarrhythmic drugs (AADs) - The study protocol will classify and analyze the following:

- Class I drugs (e.g., flecainide, propafenone, disopyramide, etc.)
- Class III drugs (e.g., amiodarone, dronedarone, dofetilide, etc.)

- AV nodal blocking agents (such as beta blocking agents [BBs] or calcium channel blockers [CCBs]; e.g., propranolol, Metoprolol, diltiazem, verapamil, etc.)

Previously Failed AAD - Any AAD that a subject has ever taken for the treatment of his/her AF, prior to enrollment, is considered a “previously failed AAD” if it meets ALL of the following conditions:

- prior to enrollment, the AAD was ineffective in controlling the subject’s AF or produced intolerable side effects leading to its discontinuation,
- the AAD is administered for the recurrence of AF, and
- the prescribed dose is equal to or lower than the highest ineffective historical dose.

New AAD – ANY of the following are considered a “new AAD” if the drug is administered to treat AF post-enrollment:

- the AAD was never taken for the treatment of AF prior to enrollment,
- the prescribed dose of the previously failed AAD is greater than the highest ineffective historical dose.

AAD Therapy in the Blanking Period (Day 0-90)

- Subjects may receive new or previously failed AADs without affecting their primary effectiveness classification. **New AADs, however, must be stopped by Day 90 or the subject will be deemed a primary effectiveness failure** (refer to Table 9.3.2A).

AAD Therapy in the Effectiveness Evaluation Period (Day 91-365)

- **New AADs**
 - Prescribed after the blanking period OR continued beyond the blanking period for AF and taken in this period will be deemed as primary effectiveness failures. New AADs prescribed for AF taken during the blanking period must be **stopped at or prior to Day 90** or the subject will be classified as a primary effectiveness failure, regardless of the subject’s 3-month follow-up visit date.
- **Previously failed AADs**
 - Started in the post-blanking period OR continued from the blanking period will not result in subject being classified as primary effectiveness failure.

Table 9.3.2A illustrates the corresponding classifications based on AAD therapy administered in the blanking and post-blanking periods.

Table 9.3.2A: AAD Usage and Impact on Primary Effectiveness Classification

AAD Type	Blanking Period	Post-Blanking Period (Day 90-Study Completion)
New AAD*	Can be initiated; subject will not be classified as a primary effectiveness failure.	Should not be initiated in the absence of AF recurrence; subject <i>will</i> be classified as a primary effectiveness failure. Should not be continued past 90-days post-ablation (if initiated in blanking). Subject <i>will</i> be classified as a primary effectiveness failure.
Previously failed AAD	Can be initiated; subject will not be classified as a primary effectiveness failure. Can be continued (from prior to study enrollment); subject will not be classified as a primary effectiveness failure.	Can be initiated; subject <i>will not</i> be classified as a primary effectiveness failure. Can be continued past 90-days post-ablation (if initiated in blanking). Subject <i>will not</i> be classified as a primary effectiveness failure.

* As noted earlier in this section, includes a prescribed dose of a previously failed AAD that is greater than the highest ineffective historical dose

9.3.3 Use of Additional Medications

The use of additional medication during the study will be at the discretion of the Investigator for clinical indications.

9.4 Pre-Procedure (Baseline) Assessments

An electronic screening log maintained at the clinical site will be used to document all patients who were reviewed for potential inclusion into the study.

Patients who sign the Patient Informed Consent Form and are randomized **will be considered part of the Main Study.** No patient will be randomized for study participation or treated with the Study Device without having first signed the approved Patient Informed Consent Form.

At each study site committed to participate in the Subpopulation Neurological Assessments (SNA) and after completion of the Calibration Roll-In Phase, consecutively eligible subjects who satisfy SNA exclusion criteria and who sign a unique SNA Patient Informed Consent Form will undergo a cerebral MRI and a general neurological assessment (including the administration of the NIHSS, mRS, MoCA) conducted by a neurologist certified in the administration of the NIHSS and mRS. All baseline neurological assessments must be completed within a 72-hour period leading up to ablation therapy. Ablation therapy will be according to the Main Study randomization.

Following enrollment, but prior to the EP procedure, information will be collected regarding the presenting illness, medical history, and current/past medical therapy.

Pre-procedure assessments are required within the time specified in Table 9.4.A.

Table 9.4A: Baseline (Pre-Ablation) Evaluations and Completion Timeframe

Baseline (Pre-Ablation) Assessment	Completion Timeframe
Transthoracic Echo (TTE) <ul style="list-style-type: none"> Assess LA size and EF% to confirm eligibility. 	Within 30 days PRIOR to Ablation Procedure
CT/MRA <ul style="list-style-type: none"> Assess baseline PV diameters to evaluate post-ablation PV narrowing or stenosis. 	Within 30 days PRIOR to Ablation Procedure
Transesophageal Echocardiogram (TEE), Intracardiac Echocardiogram (ICE), Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) Imaging for detection of left atrial thrombus: <ul style="list-style-type: none"> Subjects meeting any of the following three criteria <u>must have a pre-procedure TEE</u> to screen for the presence of LA thrombus: <ul style="list-style-type: none"> Subjects with history of AF sustained beyond 7 days or lasting less than 7 days and requiring pharmacological or electrical cardioversion who are in AF at the time of ablation. Subjects with known risk factors such as structural heart disease, presence of risk factors for stroke (i.e., CHADS₂ score >1), and atrial enlargement. Subjects who have been in AF for 48 hours or longer or for an unknown duration unless systemic anticoagulation at a therapeutic level has been maintained for at least three weeks. All other subjects who do not meet the criteria above must undergo one of the following alternative methods to screen for LA thrombus. The imaging method used is at the discretion of the investigator based on the patient's medical history, the investigator's medical judgment, and institution standard practices: <ul style="list-style-type: none"> Transesophageal Echocardiogram (TEE) Intracardiac Echocardiography (ICE) Computed Tomography (CT) Magnetic Resonance Imaging (MRI) 	Day before procedure or day of Ablation Procedure
Pregnancy test (For ALL women of child-bearing age and potential)	Within 24 hours PRIOR to Ablation Procedure
Subpopulation Neurological Assessment (SNA)	
Neurological Evaluation using the NIH Stroke Scale (for SNA subjects only)	Within 72 hours PRIOR to ablation procedure
Modified Rankin Scale (mRS) (for SNA subjects only)	Within 72 hours PRIOR to ablation procedure
Montreal Cognitive Assessment (MoCA) (for SNA subjects only)	Within 72 hours PRIOR to ablation procedure
MRI Examination of the brain (for SNA subjects only)	Within 72 hours PRIOR to ablation procedure

9.5 Treatment Description

9.5.1 TEST - Required Devices

Each site will be supplied with the protocol-specified investigational devices (“Toolkit”) required for study participation (Table 9.5.1A/B). Investigational devices must be tracked according to the device accountability requirements in Section 13.11 and stored in a secure and locked facility. These devices must be used to perform mapping and ablation procedures for subjects randomized to the TEST arm. Device and equipment set-up must be completed according to the Instructions for Use.

Table 9.5.1A: TEST (nMARQ) Required Investigational Study Devices

Investigational Devices (“Toolkit”)	Function
nMARQ™ Circular Irrigated Catheter	Used to map the targeted area of the heart and deliver RF energy to the targeted tissue
nMARQ™ Crescent Irrigated Catheter (discontinued as of January 2015)	Used to map the targeted area of the heart and deliver RF energy to the targeted tissue
nMARQ™ Multi-channel RF Generator	Transmits radiofrequency energy to the Circular and Crescent Mapping & Ablation Catheters
nMARQ™ Interface Cable	Provides a means to interface the Circular Ablation and Crescent Ablation Catheters to the Multi-Channel RF Generator
CARTO™ 3 System Version 2.5 or later	Electroanatomical mapping system for mapping and visualization information
COOLFLOW™ Irrigation Pump	Delivers heparinized saline to the nMARQ™ Irrigated Catheters for cooling during the RF energy application. (up to 60 mL/min)
NAVISTAR® THERMOCOOL®*	<p>If a focal catheter is required for completion of PVI in the TEST arm, the NAVISTAR® THERMOCOOL® Catheter is the only focal ablation catheter allowed for use with the nMARQ™ Multi-Channel RF Generator.</p> <p>The NAVISTAR® THERMOCOOL® Catheter must be used according to the investigational instructions for use when interfacing with the nMARQ™ Multi-Channel RF Generator due to the specific ablation parameters required. The catheter will not be subject to investigational device accountability tracking.</p>

***The use of the NAVISTAR® THERMOCOOL® is considered investigational when used with the nMARQ™ Multi-channel RF Generator.**

Table 9.5.1B: TEST (nMARQ™) Required Non-Investigational Devices.

Standard Equipment	Function
LASSO® Circular Mapping Catheter	To be used in conjunction with the CARTO® 3 System to verify Entrance Block. May also be used to obtain a 3-Dimensional map of the Left Atrium (LA).
Valley Lab adhesive electrical dispersive pads	Component of the RF current return path
EP lab recording equipment	Records multiple intracardiac electrograms and signals from the RF generator (power, temperature, impedance) and for performs electrical stimulation.
CARTO® System Junction Box (PIU)	Provide the interface to the catheter, generator, and the CARTO® System.

When used with the nMARQ™ Circular Irrigated Catheters, the COOLFLOW® Irrigation Pump will deliver a continuous infusion of room temperature heparinized saline (1 u heparin/1 mL saline), at a flow rate of 4 mL/minute, when not delivering radiofrequency current. During ablation, the high flow setting must be used to deliver 60mL/minute or 42 mL/minute for the Circular and Crescent Catheters, respectively.

The maximum settings for RF power, temperature and duration allowed for the nMARQ™ Circular and the Crescent Ablation Catheters are presented in Table 9.5.1C. These settings for THERMOCOOL® catheters, used with the nMARQ™ System, are presented in Table 9.5.1D.

Table 9.5.1C: nMARQ™ Circular and Crescent Irrigated Catheter – Maximum Settings for RF Power, Temperature and Duration**

		Unipolar Mode	Bipolar Mode
RF Power	Maximum	25 W	15 W
Temperature*	Maximum	45°C	43°C
Duration	Maximum	60 sec	60 sec

*The temperature displayed on the Multi-Channel RF Generator does not represent tissue temperature or electrode tissue interface temperature. The maximum temperature per the IFU is 47°C, however this protocol limits the maximum temperatures to those listed above.

**Discontinued as of January 2015.

Recommended RF Power Settings and Titration

The recommendations provided are based on data obtained from animal and clinical studies. Use clinical judgment and consider individual patient anatomy and conditions when selecting settings for RF power, temperature and duration. During ablation, monitor commonly used parameters such as intracardiac signal reduction, temperature response and impedance changes to guide therapy. Do not allow ablation electrodes to overlap during application of RF energy. If the overlap of ablation electrodes cannot be avoided during application of RF energy, stop ablation

and reduce the power setting for one of the electrodes to 1W before proceeding. Refer to the catheter IFU for the full list of warnings, precautions, directions for use, and recommendations.

Reduce the RF power setting to 20W or less if the temperature of an electrode rises during ablation but does not reach the selected temperature limit.

When ablating near adjacent anatomical structures, take precautions to minimize collateral damage to the adjacent structures.

When ablating near the esophagus (along the posterior wall of the left atrium), take precautions to avoid injuring the esophagus. These may include beginning ablation with reduced RF power, reducing application time, increasing the time between subsequent ablations, esophageal visualization and/or intraluminal esophageal temperature monitoring.

