



**Prospective Review of the Safety and Effectiveness of the
THERMOCOOL SMARTTOUCH[®] SF Catheter Evaluated
for Treating Symptomatic Persistent AF
(PRECEPT)**

Clinical Study Protocol

Protocol# STSF-159

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Table of Contents

1.0	Introduction.....	10
1.1	Background	10
1.2	Rationale.....	12
1.3	Risk Analysis.....	13
1.3.1	Description and Analysis of Risks.....	13
1.3.2	Minimization of Risks.....	14
1.3.3	Precautions.....	15
1.4	Device Description.....	16
1.4.1	Bi-directional Catheter Description (D-1348-XX-SI)	17
1.4.2	Uni-directional Catheter Description (D-1347-XX-SI).....	17
1.5	Study Catheters	17
1.6	Supply and Support of Study Catheter.....	18
2.0	Study Objective.....	18
3.0	Study Design.....	18
3.1	Subject Selection.....	19
3.1.1	Inclusion Criteria	19
3.1.2	Exclusion Criteria	19
3.2	Subject Disposition	21
3.3	Subject Withdrawal/Early Termination	21
3.4	Subjects Lost to Follow up.....	21
4.0	Study Endpoints.....	22
4.1	Primary Endpoints.....	22
4.1.1	Primary Effectiveness Endpoint	22
4.1.2	Primary Safety Endpoint.....	23
4.2	Secondary Endpoints.....	24
4.2.1	Secondary Effectiveness Endpoints.....	24
4.2.2	Secondary Safety Endpoints	24
4.3	Additional Endpoints.....	25
4.4	Health Economic Data	26
5.0	Treatment Description	26
5.1	Patient Screening.....	27
5.2	Informed Consent.....	27
5.3	Pre-Procedure Assessments.....	28
5.4	General AF Procedure Guidelines.....	28

5.5	Recommended RF Power: ^{14-17, 76-81}	29
5.6	Contact Force (CF) Settings	30
5.7	VISITAG® Settings	30
5.8	Esophageal Monitoring	31
5.9	Ablation Procedure	31
5.10	Post Ablation	32
5.11	Post Procedure Assessments	33
5.12	Standard Tests and Procedures	36
5.13	Study Medications	38
5.13.1	Anticoagulation Medications	38
5.14	Antiarrhythmic Drug (AAD) Management	38
5.14.1	Definitions	38
5.14.2	AAD Usage and Primary Effectiveness Classification	39
5.15	Heart Rhythm Monitoring	40
5.16	Neurological Assessment (NIHSS)	41
5.17	Study Equipment	41
5.17.1	Required Study Catheters and Equipment	41
5.17.2	Recommendation for Irrigation Pump Setting and RF Power Delivery	41
5.17.3	Investigator Training	42
5.18	Repeat AF Ablation Procedures	42
5.18.1	Repeat Ablation and Primary Effectiveness Classification	42
5.19	Core Laboratory	43
6.0	Adverse Events	43
6.1	Adverse Event Recording	43
6.2	Classification	44
6.2.1	Primary Adverse Event	44
6.3	Serious AEs	48
6.4	Non-Serious AEs	48
6.5	Anticipated AEs	48
6.6	Unanticipated Serious Adverse Device Effect	52
6.7	Clinical Investigation Device Failure/Malfunction/Deficiency	53
6.8	Reporting Requirements	53
6.9	Intensity or Severity	53
6.10	Outcome	54
6.11	Causality	54

6.12	Documentation.....	54
6.13	Global Safety Monitoring Committee (GSMC).....	55
7.0	Statistical Analysis Methods.....	55
7.1	Analysis Population.....	55
7.2	Analyses for Primary Endpoints	55
7.2.1	Analyses for Primary Effectiveness Endpoint	55
7.2.2	Analyses for Primary Safety Endpoint	56
7.3	Site Heterogeneity	56
7.4	Primary Effectiveness Endpoint.....	57
7.5	Primary Safety Endpoint	57
7.6	Total Sample Size.....	57
7.7	Analyses for Secondary and Additional Endpoints.....	57
8.0	Administrative Responsibilities	57
8.1	Ethics Review.....	57
8.2	Patient Informed Consent.....	58
8.3	Confidentiality.....	58
8.4	Data Management	58
8.4.1	Case Report Forms (CRFs).....	58
8.4.2	Data Reporting.....	58
8.4.3	Data Review	58
8.5	Records and Reports.....	59
8.5.1	Records	59
8.5.2	Record Retention	59
8.5.3	Procedural Data.....	60
8.5.4	Investigator’s Final Report	60
8.6	Labeling.....	60
8.7	Deviations from Protocol and Good Clinical Practice	60
9.0	Study Management	60
9.1	Study Timelines.....	60
9.2	Study Advisory Committee (SAC)	60
9.3	Investigator Responsibilities	61
9.4	Sponsor Responsibilities	62
9.5	Training	63
9.5.1	Research Team.....	63
9.5.2	Investigator Proctoring.....	63