Table 9.5.1D: NAVISTAR® THERMOCOOL® Catheter - Recommended RF Energy Delivery Parameters when connected to the nMARQ™ Generator AND used for Atrial Ablation

Parameter	Setting
Idle Flow Rate	2 mL/min
Power Setting	≤ 27 W
Temperature Setting	< 50 ° C*
Irrigation Flow Rate During RF Application	For power levels up to 27 watts, a flow rate of 17 mL/min should be used. <i>At power levels between 28-45 watts, a high flow rate of 30 mL/min should be used</i>
Application Time (max per application)	≤ 120 seconds
*The temperature displayed on the Multi-Channel RF Generator does not represent tissue temperature or electrode tissue interface temperature.	

9.5.2 CONTROL – Required Devices

For treatment within the CONTROL arm, non-investigational THERMOCOOL® Navigational catheters widely available to all sites will be required for study participation (Table 9.5.2A). These devices must be used to perform mapping and ablation procedures for subjects randomized to the CONTROL arm. Device and Equipment set-up must be completed according to the Instructions for Use.

Table 9.5.2A: CONTROL (THERMOCOOL® Navigational) Required Non-Investigational Devices

Standard Equipment	Function
THERMOCOOL® Navigational Family of catheters	A commercially available THERMOCOOL® Navigational catheter (NAVISTAR® THERMOCOOL® Catheter, THERMOCOOL® SF Catheter.) Delivers radiofrequency energy to the target tissue.
Stockert RF Generator	Transmits radiofrequency energy to RF ablation catheters.
LASSO® Circular Mapping Catheter	To be used in conjunction with the CARTO™ 3 System to verify Entrance Block. May also be used to obtain a 3-Dimensional map of the Left Atrium (LA).
Adhesive electrical dispersive pads	Component of the RF current return path
EP lab recording equipment	Records multiple intracardiac electrograms and signals from the RF generator (power, temperature, impedance) and for performs electrical stimulation.
CARTO® 3 System Junction Box (PIU)	Provide the interface to the catheter, generator, and the CARTO® System.

9.6 General AF Procedure Guidelines

Processes required as part of the study are indicated in **BOLD**. All devices must be used according to the accompanying IFU and package labeling.

9.6.1 Electrophysiology study and pre-ablation procedures:

- Anesthesia should be delivered per the standard EP lab procedures.
- **REQUIRED:** An appropriate strategy to minimize risk of esophageal injury **MUST** be used to ensure the physician has accurate information about the location of the esophagus relative to intended sites of ablation. The method used to localize the esophagus will be collected in the CRFs.
 - At least one of the following methods **MUST** be used for esophageal localization:
 - **Use of an esophageal temperature probe**
 - **Esophageal visualization with CartoSound and/or ICE**
 - **Esophageal visualization using barium swallow**
- Placement of Diagnostic Catheters:
 - CS catheter in the coronary sinus (CS) for pacing purposes.
 - LASSO® Catheter for diagnostic purposes.
 - Other catheters may be placed at the discretion of the investigator.
- A standard electrophysiology (EP) study may be performed at the discretion of the investigator and per standard EP lab protocol if not already performed.
- A single or double transseptal (TS) puncture should be performed per standard EP Lab procedures. A patent foramen ovale (PFO) may be used, if applicable.

- **One of the following compatible sheaths are REQUIRED to be used with the TEST Catheters to access the LA:**
 - **8.5F or 9.5F Agilis™ NxT Steerable Introducers Dual-Reach™ Sheath**
 - **9.0F Bard® Channel™ Steerable Sheath**
 - **8.5F Heartspan Fixed Curve Braided Transseptal Sheath**
 - **8.5F Zurpaz Steerable Sheath**
 - **10.0F Bard® DiRex Steerable Sheath**
- Systematic anticoagulation with heparin should be administered with activated clotting time (ACTs) **checked at least every 30 minutes to maintain target ACT of > 325 seconds.**
- Use of CARTOMERGE™ is recommended, utilizing the subject's baseline CT. MRA or rotational angiography (PV venograms or intracardiac echocardiography [ICE]) may be performed, at the discretion of the investigator, per standard EP lab protocol to verify location, morphology, and dimensions of each PV.
- Prior to ablation in the region of the RSPV, precautionary measures to evaluate proximity to the phrenic nerve, such as pacing maneuvers, are **REQUIRED.**
- If the subject is in AF, cardioversion may be performed at the discretion of the investigator prior to the ablation procedure.

9.6.2 TEST Group

9.6.2.1 Mapping and Ablation procedure

- **Use of the CARTO® 3 System is REQUIRED** for mapping of Left Atrium (LA), pulmonary veins, and to acquire RF lesions tags.
- Mapping may be completed using the FAM / MEM functionality with the Test (nMARQ™) catheter or with a standard mapping catheter (THERMOCOOL® or LASSO®).
 - **If available, the ConfIDENSE module should not be used with the nMARQ system.**
- Once the PVs ostia have been defined, position the TEST catheter near the ostium of the targeted PV and find the optimal position of the catheter to maximize the contact with all or most of the electrodes.
 - **If available, the Visitag module should not be used during ablation with the nMARQ system.**
- When the position is satisfactory, commence energy delivery with the Test Catheter, observing the irrigation rate recommendations. The RF energy can be delivered either in bipolar or unipolar configuration per application, at the physician's discretion.
- Ablation of the PVs should be performed at least peri-ostial to isolate the left and right-sided PVs and to ensure RF is not delivered beyond the PV ostia into the vein.
- During the ablation procedure, the investigator will assess the fluid status of the subject and determine if diuresis is necessary, and treat accordingly.

- All subjects will undergo PV ablation until PVI is achieved and confirmed by entrance block.
- If necessary and at the physician's discretion, a commercially available NAVISTAR[®] THERMOCOOL[®] Catheter may be inserted to complete PVI or ablate other identified targets as described in section 9.6.5.

NOTE: Only a NAVISTAR[®] THERMOCOOL[®] Catheter may be used for touch-up with the nMARQ[™] Multi-channel RF generator. The THERMOCOOL[®] SF Catheter can **NOT** be used for this purpose.

NOTE: CARTO[®] 3 mapping of the anatomical location of the PV's and RF lesions is **REQUIRED**. At the completion of the procedure, two back-up copies should be made: one to keep on file in the onsite Study Subject File and one to provide to the Sponsor for the Master Study Files.

9.6.2.2 Verification of ablation procedure(s)

- **Verification of isolation of the targeted PVs by demonstrating entrance block into each targeted PV is REQUIRED.**
 - **A 30 minute waiting period is REQUIRED from the last RF application at a PV target before verification may be confirmed.** The time of the last RF application in a PV target and the time of entrance block verification **MUST** be documented in the medical record as source documentation. If reconduction is noted, additional RF applications should be applied and a second 30 minute waiting period will be required to recheck for entrance block. If reconduction is still noted, additional RF applications should be applied but a third 30 minute waiting period is not required prior to recheck for entrance block.
- To verify entrance block, analyze electrograms in sinus and/or atrial paced rhythm to confirm that no PV potentials are present.
 - Administering adenosine (ATP) and/or isoproterenol for induction prior to verification of entrance block is **REQUIRED**
- Demonstration of entrance block **MUST** be confirmed and documented by both the Test Catheter (if it can be accessed into the PV) and the LASSO[®] Circular Mapping Catheter.
 - First: confirmed and documented by the Test (nMARQ[™] Circular Catheter).
 - Second: confirmed and documented by the LASSO[®] Circular Mapping Catheter.
- Exit block, in addition to entrance block, may be demonstrated but is not required.
- The ablation procedure is considered complete when confirmation of entrance block in targeted PVs is confirmed.

9.6.3 CONTROL Group

9.6.3.1 Mapping and ablation procedure

- **Use of the CARTO[®] 3 System is REQUIRED** for mapping of Left Atrium (LA), pulmonary veins, and to acquire RF lesions tags.
- The mapping and ablation procedure in the Control Arm should follow standard PVI process.

- **If available, the ConfIDENSE module should not be used in the CONTROL arm of the study.**
- **If available, the Visitag module should not be used in the CONTROL arm of the study.**
- When the THERMOCOOL[®] Navigational catheter position is satisfactory, commence energy delivery observing the irrigation rate recommendations.
- Ablation of the PVs should be performed at least 1-2 cm outside the PV ostia to isolate the left and right-sided PVs and to ensure the lesions are not inside the PV ostia.
- During the ablation procedure, the investigator will assess the fluid status of the subject and determine if diuresis is necessary, and treat accordingly.
- All subjects will undergo PV ablation until entrance block is confirmed.

9.6.3.2 Verification procedure

- Verification of isolation of the targeted PVs by demonstrating entrance block into each targeted PV is **REQUIRED**.
 - A 30 minute waiting period is required from the last RF application at a PV target before verification may be confirmed. The time of the last RF application in a PV target and the time of entrance block verification **MUST** be documented in the medical record as source documentation. If reconduction is noted, additional RF applications should be applied and a second 30 minute waiting period will be required to recheck for entrance block. If reconduction is still noted, additional RF applications should be applied but a third 30 minute waiting period is not required prior to recheck for entrance block.
- To verify entrance block, analyze electrograms in sinus and/or atrial paced rhythm to confirm that no PV potentials are present.
 - Administering adenosine (ATP) and/or isoproterenol for induction prior to verification of entrance block is **REQUIRED**
- Demonstration of entrance block **MUST** be confirmed and documented using the LASSO[®] Circular Mapping Catheter.
- Exit block, in addition to entrance block, may be demonstrated but is not required.
- The ablation procedure is considered complete when confirmation of entrance block in targeted PVs is confirmed.

9.6.4 Procedural data to be collected

- The following procedural information will be collected during each ablation procedure:
 - RF Ablation parameters per application (power, temperature, flow rate, duration, impedance rise/fall, mode of RF delivery (bipolar or unipolar))
 - Device(s) utilized for RF delivery (per targeted PV)
 - Device(s) utilized for verification (per targeted PV)
 - Duration of mapping time
 - Duration of RF application time with study catheter (Test or Control) for AF targets

- Duration of Fluoroscopy time during mapping
- Duration of Fluoroscopy time during ablation
- Total procedure time
- Fluid delivered by the Study Catheter
- For SNA subjects only, the number of catheters exchanged during each ablation procedure will be documented

9.6.5 Optional ablation procedure(s) based on clinical findings:

Additional RF lesions with the assigned catheter system may be performed in the left atrium at the investigator's discretion based on treatment need. When additional RF lesions are placed during an ablation procedure, these treatments must be clearly documented (location and justification) in the procedure notes and on the study case report forms.

As noted in the 2012 HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of atrial fibrillation, **optional ablation targets** may include but are not limited to the following:

- If a focal trigger is identified outside a PV during the ablation procedure, ablation of that focal trigger should be considered.
- Ablation of the cavotricuspid isthmus is recommended in patients with a history of typical atrial flutter or inducible cavotricuspid isthmus dependent atrial flutter (using the ThermoCool catheter for roll-in subjects and those in the Test arm).

NOTE: RF power should be reduced when creating lesions on the posterior wall near the esophagus.

NOTE: Catheters are for single use only as indicated in the Instructions for Use.

9.7 Post Procedure (pre-discharge) Assessment

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

- 12 Lead ECG (if standard of care)
- Transthoracic Echocardiogram (TTE)
- For SNA subjects only
 - MRI examination of the brain
 - Neurological examination, including NIH Stroke Scale

9.8 Follow-up Visit Assessment

The subject will be required to complete follow up visits through 3 years post initial ablation procedure. The follow-up visits at 1 month, 3 months, 6 months, 9 months, and 12 months will consist of an office visit.

Discharged subjects will receive a telephone call at 7 days post ablation procedure to assess any occurrence of Primary Adverse Events; otherwise, in-hospital surveillance will capture any

Primary Adverse Events. Additionally subjects will be followed up at 2 years and 3 years post-ablation by telephone to assess any late occurring adverse events and any patient reported recurrences of AF.

Follow-up visits should be scheduled according to the following timeframes: 1 month -23/+12 days (M-1, day 7-42), 3 month ± 20 days (M-3, day 70-110), 6 months ± 30 days, (M-6, day 150-210), 9 month ± 40 days (M-9, day 235-315) and 12 month ± 45 days (M-12, day 316-405). Follow-up visit schedule will not reset if subject undergoes a repeat AF ablation procedure.

The 2 and 3 year post-ablation telephone calls should occur within ± 45 days of their index ablation procedure anniversary.

9.9 Summary of Subject Assessment

At each visit, the following assessments should be performed:

Table 9.9A: Summary of Subject Assessments

Assessments	BL	D/C	D7	M1 D7-42	M3 D70-110	M6 D150-210 M9 D235-315	M12 D316-405	UNS	Y2 ±45D Y3 ±45D
Clinic visit	•			•	•	•	•	•	
Patient Information (Demographics) and Consent	•								
Medical history	•								
Pregnancy Test ¹	•								
TTE ²	•	•							
Imaging for detection of LA thrombus (e.g., TEE, ICE, CT, MRI) ³	•								
ECG ⁴	•	•		•	•	•	•	•	
TTM ³					•	•	•	•	
CT/MRA nMARQ GROUP ONLY	• ⁶				•				
Cardiac medication	•			•	•	•	•	•	
Adverse events	•	•	• ⁷	•	•	•	•	•	• ⁷
AFL/AT/AF recurrence and repeat ablation				•	•	•	•	•	• ⁷
CCS-SAF Scale	•				•	•	•		
Cerebral MRI ⁸	• ⁹	• ¹⁰		• ¹¹	• ¹¹	• ¹¹	• ¹¹	• ¹²	
Neurological Exam ⁸	• ⁹	• ¹⁰		• ¹¹	• ¹¹	• ¹¹	• ¹¹	• ¹²	
NIH Stroke Scale ⁸	• ⁹	• ¹⁰		• ¹¹	• ¹¹	• ¹¹	• ¹¹	• ¹²	
mRS	• ⁹				•				
MoCA	• ⁹			•	• ¹¹	• ¹¹	• ¹¹	• ¹²	

1. In all women of child-bearing age and potential. To be completed within 24 hours prior to ablation procedure.
2. Completed within 30 days prior to ablation period.
3. To be completed the day before or the day of the ablation procedure.
4. To be collected if completed as standard of care.

5. Dispensation of TTM device at Month 3.
6. Within 30 days prior to ablation procedure.
7. To be assessed via phone follow-up.
8. Only for SNA subjects.
9. To be performed within 72 hours prior to ablation procedure.
10. To be completed within 72 hours post-ablation procedure.
11. To be undertaken if neurologic symptoms and/or cerebral ischemic lesions identified in a prior evaluation.
12. To be completed only if: (i) a previously mandated test was missed; or, (ii) subject reports neurologic difficulties between scheduled follow-up visits and unscheduled assessment per investigator approval.

9.10 Descriptions of Procedures

12-lead Electrocardiogram (ECG) – Standard of Care

Data from 12-lead ECG recordings will be collected as described in Table 9.9A. Data from unscheduled ECG's between two consecutive follow-up visits will be collected and reported on the appropriate eCRF (i.e., unscheduled visit eCRF). Copies of ECG reports should be filed in the subject's medical chart with the participating investigator.

Arrhythmia Monitoring - Standard of Care

Additional arrhythmia monitoring data will be collected if standard of care (e.g., Holter monitoring).

Cardiac Computed Tomography (CT) / Magnetic Resonance Angiogram (MRA) – nMARQ (TEST) GROUP ONLY

A cardiac multi slice CT or MRA must be performed according to requirements in Table 9.9A. For each nMARQ subject, the same imaging technique (CT or MRA) should be used pre-ablation and post-ablation, and the exam must follow the CT/MRA protocol supplied by the core lab. Pre-ablation and post-ablation CT/MRAs will be analyzed by a core lab to evaluate PV Stenosis.

Cardiac Medication

All cardiac medications and the indication for which they are prescribed will be documented in subject charts and reported on the appropriate eCRF(s). If an AE is related to intake of medications, details must be provided on the appropriate eCRF(s).

CCS-SAF scale (Dorian *et al.*, 2006)

Subjects will be classified by the physicians (on the eCRF) according to the CCS-SAF scale pre-ablation, and at the 3, 6, 9 and 12 month follow-up visits.

Pregnancy Test

A pregnancy test must be obtained within 24 hours prior to the ablation procedure for ALL female patients of child-bearing age and potential.

Transtelephonic Monitoring (TTM)

Each subject will be provided with a TTM device at the 3-month follow-up visit. Transmissions will be required monthly beginning on Day 91 from their index ablation procedure per the following schedule:

- A minimum of 1 transmission per month will be required beginning Day 91 (following completion of the 3 month blanking period) through the 12-month follow-up visit.
- Additionally, any symptom-triggered episode that occurs from the end of the blanking period through the 12-month follow-up visit should be recorded and transmitted. The core lab representative receiving the transmission will ask the subject to report arrhythmia-related symptoms experienced during each recording.

Transesophageal Echocardiography (TEE)

Transesophageal echocardiography may be completed according to the requirements in Table 9.9A. TEEs are performed to exclude atrial thrombus or other structural contraindications to an 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.

Transthoracic Echocardiography (TTE)

Transthoracic echocardiograms must be performed according to requirements in Table 9.9A. TTE should be completed within 30 days prior to the study ablation procedure, and must be repeated before discharge to evaluate volume parameters, valve abnormalities, LA dimensions, and exclude presence of pericardial effusion. Copies of TTE reports should be filed in the subject's medical chart.

Cerebral Magnetic Resonance Imaging (MRI; SNA subjects only)

A cerebral MRI must be completed as described in Table 9.9A. Pre-ablation and post-ablation cerebral MRIs will be analyzed (blinded) by a central core lab to determine the frequency, size, and anatomic location of cerebral micro-emboli, if any. If there are findings noted on the post-ablation cerebral MRI, a follow-up MRI will be required at each follow-up visit until resolution is observed.

Montreal Cognitive Assessment (MoCA) (SNA subjects only)

The SNA subjects will undergo a neurological assessment using the MoCA at baseline and 1M post-ablation. Also, possibly at other follow-up visits, pending previous findings of microemboli/neurologic deficits.

Modified Rankin Scale (mRS) (SNA subjects only)

The SNA subjects will undergo a neurological assessment using the mRS at baseline and 3M post-ablation. This assessment will be performed by a neurologist certified in the administration of the mRS.

Neurologic Exam (SNA subjects only)

A medical staff member, who is not an investigator or part of the reMARQable study team, and who is a member of the neurology department, must perform neurologic exams at pre- and post-

ablation and possibly at other follow-up visits, pending previous findings of microemboli/neurologic deficits.

NIH Stroke Scale Assessment (SNA subjects only)

The SNA subjects will undergo a neurological assessment using the NIH Stroke Scale at baseline, post-ablation, and possibly at other follow-up visits, pending previous findings of microemboli/neurologic deficits. This assessment will be performed by a neurologist certified in the administration of the NIHSS

Table 9.9A displays the required schedule for subject treatments and evaluations for the Test and Control Groups. All subjects will be followed through 3 years post-ablation. Subjects who undergo a repeat ablation procedure will continue follow-up according to the schedule of their index (first) ablation procedure. Thus, subject visits will be counted from the index ablation procedure, not from the repeat ablation procedure.

9.11 Unscheduled Visits

If a subject returns for a visit outside of the protocol-defined visit schedule provided in Table 9.9A, the visit will be considered “unscheduled” (UNS). An Investigator may request an unscheduled visit in the presence of a new or worsened 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.

9.12 Repeat Ablation Procedures

Repeat ablation(s) may be performed at the discretion of the investigator. The devices used for any repeat ablation **MUST** be the same as the assigned catheter system during the blanking period. A change to the assigned catheter system for repeat ablations during the blanking period will result in that subject being considered a chronic effectiveness failure. All necessary eCRFs must be completed for all repeat ablation procedures. Imaging for detection of LA thrombus should be completed pre-procedure and pre- and post-procedure TTEs for detection of pericardial effusion should also be completed for repeat procedures. Additionally, for subjects receiving warfarin therapy, every effort should be made to keep the INR ≥ 2.0 pre-procedure for repeat procedures.

Physicians should determine and document in eCRF if recurrence due to reconnection of target PVs or due to non-PV targets. The follow up schedule will remain based on the initial ablation procedure. If more than 2 repeat ablation procedures are required during the blanking period, this will be considered a chronic effectiveness failure. Additionally, if a repeat ablation procedure is conducted, during the effectiveness evaluation period, it will be considered a chronic effectiveness failure. An exception may be made for extenuating circumstances preventing the hospital from being able to schedule a repeat ablation within the blanking period. The occurrences will be evaluated by the Sponsor on an individual basis and documented approval must be granted.

9.13 Core Laboratory for Evaluation Tests

An independent central core laboratory or expert physician^a will conduct blinded/objective evaluations of TTM, CT/MRA, and cerebral MRI. Initial evaluations may be performed by personnel trained in specific evaluation of these tests; ultimately, all tests will be reviewed by a physician expert who is certified/well qualified to make such assessments (e.g., cardiologist, experienced EP technician, neuroradiologist^b, or neurologist). AF episodes will be evaluated per the definitions provided in this protocol (refer to Study Definitions).

^a *For neurological assessments, including NIHSS Scoring, final assessments are to be done by a neurologist in the investigational site who remains unaware of the study device or treatment arm to which a subject has been randomized.*

^b *Protocol-based MRI assessments of subjects in the SNA or subjects who, post-ablation, have new onset neurological deficits will have 2 or up to 3 neuroradiologists assess submitted images per written Core Laboratory procedures.*

10.0 Adverse Events

10.1 Definitions / Classifications

10.1.1 Adverse Event (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 adverse events if the investigator determines they are clinically significant.

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/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.
- Reablation for AF or pre-existing AFL/AT.

10.1.2 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
 - a 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.

10.1.3 Primary Adverse Event

A **Primary AEs** is an event listed in Table 10.1.3A which occurs within the first week (7 days) following an ablation procedure. Primary AEs are considered SAEs.