9.6 Sponsor Contact Information 64

9.7 Initiation of the Investigation 64

9.8 Monitoring the Study 64

9.9 Termination of the Study..... 64

9.10 Device Accountability 65

 9.10.1 Device Accountability..... 65

9.11 Device Returns 65

9.12 Electronic Case Report Forms 66

9.13 Source Documentation 66

9.14 Subject Confidentiality/Record 66

9.15 Data Management..... 66

10.0 References..... 67

11.0 APPENDIX A: STUDY DEFINITIONS..... 75

Protocol Agreement Form

Study Title: Prospective Review of the Safety and Effectiveness of the THERMOCOOL SMARTTOUCH[®] SF Catheter Evaluated for Treating Symptomatic PersistenT AF (PRECEPT)

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.

Principal Investigator
Name (PRINT)

Signature

Date

Protocol Summary

Prospective Revue of the Safety and Effectiveness of the THERMOCOOL SMARTTOUCH[®] SF Catheter Evaluated for Treating Symptomatic Persistent AF (PRECEPT)

- Title:** Prospective Revue of the Safety and Effectiveness of the THERMOCOOL SMARTTOUCH[®] SF Catheter Evaluated for Treating Symptomatic Persistent AF (PRECEPT)
- Design:** This is a prospective, multicenter, non-randomized clinical evaluation utilizing the THERMOCOOL SMARTTOUCH[®] SF catheter compared to a predetermined performance goal.
- Purpose:** The purpose of this study is to demonstrate the safety and effectiveness of the THERMOCOOL SMARTTOUCH[®] SF catheter in the treatment of drug refractory symptomatic persistent atrial fibrillation (PsAF) following standard electrophysiology mapping and RF ablation procedures.
- Enrollment:** Up to 367 subjects will be enrolled.
- Clinical Sites:** Up to 35 sites (approximately 30 in the US and up to 5 OUS).
- Subject Population:** Subjects with drug refractory symptomatic PsAF who are undergoing their first AF ablation procedure that meet the ACC/ESC/HRS criteria for persistent AF are eligible.
- Primary Endpoints:** The primary effectiveness endpoint for this study will be freedom from documented atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL) episodes through 15-month follow-up (post 3-Month Medication Adjustment Period followed by a 3-Month Therapy Consolidation period (Day 181-450)).
- The primary safety endpoint is the incidence of any early onset (within 7 days of the initial and repeat AF ablation procedure) Primary Adverse Events (AE), which are listed below:
- Death
 - Atrio-esophageal fistula*
 - Cardiac Tamponade**†/Perforation⁺
 - Myocardial infarction (MI)
 - Stroke / Cerebrovascular accident (CVA)^{†, ††}
 - Thromboembolism
 - Transient Ischemic Attack
 - Diaphragmatic paralysis
 - Pneumothorax
 - Heart block
 - PV stenosis*
 - Pulmonary edema (Respiratory Insufficiency)
 - Pericarditis
 - Major Vascular access complication / bleeding
- * Pulmonary vein (PV) stenosis and atrio-esophageal fistula that occurs greater than one week (7 days) post-procedure shall be deemed Primary AEs.
- ** Hemodynamic compromise or instability is defined as Systolic BP < 80 mm Hg.
- + Cardiac Tamponade/Perforation that occurs up to 30 days post ablation will be deemed Primary AEs.
- † Subjects with non-focal global encephalopathy will not be reported as a stroke without unequivocal evidence based upon neuroimaging studies.

†† Modified Rankin score assessments should be made by qualified individuals according to a certification process.
If there is discordance between the 30 and 90 day Modified Rankin scores, a final determination of major versus minor stroke will be adjudicated by the neurology members of the Global Safety Monitoring Committee.