Table 10.1.3A: Primary Adverse Events

Primary Adverse Event	Description/Criteria
Death	Adverse event resulting in patient death.
Atrio-esophageal Fistula*	Connection between the atrium and the lumen of the esophagus as evidenced by documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium.
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 which results in hemodynamic compromise [†] , requires elective or urgent pericardiocentesis, or results in a 1 cm or more pericardial effusion as documented by echocardiography. <ul style="list-style-type: none"> Cardiac tamponade/perforation should also be classified as: <ul style="list-style-type: none"> Early – diagnosed prior to discharge Late – following initial discharge from the hospital (see Safety requirement below)
Myocardial Infarction	Presence of any one of the following criteria: <ul style="list-style-type: none"> Detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB) which 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
Stroke	Stroke/CVA is an acute symptomatic episode of neurological dysfunction attributed to a vascular cause (ischemia or hemorrhage) in which symptoms last more than 24 hours, or if symptoms last less than 24 hours, a brain imaging study demonstrates infarction.
Cerebrovascular Accident (CVA)	
Thromboembolism	Formation in a blood vessel of a clot (thrombus) that results from the breaking loose of all or part of an existing thrombus, which is then carried by the blood to lodge in/occlude a more distal vascular site.
Transient Ischemic Attack	Acute episode of temporary (<24 hrs) and focal loss of cerebral function of vascular (occlusive) origin as determined by the consulting neurologist.
Diaphragmatic Paralysis	Change in baseline diaphragmatic functioning as evidenced by elevation of the diaphragm above the normal range but not due to a pulmonary process such as atelectasis.
Pneumothorax	Adverse event resulting in air introduction into the pleural cavity of the chest between the lung and the chest wall necessitating chest tube placement or surgical intervention.
Heart Block	Impairment of AV conduction requiring intervention due to inappropriate RF application.
Pulmonary Vein Stenosis*	≥70% diameter reduction of pulmonary vein from baseline CT/MRA scan.
Pulmonary Edema (Respiratory Insufficiency)	Respiratory insufficiency resulting in pulmonary complications necessitating intubation or other significant intervention (including diuretics administered specifically for treating pulmonary edema): <ul style="list-style-type: none"> Pneumonia – infiltrate, fever and leukocytosis ARDS Pulmonary edema

Primary Adverse Event	Description/Criteria
Pericarditis	Major: results in effusion which leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization or persists for more than 30 days after ablation.
Hospitalization (initial and prolonged)	Adverse event resulting in admission to the hospital or prolongation of expected hospital stay due to an AF ablation procedure or a study device-related cause. Excludes hospitalization solely due to arrhythmia recurrence or non-medically urgent cardioversion.
Vascular Access Complication	Vascular access complication (e.g., groin hematoma, AV fistula, pseudoaneurysm) requiring intervention (e.g., surgical repair, blood transfusion) or admission or prolonged hospitalization.

* Atrio-esophageal fistula and pulmonary vein stenosis that occur greater than one week (7 days) post-procedure shall be deemed Primary AE.

† Hemodynamic compromise or instability is defined as Systolic BP <80 mmHg.

10.1.4 Adverse Device Effect / Serious Adverse Device Effect

An adverse device effect is an adverse event related to the use of the investigational medical device. A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of an SAE.

10.1.5 Anticipated Adverse Events

An anticipated AE is an event that has been reported in previous studies of RF ablation/drug therapy, and can be anticipated in this current study per the risk analysis. Table 10.1.5A provides a comprehensive list of anticipated AEs.

Table 10.1.5.A: Anticipated Adverse Events

Anticipated Adverse Events	
1.	Acute Respiratory Distress Syndrome (ARDS)
2.	Air embolism
3.	Allergic reaction
4.	Anaphylactic shock
5.	Anemia
6.	Allergic reaction to Anesthesia (e.g., hair loss)
7.	Apnea - sedation induced
8.	Arrhythmia: bradycardia
9.	Arrhythmia: tachycardia
10.	Arrhythmia: pro-arrhythmias
11.	Arrhythmia: ventricular tachyarrhythmia / pro-arrhythmia
12.	Aspiration pneumonia
13.	Asthmatic attack
14.	Atelectasis
15.	Atrial fibrillation*

16.	Exacerbation of pre-existing arrhythmia*
17.	Atrio-Esophageal fistula
18.	Atypical left atrial flutter
19.	AV fistula
20.	Bleeding complications
21.	Bleeding requiring transfusion
22.	Cardiac arrest
23.	Cardiac perforation
24.	Tamponade
25.	Cardiac thrombo-embolism
26.	Cerebro-vascular accident (CVA) / stroke
27.	Chest pain/discomfort
28.	Complete heart block, temporary or permanent
29.	Conduction block: ongoing / resolved
30.	Congestive Heart Failure
31.	Coronary artery dissection
32.	Coronary artery occlusion
33.	Coronary artery spasm
34.	Coronary artery Thrombosis
35.	Death
36.	Deep venous thrombosis
37.	Dislodgement of ICD (Implantable Cardioverter Defibrillator)
38.	Dislodgement of permanent pacing leads
39.	Disseminated Intravascular Coagulation
40.	Dyspnoea
41.	Endocarditis
42.	Epistaxis
43.	Expressive aphasia
44.	Fainting
45.	Fatigue
46.	Gastro-intestinal NOS
47.	Gastric reflux
48.	Nausea
49.	Gastrointestinal diverticulosis
50.	Heart Failure
51.	Hematoma (local) /ecchymosis
52.	Hemorrhage
53.	Hemothorax
54.	High / increased creatine phosphokinase (CPK)
55.	Hypotension
56.	Hypoxia
57.	Infection, localized

58.	Infection, systemic
59.	Laceration
60.	Leakage of air or blood into the lungs or other organs due to perforation
61.	Liver toxicity
62.	Mobile strands in Inferior Vena Cava
63.	Myocardial Infarction
64.	Neurological disorders (tremor)
65.	Neurological disorders (poor coordination)
66.	Neurological disorders (headache)
67.	Obstruction to the vascular system
68.	Perforation to the vascular system
69.	Damage to the vascular system
70.	Pericardial effusion resulting in tamponade
71.	Pericardial effusion without tamponade
72.	Pericarditis
73.	Peripheral embolus
74.	Peripheral nerve injury
75.	Peripheral thromboembolism
76.	Phlebitis
77.	Phrenic nerve damage
78.	Diaphragmatic paralysis
79.	Pleural effusion
80.	Acute Respiratory Distress Syndrome (ARDS)
81.	Pneumothorax
82.	Pseudoaneurysm
83.	Pulmonary edema
84.	Heart failure
85.	Pulmonary embolism
86.	Pulmonary hypertension
87.	Pulmonary toxicity, like acute pulmonary syndrome
88.	Pulmonary vein dissection
89.	Pulmonary vein Stenosis
90.	Pulmonary vein thrombus
91.	Pump failure
92.	Renal failure
93.	Respiratory depression
94.	Respiratory failure
95.	Retroperitoneal hematoma
96.	Rhabdomyolysis, including produced by body position or propofol
97.	Sedation induced CO2 retention with lethargy and cholecystitis
98.	Seizure
99.	Sepsis

100.	Skin burns (due to cardioversion, tape, etc)
101.	Skin discoloration
102.	Skin injury / muscle or connective tissue injury due to body position, electrical cardioversion
103.	Skin rash
104.	Thrombocytopenia
105.	Thromboembolism
106.	Thrombosis
107.	Thyroid disorders
108.	Transient extremity numbness
109.	Transient ischemic attack (TIA)
110.	Unintended complete or incomplete AV, Sinus node, or other heart block or damage
111.	Urinary retention
112.	Urinary tract infection
113.	Urinary tract injury or infection related to the urinary catheter
114.	Valvular damage/insufficiency
115.	Vasovagal reactions
116.	Vision change
117.	Volume overload
118.	Worsening obstructive, restrictive, or other form of pulmonary disease
119.	X-ray radiation injury of skin, muscle and/or organ

*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.

10.1.6 Unanticipated 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.

10.1.7 Non-Serious Adverse Events

A non-serious AE is any event that results in minimal transient impairment of a body function or damage to a body structure, and does not require any intervention listed under the criteria for “serious adverse event”.

10.1.8 Study Device Failure or Malfunction

A device has failed if it does not perform according to the Instructions for Use 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.).

10.2 Causality

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

Table 10.2A: Adverse Event Causality Classifications

Caused By	Relation	Definition of Relation
Device	Definitely	The device directly caused or contributed to the AE.
	Possibly	The device may have caused or contributed to the AE.
	Unrelated	The AE is not associated with the device.
Procedure	Definitely	The AE is an untoward medical occurrence directly associated by timing and/or pathophysiology with the standard electrophysiology or AF ablation procedure described in this protocol that would not have happened if the procedure had not been performed.
	Possibly	The AE may be associated by timing and/or pathophysiologic with the standard electrophysiology procedure described in this protocol.
	Unrelated	The AE is not associated with the standard electrophysiology or AF ablation procedure described in this protocol.

10.3 Intensity / Severity

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

Table 10.3A: Adverse Event Intensity / 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.

10.4 Outcome

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

Table 10.4A: 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
Improved	Subject's condition improved, but residual effects remain
Unchanged	AE is ongoing
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)

10.5 Adverse Event Reporting and Documentation Requirements

10.5.1 Adverse Event Reporting Requirements

Each AE must be reported to the Sponsor regardless of classification, seriousness, intensity, outcome or causality. Adverse events will be recorded on the electronic case report forms (eCRFs) 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.

All serious AEs, UADE/SADE/USADE, and Study device failure/malfunction, whether or not they are related to the device or procedure, **must be reported** to the Sponsor, via eCRF, **immediately upon awareness of the event** by the study site personnel.

Study Device Deficiencies (failure or malfunction) associated with an AE must be reported to the Sponsor immediately upon awareness of the event by the study site personnel (both the device failure and AE), documented on the appropriate eCRF and **the device returned** according to the Sponsor's instructions.

Under no circumstances should UADEs be reported later than 10 business days.

Biosense Webster will ensure that investigators are instructed to return devices suspected of causing an AE or SAE (i.e., definitely 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 10.5.1A.

Table 10.5.1A: AE Reporting Requirements

Type of Adverse Event	Reporting Requirements
Serious Adverse Events (including Primary AEs)	Report to sponsor immediately upon awareness
UADE, USADE & SADE	Report to sponsor immediately upon awareness
Study device failure/malfunction associated with an AE	Report both study device failure and AE to Sponsor immediately upon awareness
All other Adverse Events	Routine reporting via EDC

10.5.2 Complaint Reporting

Devices must be returned if suspected of malfunctioning or if suspected of causing an AE (as described in the AE Section of this protocol).

Complaints related to non-Biosense Webster, Inc. products must be handled according to institutional policies, EC / EB (or equivalent) policies, and local regulations.

All “device-related AEs AND BW device is used” AND/OR “Procedure-related AEs and BW device is used” need to be reported to Biosense Webster’s Complaints Management Department within 24 hours for SAEs and within 2 working days for any other AEs after site awareness date in accordance with current Biosense Webster procedures. Institutional policies, EC / EB (or equivalent) policies, and local regulations must also be followed, as applicable. General complaints and/or product malfunctions for Biosense Webster, Inc. products not affecting subject safety or welfare are to be reported according to current Biosense Webster procedures and other policies as necessary (i.e., institutional policies, EC / EB [or equivalent] policies, and local regulations).

10.5.3 Adverse Event Documentation

Each AE must be reported regardless of classification and 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 Adverse Events section of this protocol. All AEs must be assessed by the study investigator and properly documented by completing the subject’s medical records (source documents) and appropriate eCRF. All AEs must be monitored until they are adequately resolved or explained. Additional 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 / IRB, 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.

10.6 Global Safety Monitoring Committee

All AEs will be monitored until they are resolved or explained. Each AE will be reported regardless of severity, outcome, or causality. In order to minimize risks to subjects enrolled in the study, the Sponsor will convene a formal Global Safety Monitoring Committee (GSMC) at frequent intervals to review the safety data and recommend appropriate action(s) to ensure subject safety.

In addition to review of the accumulated safety data, the committee will be tasked with independently adjudicating all SAEs reported by the investigators in the study. The committee will be responsible for adjudicating severity and causality of the SAEs, and overall SAE event rates.

11.0 Statistical Analysis

One objective of the Main Study is to demonstrate non-inferiority of the nMARQ (Test) Group compared to the TC (Control) Group based on the difference in the primary safety endpoint using a non-inferiority margin of 8% for subjects with symptomatic PAF.

Another primary objective of the Main Study is to demonstrate non-inferiority of the nMARQ (Test) Group compared to the TC (Control) Group based on the difference in the primary effectiveness endpoint using a non-inferiority margin of 15% for subjects with symptomatic PAF.

The objective of the SNA is to evaluate, within a subset of the Main Study PAF population, the comparative incidence of symptomatic and asymptomatic post-ablation cerebral micro-emboli in the Test and Control groups and the presence or absence of emboli-related central nervous system (CNS) deficits for subjects with symptomatic PAF who are randomized and successfully complete the brain MRI and neurological assessments.

11.1 Overview of Study Design

A Bayesian adaptive trial design is employed. Several Bayesian aspects will be employed and crucial parameters of the trial will be determined by the accruing data using a completely prospective design. The following is an overview of the design:

- 1) The sample size of the trial will be determined by Bayesian adaptive techniques. At the 250, 300, 350, 400, and 450 interim looks the trial may stop for *expected success* or for *futility*. If the trial stopped for *expected success* then all subjects will be followed through to the final efficacy endpoint (12-months post procedure). A cap of 500 subjects will be employed.
- 2) An interim analysis will be conducted 16-weeks after enrollment ends for *early success*. If the predictive probability of final success is greater than 99%, then trial success will be declared. All subjects will have complete safety data and all subjects will be followed through their trial completion.

11.2 General Considerations

A comprehensive statistical analysis plan (SAP) will provide full detail on all planned analyses for this study. Any changes (deviations) to the planned analysis methods and the justifications for making the changes will be reported in the final clinical study report.

In general, descriptive statistics will summarize all primary, secondary, effectiveness, safety, and other endpoints as appropriate. For continuous variables, number of subjects/events, mean, standard deviation, median, 25% percentile, 75% percentile, minimum, and maximum will be provided. For categorical variables, frequency and percentage will be presented for each category.

Confidence intervals for binary variables, including the primary outcome variables, will be computed using the exact binomial distribution. Categorical variables will be compared using Chi-square or Fisher's exact test, with the Monte Carlo option used where computationally necessary. Confidence intervals for continuous variables will be computed using the t-statistic. Continuous variables will be compared using ANOVA or Kruskal-Wallis test.

Unless otherwise specified, the exact form of each statistical algorithm will be the default of SAS®.

The data collected during the course of the trial will be presented in a listing format.

11.3 Sample Size and Power Calculation

11.3.1 Main Study

Trial simulation was carried out to evaluate the performance characteristics of the trial. For each scenario, 10,000 simulated trials were summarized to create the performance characteristics of that trial. Under the assumptions of equivalent effectiveness success rate at 55% and equivalent safety event rate at 8.6% in both groups, at an experiment-wise error rate of 0.05, an adaptive sample size of 250-500 (mean sample size of 417) will provide 80% power for trial success, meeting both effectiveness and safety endpoints, and 82.8% power and 87.4% power for meeting effectiveness and safety endpoints individually. The probability of early trial success is 36.8%. In the simulation, the non-inferiority margin is 15% for effectiveness and 8% for safety. The primary AE rate in the first 7-days is simulated as a Bernoulli random variable with a specified probability; the occurrence of effectiveness failure and timing of the failure are based upon a three-piece exponential time-to-failure model. The detailed descriptions of the simulation assumptions as well as simulation under various scenarios are summarized in Appendix A.

These trial simulations assume a primary AE rate of 8.6% for both Test and Control groups under the alternative hypothesis. Based on P030031/S011 data, the overall primary AE rate was 10.8%. However, this primary AE rate included 3 study subjects deemed primary safety failures solely due to hospitalization for AF recurrence. The incidence of primary AEs excluding those 3 subjects was 8.6%. Thus, an 8.6% primary AE rate is used for the purpose of trial simulations.

These trial simulations assume an equivalent success rate of 55% for both Test and Control groups under the alternative hypothesis using the chronic definition of effectiveness failures as defined in Section 8.1. These assumptions are based upon review of data from recent pivotal P030031/S011 AF THERMOCOOL® Trial where the chronic success rate in the NAVISTAR® THERMOCOOL® Group at 1 year follow-up was 62.7% (64/102) for all sites and 43.3% (29/67) for US data only. Therefore, it is estimated that the chronic success rate for both the nMARQ™ System and THERMOCOOL® at 12 month follow-up will be around 55%.

11.3.2 Adaptive Sample Size

The sample size in the Main Study may vary from 250 to 500 due to the adaptations to the trial. Details regarding the adaptations are located in the Interim Analysis section of this protocol.

11.3.3 SNA Population Sample Size

At least 60 subjects (≥ 30 Test subjects and ≥ 30 Control subjects) from the already enrolled and randomized subjects of the Main Study will be selected in sequence for the SNA. The sample size is not intended for statistical comparisons by treatment group; however, 30 subjects in each arm will provide at least 91% probability of observing at least one event if the true event rate is at 8-14%.

11.3.4 Total Sample Size

Biosense Webster proposes the sample size for this IDE study to be up to 777 subjects (500/0.95+250), based upon the 250-500 subjects required for the effectiveness evaluation, up to 250 Calibration Roll-in subjects and 5% potential subject attrition rate before randomization. Up to 250 roll-in subjects using the nMARQ™ System are expected in this study because up to 50 sites will enroll up to 5 roll-in subjects each to reduce the influence of learning curve on effectiveness results. It is also estimated that no more than 5% of enrolled patients will either not meet the inclusion/exclusion criteria or be lost to contact or withdrawn prior to the randomization. The enrollment will be concluded when study outcomes meet the early stopping criteria or when 500 subjects have been randomized in the Main Study.

11.4 Analysis Populations

The study contains two treatment arms with subjects receiving either nMARQ or TC ablation. The following analysis populations will be used to complete the analyses prespecified in this study:

Intent-to-treat population (ITT): The ITT subject population will include all randomized patients who have the ablation catheter inserted. They will be analyzed as randomized. Lost-to-follow-up and withdrawn / early termination subjects post randomization are included in the ITT population. Calibration Roll-in cases will not be included.

As-treated population (AT): The AT subject population will include all randomized patients who have the ablation catheter inserted. They will be categorized by the treatment received if this deviates from the treatment randomized. Calibration Roll-in cases will not be included.

Per Protocol Population (PP): The PP subject population will include randomized subjects who satisfy the following criteria. Calibration Roll-in subjects will not be included.

- have undergone RF ablation,
- are treated with the study catheters as randomized (nMARQ or TC),
- are in compliance (no major protocol deviations) with the study protocol, and
- have been treated for the study-related arrhythmia.

SNA Population (SNAP): The SNAP will include all subjects who are enrolled and randomized within the Main Study and who further satisfy specific inclusion and exclusion criteria and provide additional consent to participate in the SNA. Eligible SNA subjects will have undergone RF delivery with the study ablation catheters and will have successfully completed pre- and post-ablation brain MRI examinations, NIHSS Questionnaires, and general neurological

assessments.

Safety Population (SP): The SP will include all subjects who have undergone insertion of an ablation catheter. The subjects will be analyzed according to the treatment they actually received regardless of the Group they are randomized to. The calibration roll-in cases will be included in the SP.

11.5 Statistical Analyses for the Primary Endpoints

Formal statistical hypothesis are formulated for the primary statistical analyses as described below. Inferential statistics for the primary safety and efficacy endpoints may be presented on the device label. The study will be declared successful if the claim of non-inferiority is met for both the primary safety and primary efficacy endpoints.

11.5.1 Primary Safety Endpoint

The primary safety analysis is on the 7-day early onset event rate (except for PV stenosis and atrio-esophageal fistula). The AT population is used as the analysis population.

In order to have consistent mathematical notations for both effectiveness and safety endpoints, event-free rate is used for the safety hypothesis and analyses. The probability of a subject being event-free (success) in the experimental arm is α_2 and in the control arm is α_1 . The hypothesis of non-inferiority is

$$\alpha_2 > \alpha_1 - \delta_s,$$

where the non-inferiority δ_s value of 0.08 is used.

The posterior distribution for the failure-free rate is determined using a non-informative prior distribution (Beta(1,1) priors independently for each arm).

The claim of non-inferiority will be accepted if the posterior probability of non-inferiority is larger than 0.9675. That is, if,

$$\Pr(\alpha_2 > \alpha_1 - \delta_s | \text{ Trial Results}) \geq 0.9675$$

11.5.2 Primary Effectiveness Endpoint

The primary effectiveness analysis is a non-inferiority test based on the 3 to 12 month failure-free rate. The ITT population is used as the analysis population based on the treatment group as randomized. Any missing data will be imputed using Bayesian multiple imputation as described in the 'Handling or Missing Data' section in this protocol.

The probability of a subject being failure-free (success) in the experimental arm is π_2 and in the control arm is π_1 . The hypothesis of non-inferiority is

$$\pi_2 > \pi_1 - \delta_E,$$

where the non-inferiority δ_E value of 0.15 is used.

The posterior distribution for the control failure-free rate calculated based on a non-informative prior distribution (Beta(1,1) priors independently for each arm).

The claim of non-inferiority will be accepted if the posterior probability of non-inferiority is larger than 0.980. That is, if,

$$\Pr(\pi_2 > \pi_1 - \delta_E | \text{Trial Results}) \geq 0.980$$

The critical values of 0.980 and 0.9675 for each of the two endpoints are used in order to control the experimentwise type I error for the trial given the adaptive design. The type I error of the design is controlled at the 0.05 one-sided level. The type I error control is demonstrated by the simulations in Appendix A.

The primary effectiveness analyses will also be performed in the AT and PP populations as sensitivity analyses.

If the primary effectiveness success rate is less than 40% for either the Test group or the Control group, then additional analyses will be conducted to examine the poor device performance as follows.

- 1) The subject demographic and baseline characteristics will be compared between the current study and the P030031/S011 study where the chronic effectiveness endpoint was 62.1% (64/103) with a 95% confidence interval of 50.7% to 72.7% using the exact binomial method; If there is major difference in some of the covariates predicting the primary effectiveness endpoint, then covariates adjusted analyses will be performed for the primary effectiveness endpoint in the current study.
- 2) Multivariate regression analyses will be performed to identify the characteristics predicting the low performance;
- 3) Subgroup analyses will be performed to examine the impact of the characteristics that drive the low performance (e.g. by site, operators, regions, age, gender, ablation parameters, LA size etc.)

11.5.3 Site Heterogeneity

Each site should not enroll more than 20% of the total enrollment to minimize the possibility that the study results could be highly influenced by a few sites. We will combine sites with less than five randomized subjects according to the geographic regions. Using this pre-determined criterion, sites with less than five randomized subjects within the same geographic region will be

combined such that the combined center(s) would have five or more randomized subjects and no more than 5 sites combined.

Although the primary endpoint analyses are based on a Bayesian framework, site heterogeneity will be investigated using a set of frequentist analyses. A Breslow-Day test will be conducted to examine the homogeneity across sites for the associations of the primary effectiveness and safety endpoints with treatment groups. A p-value less than 0.15 will be considered statistically significant for an assessment of homogeneity across the treatment sites. A non-significant result, or a significant result that is only quantitative in nature, will support pooling of sites for the primary analyses. If the sites are not poolable, the following additional sensitivity analyses will be performed:

1. GEE models with the primary endpoints as the outcome and a fixed effect for treatment and a random effect for site will be used to estimate the treatment effect adjusting for site.
2. Logistic regression models with the primary endpoints as the outcome and fixed effects for treatment and site will be used to estimate the treatment effect adjusting for site.

If the sites are determined not to be poolable, then the overall treatment effect and its confidence interval will be estimated from the model in which sites are treated as random effects for the primary safety and effectiveness analysis. The claim of trial success will be based upon the totality of the data. The sensitivity analyses treating sites as random effects examine the impact of site heterogeneity on the primary endpoints.

11.5.4 Handling of Missing Data

The primary effectiveness analysis will use the ITT population and as such there is potential for subjects to have missing data. Any missing data in this analysis will be imputed using Bayesian multiple imputation method. This approach will enable the primary effectiveness analysis to be done on the full ITT population. The subjects who discontinued the study due to device related reasons will be treated as primary effectiveness failures in the ITT population.

In the adaptive design interim analyses and at the trial completion, the following longitudinal model is used to handle incomplete and missing data. The posterior distribution of the effectiveness success rate is updated using multiply imputed data from each subject with incomplete data⁷¹. The model is a piecewise exponential model, with different parameters for each treatment arm. The following model is used for the time-to-failure during the effectiveness observation phase (13-52 weeks after procedure).

The time-to-failure in treatment arm t is assumed piecewise exponential with three distinct intervals (from (0,2], (2,8], and (8,39] weeks). The probability of a failure during each interval is exponentially distributed, with a different hazard rate. The model is:

$$f(t) = \exp(-th(t)),$$

where

$$h(t) = \begin{cases} \gamma_{a,1} & 0 < t \leq 2 \\ \gamma_{a,2} & 2 < t \leq 8 \\ \gamma_{a,3} & 8 < t \leq 39 \end{cases} .$$

The exponential parameter in each interval is a function of the interval and the treatment arm (a=1 is control; a=2 is experimental). The prior distribution for each exponential parameter is based on the data from the THERMOCOOL[®] Pivotal trial, on the THERMOCOOL[®] arm. The following priors, down weighted by a factor of 5 (meaning the data from each subject in the historical study is weighed as 1/5 of a subject). This downweighting is used to insure the prospective trial data for each arm is weighed more heavily. The independent priors are (in the scale of weeks)

$$[\gamma_{a,1}] \sim \text{Gamma}(26/5, 160.8/5)$$

$$[\gamma_{a,2}] \sim \text{Gamma}(3/5, 416.8/5),$$

and

$$[\gamma_{a,3}] \sim \text{Gamma}(7/5, 1652.4/5).$$

In each piece of the exponential function, the prior distribution is updated using the observed number of events and total exposure time from the data. The predictive distribution of each subject, and each prospective new subject, is calculated using this longitudinal modeling. From the gamma posterior distribution, 10,000 hazard rates were sampled. Based upon the 10,000 triplets of hazard rates for all of the three pieces, the probability of effectiveness success and event-free rate at 12 month follow-up time will be calculated. No baseline covariates were used in the imputation model.

As a sensitivity analysis at each interim analysis, including the early success analysis, the results for an 11-piece exponential model will be presented. This model is very flexible, and will provide robustness to the 3-piece model assumptions and the prior distributions used. The 11-piece exponential is:

The time-to-failure in treatment arm t is assumed piecewise exponential with eleven distinct intervals. The probability of a failure during each interval is exponentially distributed, with a different hazard rate per interval. The model is:

$$f(t) = \exp(-th(t)),$$

where

$$h(t) = \begin{cases} \gamma_{a,1} & 0 < t \leq 2 \\ \gamma_{a,2} & 2 < t \leq 4 \\ \gamma_{a,3} & 4 < t \leq 8 \\ \gamma_{a,4} & 8 < t \leq 12 \\ \gamma_{a,5} & 12 < t \leq 16 \\ \gamma_{a,6} & 16 < t \leq 20 \\ \gamma_{a,7} & 20 < t \leq 24 \\ \gamma_{a,8} & 24 < t \leq 28 \\ \gamma_{a,9} & 28 < t \leq 32 \\ \gamma_{a,10} & 32 < t \leq 36 \\ \gamma_{a,11} & 36 < t \leq 39 \end{cases} .$$

The exponential parameter in each interval is a function of the interval and the treatment arm (a=1 is control; a=2 is experimental). The prior distribution for each exponential parameter is assumed to be very weak. The independent priors are (in the scale of weeks)

$$[\gamma_{a,j}] \sim \text{Gamma}(0.001, 0.001) \quad \text{for } a=1,2; j=1,\dots,11.$$

For the safety outcome there is no interim information available on subjects and so there is no longitudinal aspect for safety. In order to multiply impute final data for the adverse event rate we simulate the probability of a successful (no primary adverse event) using independent Beta(1,1) distributions.

Additional frequentist sensitivity analyses will be used to test the robustness of the primary effectiveness results with regards to missing data. They include but not limited to the following:

1. Kaplan-Meier analysis: this analysis will include all subjects in the ITT population and missing data will be censored at their last observations. The analyses will be stratified by the two treatment groups as randomized. Non-inferiority testing will be performed using the survival probabilities of the two treatment groups at 12 months follow-up.
2. The success rate at 6, 9 and 12-month will be presented for subjects in the ITT population treating the endpoint as a binary variable. The subjects who discontinued the study due to device related reasons will be treated as primary effectiveness failures in the ITT population. Other subjects with missing effectiveness outcomes will be excluded from the analyses. The point estimate for each treatment arm and the one-sided 95% confidence interval around the point estimate will be presented. The point estimate around the treatment difference (nMARQ-TC) and the one-sided 95% confidence interval around the difference will also be presented.

3. Tipping-point analysis: to examine the sensitivity of conclusions to missing data.

Tipping-point analysis will also be used as sensitivity analysis for the primary safety endpoint.

11.5.5 Additional Analyses for Primary Effectiveness and Safety Endpoints

Logistic regression analyses: Multivariate logistic regression analyses will be performed to examine the impact of potential demographic and baseline characteristics covariates (e.g., age, gender, ethnicity, LA size, AF duration, medical history, etc.) on the primary outcomes. The outcome variables (i.e., primary effectiveness and safety outcomes) will be the dependent variables and the covariates will be treated as independent variables with treatment group forced in the model. Model selection methods (e.g., forward selection, etc.) will be applied to identify the best set of predictors for the outcomes. Significant interaction effects between the covariates and treatment groups will also be examined. The identification of relevant predictors provides additional characterization and interpretation of the primary effectiveness and safety outcomes. These analyses will be performed in the PP population as treated.

Learning Curve Analyses: To further characterize if there is a learning curve for the nMARQ™ catheter system, subset analyses only including and excluding the first 3, 5, 7, etc. subjects randomized to nMARQ will be performed. Logistic regression analysis may be performed to examine the association of ablation experience with the predicted success rate.

AT Analysis of the Primary Effectiveness Endpoint: The primary effectiveness analyses will be repeated with the AT population. We acknowledge that no formal statistical hypothesis will be formulated for the secondary effectiveness analyses.

Per-Protocol Analysis of the Primary Endpoints: The primary effectiveness and safety analyses will be repeated with the PP population. We acknowledge that no formal statistical hypothesis will be formulated for the secondary effectiveness analyses.

Sensitivity Analyses of the Primary Effectiveness Endpoint: Any subjects with repeat ablations post-blanking period will be treated as primary effectiveness failures to test for the impact of the exemptions for extenuating circumstances preventing the hospital from scheduling a repeat ablation within the blanking period.

Subgroup Analyses: In order to examine the impact of potentially important confounders on the relationship between the treatment effect and the primary effectiveness and safety endpoints, the following subgroup analyses will be performed:

- Gender
- Catheter used, crescent or circular, in the nMARQ (Test) Group
- Generator used in the nMARQ (Test) Group
- Outperforming sites versus the remaining sites if the sites are determined to be not poolable
- Type of oral anticoagulant used
- Activation of Power Reduction Adjustment (PRA) algorithm (if used)

11.6 Adaptive Design Interim Analyses

11.6.1 Adaptive Sample Size

A Bayesian adaptive approach to sample size selection is used. A minimum total sample size of 250 and a maximum of 500 are considered. A sample size interim look is made when 250 subjects have been accrued. If trial success with the current 250 is highly likely accrual will be stopped for expected success and all subjects will be followed through their full follow-up and a final analysis done when all subjects have completed their primary follow-up at 12 months. If trial success at the maximum sample size of 500 is unlikely then the trial will stop for futility. If accrual continues, another sample size look is made every 50 subjects accrued, until accrual is stopped or the maximum randomized sample size of 500 is reached. Trial success is defined as meeting both the primary efficacy and safety thresholds for success.

11.6.2 Sample Size Interim Analyses

Interim looks are made before accrual is stopped. At these looks predictive probabilities of trial success (both efficacy and safety) for the current sample size and the maximum sample size are calculated. All interim results available are used to calculate the predictive probability of trial success for the currently accrued subjects. A longitudinal model (as described in Section 11.5.4) is used for the prediction of subjects with incomplete efficacy data. A decision is made whether to stop at the current sample size or to continue accrual. These sample size looks are made at sample sizes of 250 enrolled, and then every 50 subjects enrolled until accrual stops or the maximum sample size of 500 is reached. Let PP_n be the predictive probability of trial success for a trial with the current sample size of n and PP_{max} the predictive probability of trial success if the trial is carried out to the maximum sample size (500). The following rules are used to guide the sample size selection. These predictive probabilities are probabilities of winning on both the efficacy and safety endpoints.

If $PP_n > S_n$ then the sample size is considered sufficient for non-inferiority, and accrual stops. If $PP_{max} < 0.05$ then accrual is stopped for futility. The cut-offs for expected success are:

n	S_n
250, 300	0.95
300, 350, 400, 450	0.90

11.6.3 Early Success Claim Interim Analyses

An interim analysis will be conducted 16 weeks after enrollment ends for early success. If the predictive probability of final success is greater than 99%, then trial success will be declared early. All subjects will have complete safety data and all subjects will be followed through their trial completion.

Trial simulations are carried out in order to evaluate the performance (operating) characteristics of the trial. The simulations mimic the design exactly as described above. The same models are simulated as will be used in the design. The timing of the trial is also mimicked. The efficacy period is after a 12-week blanking period, and lasts 39 weeks. The safety endpoint is assumed known for all subjects in the trial (in practice there will be a handful that do not have complete safety data). Simulation details are attached in Appendix A.

11.7 Secondary Effectiveness Endpoints Analyses

11.7.1 Acute Effectiveness (PVI Confirmation)

Acute Effectiveness is defined as PVI documented by confirmation of entrance block (i.e., complete PVI [CPVI]). The number and percentage of subjects with CPVI will be presented for each treatment group and compared between the two groups using Fisher's exact test. Further analyses to characterize the CPVI will be included in the SAP.

11.7.2 One-Year Effectiveness

For the secondary effectiveness endpoint of freedom from AF/AFL/AT off antiarrhythmic drug therapy as assessed from the end of the 3-month blanking period to 12 month following the ablation procedure, the following analyses will be performed in the ITT population:

- The success rate at 6, 9 and 12-month will be presented for subjects in the ITT population treating the endpoint as a binary variable. The subjects who discontinued the study due to device related reasons will be treated as primary effectiveness failures in the ITT population. Other subjects with missing effectiveness outcomes will be excluded from the analyses. The point estimate for each treatment arm and the one-sided 95% confidence interval around the point estimate will be presented. The point estimate around the treatment difference (nMARQ-TC) and the one-sided 95% confidence interval around the difference will also be presented.
- Kaplan-Meier analysis: this analysis will include all subjects in the ITT population and missing data will be censored at their last observations. The analyses will be stratified by the two treatment groups as randomized. The confidence intervals around the difference in survival probabilities of the two groups (nMARQ-TC) at 12 months follow-up will be presented.

11.7.3 Long-Term Effectiveness

For the long-term effectiveness endpoint of freedom from AF/AFL/AT off antiarrhythmic drug therapy as assessed from the end of the 3-month blanking period to 2 and 3 year following the ablation procedure, the following analyses will be performed in the ITT population:

- The success rate at 2 and 3 year follow-up will be presented for subjects in the ITT population treating the endpoint as a binary variable. The subjects who discontinued the study due to device related reasons will be treated as primary effectiveness failures in the ITT population. Other subjects with missing effectiveness outcomes will be excluded from the analyses. The point estimate for each treatment arm and the one-sided 95% confidence interval around the point estimate will be presented. The point estimate around the treatment

difference (nMARQ-TC) and the one-sided 95% confidence interval around the difference will also be presented.

- Kaplan-Meier analysis: this analysis will include all subjects in the ITT population and missing data will be censored at their last observations. The analyses will be stratified by the two treatment groups as randomized. The confidence intervals around the difference in survival probabilities of the two groups (nMARQ-TC) at 2 and 3 year follow-up will be presented.

11.7.4 Secondary Effectiveness Endpoint Analyses

We acknowledge that no formal statistical hypotheses will be formulated for the secondary effectiveness endpoints. We will not present the inferential statistics for these endpoints in the final device labeling.

The secondary effectiveness endpoints analyses will be conducted in ITT population.

11.8 Secondary Safety Endpoints Analyses

The secondary safety analysis will be conducted based on the SP population. The Roll-in subjects will only be included in the secondary safety analyses and will be analyzed separately from subjects included in the Main Study.

11.8.1 Incidence of AEs and SAEs during 12 Month Follow-up

Serious AEs will be reported by three timeframes (ablation to ≤ 7 days, >7 to 30 days post ablation and >30 days). AEs and serious AEs will be evaluated by causality and severity and treatment groups using descriptive statistics.

11.8.2 PV Stenosis at 3 Months Post Ablation

Incidence of PV stenosis ($<50\%$, $50-70\%$, $\geq 70\%$ diameter reduction in diameter of pulmonary vein from baseline CT/MRA scan) will be reported as the rate of incidence for Test subjects undergoing an RF ablation procedure. This rate of incidence as well as the 95% confidence intervals will be presented descriptively for test group.

11.8.3 Incidence of AEs and SAEs during 2nd and 3rd Year Follow-up

The AEs and SAEs during the 2nd and 3rd year follow-up period will be summarized by AE categories, causality, severity and treatment groups using descriptive statistics.

11.9 Analyses for Additional Endpoints

Procedural Data

Procedural data such as procedure duration, fluoroscopy duration, power, fluid delivery, output and balance will be summarized with descriptive statistics in each treatment group. These analyses will be conducted in the ITT population.

- % PVI isolation with the study device(s) by subject and by PV

- Repeat Ablation Rate (For AF or Atrial Tachycardia)
- Cardiac Specific Hospitalization Rate
- Total Fluoroscopy Time
- Overall Procedure Time
- RF Ablation parameters per application (power, temperature, flow rate, duration, impedance rise/fall, mode of RF delivery (bipolar or unipolar))
- Device(s) utilized (per targeted PV)
- Duration of mapping time
- Duration of RF application time

SNA Endpoints (subset of patients)

Changes from baseline in NIH Stroke Score (4 point change in either direction constitutes significant change⁷²), MoCA, mRS, other neurological findings and MRI (lesion diameter and volume) during follow up will be summarized using descriptive statistics by treatment groups and also by type of oral anticoagulant used.

Incidences of abnormal neurological findings and cerebral microemboli pre- and post- ablation identified on MRI evaluations will be reported by treatment groups and also by type of oral anticoagulant used.

The lesion diameter and volume of each cerebral embolus will be summarized by treatment groups, type of anticoagulant used, and overall for each follow-up visit. The relationship between change in NIH Stroke Scale score from baseline, and ablation parameters (e.g. ACT, INR, procedural time, ablation time, fluid delivered via study catheter, maximum power and maximum temperature, bipolar and unipolar use, TC use for touch-up, etc.) and the incidence of ACE and lesion size post-ablation may also be examined if appropriate.

12.0 Administrative Responsibilities

12.1 Institutional Review Board (IRB; or Equivalent) Review

The investigator will obtain written and dated approval from the responsible IRB (or equivalent) for the study protocol (or amendment[s]) and informed consent before enrolling study subjects. Biosense Webster and the IRB (or equivalent) 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.

A stamped copy of the IRB (or equivalent) approval letter and Informed Consent Form addressed to the investigator must be submitted to Biosense Webster certifying study approval prior to subject enrollment. Investigators are responsible for submitting and obtaining initial and continuing review (per local requirements) of the study by their IRB (or equivalent).

The investigator may implement a deviation from the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval. If such deviation occurs, the implemented deviation and the reasons for it should be submitted to Biosense Webster, the IRB/IEC, and the regulatory authority(ies) (if applicable), as soon as possible.

12.2 Informed Consent

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

There are two Patient Informed Consent Forms (ICF); one for the Main Study and one for the SNA. Biosense Webster and the reviewing IRB (or equivalent) must approve any modifications to a Patient ICF prior to subject enrollment in the respective phase of the study. A Patient ICF may be translated as appropriate. A copy of an approved Patient ICF must be maintained by each investigator in a designated study administrative file.

The investigator or designated member of the research team will obtain written informed consent from the subject.

Prior to obtaining informed consent:

- The investigator or designee should provide information in both oral and written form in a language and at a level of complexity understandable to the patient
- The background of the proposed study and the potential benefits and risks of the study should be explained to the subject
- Patients or his/her legal representative must be given ample time and opportunity to inquire about details of the study and all questions about the study should be answered to the satisfaction of the patient or the representative

- The study ICF should be signed and personally dated by the patient, or his/her legal representative, and by the person who conducted the informed consent discussion (investigator or designee)
- The patient or legal representative must sign the ICF prior to undergoing study-specific exams or tests that fall outside of the standard of care.

Patients should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the study.

The original signed ICF must go in the patient file and a signed copy of the ICF must be given to each subject.

12.3 Subject Confidentiality

All information and data sent to Biosense Webster concerning subjects or their participation in this study will be considered confidential. Only authorized Biosense Webster personnel or representatives, local government authorities, or the FDA acting in their official capacities will have access to these confidential files. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the subject.

12.4 Data Monitoring

Case Report Forms (CRFs)

Electronic CRFs will be used to collect all subject data during the study.

Data Reporting

The Investigator, or a designated individual, is responsible for recording all data from the trial on the eCRFs supplied by Biosense Webster. The Investigator or a delegated 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 eCRFs will be reviewed and monitored at the investigational site by Biosense Webster personnel or designee at regular intervals throughout the trial. 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.

Data Review

All eCRFs will be tracked at Biosense Webster. Missing or unclear data will be requested 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. Biosense Webster will be responsible for auditing the database and confirming the overall integrity of the data.

12.5 Labeling

The study device labels have been prepared and approved in accordance with all necessary regulations.

12.6 Management of Protocol Deviations

The Investigator will not deviate from the protocol without prior notification to and approval from Biosense Webster, Inc. except for isolated instances where minor changes are made that will not increase the subject's risk or affect the scientific integrity of the study. In medical emergencies, prior approval for protocol deviations will not be required, but Biosense Webster clinical operations personnel must be notified within 5 days of the deviation.

13.0 Study Management

13.1 Study Timelines

Study Duration: The study is expected to last 7.5 years including the enrollment phase. The enrollment phase is expected to take 4.5 years from the enrollment of the first subject, including the time in which enrollment was suspended. The primary safety and effectiveness study endpoint assessments will be completed after 12 months follow up and this data is intended to be submitted in support of the PMA.

13.2 Study Advisory Committee (SAC)

A Study Advisory Committee will be assigned to this study. The responsibilities of the SAC include:

- Consultation on study design, protocol development, and investigator training
- Ensure investigators' compliance with the protocol
- Emergent Issues:
 - Advising the Sponsor of any unforeseen medical issues identified during the clinical study
 - Addressing patient medical concerns or conditions raised by investigators as related to the use of the investigational device or ablation procedure
- Review of evidence results (assist in data interpretation)
- Publication Committee (strategy and consultation)
- Supporting the Sponsor's efforts in conducting meetings with the regulatory agencies, as appropriate.

13.3 Interim Monitoring Committee

Biosense Webster has implemented an Interim Monitoring Committee (IMC) for this study. The IMC is an independent expert advisory group commissioned to evaluate and suggest modifications to the adaptive design analysis plan for the study while eliminating operational bias of the Sponsor. The IMC and a separate unblinded programming team will have access to aggregated, unblinded study information. The IMC is responsible for conducting the interim Bayesian analyses, verifying that the algorithms are performing correctly, ensuring that the trial adaptations are being conducted as planned, and making recommendations to the senior management of the Sponsor, who are blinded to the study data as specified in the IMC charter. In order to preserve the blind and integrity of the data, teams of blinded and unblinded personnel have been formed for the study and their roles and responsibilities are defined in a Biosense Webster internal procedure document. This document outlines the procedures for the creation of the raw dataset, the protection of unblinded data and data analyses, the review and QC of data and analyses, and the dissemination of unblinded data and analyses for IMC Meetings. The IMC is not responsible for the adjudication and review of adverse events, that remains the role of the Global Safety Monitoring Committee.

The IMC members will be independent of the Sponsor and will consist of two statisticians, at least one of whom had Bayesian adaptive trial expertise, and one medical doctor (not participating in the study execution).

The IMC Charter for the reMARQable study provides details on the committee members and procedural workflow.

13.4 Investigator Responsibilities

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

- Compliance with the study protocol
- Providing the Sponsor with signed, dated Investigator Agreement
- Maintaining an accurate and current Delegation of Responsibility log which identifies all individuals authorized to perform work for the study and assuring compliance by all site personnel with the provisions of the protocol
- Completing the appropriate training on the device and the study protocol prior to enrolling and treating subjects
- Maintaining accurate and current logs for the study such as: Screening Log
 - Subject log, Device Accountability Log
- Obtain initial IRB (or equivalent) approval and annual review/approval thereafter for the study protocol and informed consent
- Supply the Sponsor with a current curriculum vitae and Financial Disclosure for each Investigator and research staff member
- Supply the Sponsor with a current medical license for each study investigator
- Obtain informed consent form and enroll patients
- Perform medical procedures
- Order all tests required by the study protocol
- Follow subjects until the end of the study protocol
- Accurately complete and sign eCRFs in a timely manner
- Maintaining 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 all relevant study-related information with delegated study staff
- Inform the appropriate entities (e.g., Sponsor, IRB) in a timely manner regarding the occurrence of any AEs and/or product malfunctions.
- Making sufficient effort to maintain contact with all treated subjects who fail to comply with the follow-up requirements
- Maintaining study records per applicable regulations
- Preparing periodic IRB updates and final report, as required

13.5 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
- Select members for the Global Safety Monitoring Committee (GSMC)
- Obtain signed study contracts from investigators/hospitals, CROs and other involved parties
- Ship investigational 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 (e.g. FDA)
- Prepare and distribute (e.g., FDA, Investigator) reports summarizing status of the study no less than annually
- Update Report of Priors, IFU, and Risk Analyses
- Update investigators on safety issues, if needed
- Prepare and submit final submissions to applicable regulatory agencies
- Report to study investigators and regulatory agencies, as required
- Have AEs reviewed by the GSMC, as required
- Report atrio-esophageal fistulas (regardless of outcome) and deaths associated with atrio-esophageal fistulas to the FDA within 10 days of awareness.

13.6 Training

Clinical site personnel training will be the responsibility of the Sponsor. Prior to commencement of the study, appropriate protocol and device training will be provided to each site that participates in the study. Investigators selected to participate in the study will have prior experience with the NAVISTAR[®] THERMOCOOL[®] catheters and CARTO[™]3 system and will undergo device training in accordance with the documented study training plan which will include pre-clinical bench data, human clinical study data, didactics, and biophysics. The research sites will be able to order investigational product only after a participating study physician has completed the required BWI training.

To ensure uniform data collection and protocol compliance, the Sponsor will conduct a training session that will include reviewing the protocol, eCRF and data collection process, randomization process and adverse event reporting process.

13.7 Sponsor Contact Information

Kendra McInnis
Associate Director, Clinical Research Biosense Webster, Inc.
3333 Diamond Canyon Road
Diamond Bar, CA 91765
909-839-7284

13.8 Investigator Selection

In order to mitigate the effect of the learning curve, sites experienced with using the CARTO™ 3 System or CARTO™ XP System and THERMOCOOL® family of catheters will be selected for the study.

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 Investigational Plan.

13.9 Initiation of the Investigation

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 Investigational Plan. Each site that participates in the study will be provided with the appropriate training prior to commencement of the study.

13.10 Data Reporting and Monitoring

The Investigator, or a designated individual, is responsible for recording all data from the trial on the eCRFs supplied by Biosense Webster. The Investigator or a delegated individual is required to electronically sign the eCRF on the appropriate pages to verify that s/he has reviewed and attests to the correctness of the recorded data. The Investigator and institution must permit inspection of the trial files and subject eCRFs by such representatives and/or responsible government agencies.

Biosense Webster personnel or designee will review and monitor completed eCRFs at regular intervals throughout the trial. 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
- Confirmation that randomization procedures are being followed
- 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 Regulatory Binder
- 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.

Missing or unclear data will be requested 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.

13.11 Termination of the Study

At the termination of the investigation, each site will undergo a monitoring visit to conclude any outstanding issues, resolve all data discrepancies and make sure any outstanding eCRFs are submitted, reconcile disposition of all investigational devices, discuss requirements for the final report with the Investigator, and discuss any other items relevant to the conclusion of the study. This termination visit will be documented by a written report.

Any incidence of unanticipated serious adverse device effect may result in early termination or suspension of the clinical study. All enrolled subjects will continue to be followed per the study protocol requirements.

13.12 Device Accountability

All Investigational Study Devices will be labeled as “**Investigational Device**” and are only to be used for subjects enrolled in this clinical study within the US. In regions where the nMARQ system is approved, equivalent, commercially-marketed devices will be used.

The Sponsor will keep records of all investigational devices shipped to 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 that each device was used in the study and disposition information regarding disposal or return to the Sponsor.

The Device Accountability Log shall record the following information:

- Date of receipt
- Person who received the devices
- Quantity received
- Catalog number for catheters
- Serial/lot numbers
- Date device was used (if applicable)
- Subject ID on whom device was used (if applicable)
- Date of investigational device return

13.13 Device Returns

All Study Catheters will be labeled as “**Investigational device**” and are only to be used for subjects enrolled in this clinical study.

All shipped Study 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 case report form (eCRF). All returned devices must be properly decontaminated per hospital policy and properly labeled with the following:

- Subject identification number
- Date of event
- Return type (defective, non-defective, or adverse event)

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: Analysis Lab 103
Biosense Webster, Inc.
15715 Arrow Highway
Irwindale, CA 91706
USA

13.14 Annual Requirements

- Annual, or as required by local site and/or country requirements, reports to the IRB/EC from the Principal Investigator
- Annual, or as required by local site and/or country requirements, review and approval from the IRB/EC

13.15 Electronic CRFs

Electronic Case Report Forms (eCRFs) have been developed to capture the information outlined in this protocol. Data from these eCRFs will be used for the analysis of study outcomes.

Passwords will be issued to appropriate personnel to allow only certain levels of access to the computer system insuring confidentiality and protection of study data. For example, only the data entry personnel or the Data Manager may enter and/or verify data. All other personnel may only read the data on-screen or print out subject listings.

13.16 Source Documentation

Data entered on to the eCRFs will be taken from source documentation, such as hospital procedure reports, admission and discharge summaries, and other hospital or investigator office/clinic documents. 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 the 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 must be

printed and added to the subject's paper file. A print-out of an eCRF cannot be used as source documentation.

Regulations require that investigators 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 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.

13.17 Subject Confidentiality/Record

Representatives of the Sponsor have undergone training for HIPAA regulations and appropriate conduct for compliance with HIPAA. For the duration of this study, all representatives of the Sponsor will comply with all HIPAA regulations regarding contact with subjects, their medical record information, copying of information, protection of the subject identities, and all other aspects of HIPAA. Authorization for access to Protected Health Information by Sponsor personnel should be obtained as part of subject informed consent.

Where applicable, local subject confidentiality and data protection requirements will be followed.

13.18 Records

Records to be maintained by the investigator include:

- Study protocol/Investigational Plan and all amendments
- Signed clinical study agreement
- IRB/EC approval letter, including approved ICF document
- IRB/EC membership list
- Correspondence relating to the study
- CVs and medical licenses (as applicable) for all investigator(s)
- Financial Disclosures
- Delegation of Responsibility log

- Clinical Monitor/Site Visit sign-in log
- Subject enrollment log
- Device accountability log
- Training logs/certificates
- Lab certification and lab test normal ranges (pregnancy test)
- Reports (e.g., annual reports, final reports from investigator and Sponsor)

The following records must be maintained for each subject enrolled in the study:

- Signed Patient ICF
- All completed CRFs and supporting source documentation
- Supporting documentation of any AEs and/or death

13.19 Record Retention and Archiving

After the completion/termination of this study, records and reports will remain on file per the FDA requirement (for a minimum of two (2) years) or local regulations, whichever is more stringent. After the completion or termination of this study, records and reports may be discarded upon notification by Biosense Webster to the study site. The principal investigator must contact Biosense Webster prior to destruction of any study-related records or reports to ensure adherence to appropriate record retention process.

If the principal investigator plans to leave the study site, Biosense Webster should be contacted immediately so that arrangements can be made for transfer of records and management of any active study subjects.

13.20 Reports

Investigators are required to prepare and submit accurate and timely reports on this study to the governing IRB/EC and Biosense Webster. Serious AEs, UADEs, and AEs are to be reported to IRBs/ECs per individual IRB/EC requirements (UADEs no later than 10 business days).

Table 13.20A: Responsibilities for Preparing and Submitting Reports

Type of Report	Prepared by Investigator For	Time of Notification
Case Report Forms, eCRFs	Biosense Webster	In a timely manner
Subject death	Biosense Webster, IRB/EC	Immediately upon awareness
Subject withdrawal	Biosense Webster	Within 5 working days
Withdrawal of Institutional Review Board approval	Biosense Webster	Within 5 working days

Annual progress report	Biosense Webster, IRB/EC	Submitted annually within 60 days of the IRB annual review date.
Informed consent not obtained from subject	Biosense Webster, IRB/EC	Within 5 working days
Deviation to protect the life or physical well-being of subject in an emergency	Biosense Webster, IRB/EC	Within 5 working days

13.21 Investigator’s Annual and Final Report

Annually (or as required by local site and/or country requirements) and upon completion or termination of the Biosense Webster study, the principal investigator must submit a written report to Biosense Webster and the Investigational Review Board/Ethics Committee. The final report should be submitted within 3 months of completion or termination of the trial.

The investigator’s annual and final report may include:

- IDE number
- Device name
- Indications for use
- Brief summary of study progress in relation to investigational plan
- Number of subjects enrolled
- Number of devices received, used, and, in the final report, the final disposition of unused devices
- Brief summary of results and, in the final report, conclusions
- Summary of anticipated and unanticipated adverse device effects
- Description of any deviations from investigational plan
- Reprints of any articles published by the investigator in relation to the study

13.22 Publication Policy

Publication of study results will be coordinated between Biosense Webster, Inc. and the study author(s). Authorship will be determined prior to development of any manuscript.

13.23 Data Management

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

14.0 Regulatory / Ethical Considerations

14.1 Role of Sponsor

As the study Sponsor of this clinical 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. In this study, Biosense Webster has certain direct responsibilities. Biosense Webster will ensure adherence to the regulations as outlined in the 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.

14.2 General Duties (21 CFR 812. 40)

Sponsor's general duties consist of:

- Submitting the IDE application to FDA, obtaining FDA and IRB approvals prior to shipping the devices, selecting investigators, ensuring proper clinical site monitoring and ensuring subject informed consent is obtained.
- Where applicable, submitting or supporting submission of the application to the local regulatory authorities, and obtaining EC and regulatory body approval(s).

Sponsor is responsible for providing quality data that satisfy federal regulations and informing proper authorities of serious unanticipated adverse events and deviations from the protocol. The Sponsor will prepare written progress reports, a final report and coordinate with the core laboratories.

14.3 Selection of Investigators (21 CFR 812. 43)

Sponsor 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.

14.4 Supplemental Applications (21 CFR 812. 335 [A] and [B])

As appropriate, Biosense Webster will submit changes in the Investigational Plan to the investigators to obtain IRB/EC re-approval.

14.5 Maintaining Records (21 CFR 812. 140 [B])

Biosense Webster will maintain copies of correspondence, data, shipment of devices, adverse device effects and other records related to the clinical trial. Biosense Webster will maintain records related to the signed Investigator Agreements.

14.6 Submitting Reports (21 CFR 812. 150 [B])

Biosense Webster will submit any required regulatory reports identified in this section of the regulation. This includes unanticipated adverse device effects, withdrawal of IRB or FDA approval, current investigators list, annual progress reports, recall information, final reports and protocol deviations.

Investigational sites will contact Biosense Webster immediately upon awareness of any unanticipated adverse device effects, and within 5 days of withdrawal of IRB or protocol violations. Biosense Webster will also prepare an annual progress report and a final report for the study.

This clinical study will be conducted under applicable regulatory requirements and good clinical practice (GCP) guidelines including but not limited to:

- ISO 14155: 2011 (Clinical Investigation of Medical Devices for Human Subjects)
- Declaration of Helsinki
- ICH E6 Good Clinical Practice
- Medical Device Directive 93/42/EC
- 21 CFR 812 (Investigational Device Exemptions)
- 21 CFR 803 (Medical Device Reporting)

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