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List of Abbreviations

AAD	Antiarrhythmic drug	ICF	Informed consent form
ACC	American College of Cardiology	IDE	Investigational device exemption
ACT	Activated clotting time	IEC	Independent Ethics Committee
AE	Adverse event	IFU	Instructions for use
AF	Atrial fibrillation	IRB	Institutional Review Board
AFEQT	Atrial Fibrillation Effect on QualiTy of life	ITT	Intent-to-treat
		HIPAA	Health Insurance Portability and Accountability Act
AFL	Atrial flutter		
AHA	American Heart Association	LA	Left atrium
ANOVA	Analysis of variance	MI	Myocardial infarction
AT	Atrial tachycardia	MRI	Magnetic resonance imaging
AV	Atrioventricular	MV	Mitral valve
BP	Blood pressure	NIHSS	NIH Stroke Scale
CCS-SAF	Canadian Cardiovascular Society Severity of Atrial Fibrillation scale	PCI	Pecutaneous coronary intervention
		PIU	Patient Interface Unit
CHF	Congestive heart failure	PP	Per protocol
CF	Contact force	PsAF	Persistent atrial fibrillation
CFAE	Complex fractionated atrial electrogram	PV	Pulmonary vein
		PVI	Pulmonary vein isolation
CHADS	<u>C</u> ongestive heart failure, <u>H</u> igh blood pressure, <u>A</u> ge 75+, <u>D</u> iabetes, previous <u>S</u> troke or transient ischemic attack	PRECEPT	<u>P</u> rospective <u>R</u> ewiew of the Safety and <u>E</u> ffectiveness of the SMARTTOUCH® SF <u>C</u> atheter <u>E</u> valuated for Treating Symptomatic <u>P</u> ersistent <u>A</u> F
CPVI	Complete pulmonary vein isolation		
CRF	Case Report Form	QOL	Quality of life
CS	Coronary sinus	RA	Right atrium
CT	Computed tomography	RF	Radiofrequency
CTI	Cavotricuspid isthmus	SAC	Study advisory committee
CVA	Cerebrovascular accident	SADE	Serious adverse device effect
ECAS	European Cardiac Arrhythmia Society	SAE	Serious adverse event
ESC	European Society of Cardiology	SAP	Statistical analysis plan
FDA	Food Drug Administration	SF	Surround Flow
GCP	Good Clinical Practice	SVC	Superior vena cava
ECG	Electrocardiogram	TIA	Transient ischemic attack
EHRA	European Heart Rhythm Association	TEE	Transesophageal echocardiogram
GSMC	Global Safety Monitoring Committee	TTE	Transthoracic echocardiogram
HRS	Heart Rhythm Society	TTM	Transtelephonic monitoring
ICD	Implantable cardioverter defibrillator	UADE	Unanticipated adverse device effect
ICE	Intracardiac echocardiography	USADE	Unanticipated serious adverse device effect
		VT	Ventricular tachycardia

Prospective Review of the Safety and Effectiveness of the THERMOCOOL SMARTTOUCH® SF Catheter Evaluated for Treating Symptomatic Persistent AF (PRECEPT)

1.0 INTRODUCTION

1.1 Background

Atrial fibrillation (AF) is the most common sustained arrhythmia in humans. It affects anywhere from 0.4% to 1% of the general population, and increases in prevalence with age, from < 1% in young adults to 8% in patients over 80 years of age.^{1,2} AF is a complex, progressive disease that results in structural and electrical remodeling in the heart. In 2006, a 3-category classification system was established to distinguish and standardize the different levels of AF:³

- Paroxysmal: 2 or more AF episodes that terminate spontaneously within 7 days;
- Persistent (PsAF): AF sustained beyond 7 days or lasting less than 7 days but necessitating termination by intervention; and
- Longstanding persistent: AF greater than one year's duration.

The 2012 HRS/EHRA/ECAS Consensus Statement on catheter and surgical ablation recommended that patients be categorized by their most frequent pattern of AF during the six months prior to ablation.⁴ The 2006 ACC/AHA/ESC AF Management guidelines include the recommendation that catheter ablation be considered in persistent AF patients who are severely symptomatic after failure of one or more AADs plus rate control.³

Radiofrequency (RF) catheter ablation has provided excellent results for treating many types of supraventricular arrhythmias.^{1,5} Its utility in treating paroxysmal AF has already been established; studies have shown high rates of elimination of the arrhythmia.^{6,7} In a randomized clinical trial comparing catheter ablation to AAD therapy, RF ablation with the NAVISTAR® THERMOCOOL® catheter was associated with elimination of symptomatic atrial arrhythmias in 70% of patients, and elimination of any atrial arrhythmia irrespective of symptoms in 63% of patients at 1 year.⁷ One of the goals of the present study is to extend these findings in the persistent AF population. The 2012 HRS/EHRA/ECAS Consensus Statement notes that there have been no prospective multicenter randomized clinical trials of ablation versus antiarrhythmic drug therapy that have precisely defined the outcomes of AF ablation in patients with persistent AF or longstanding persistent AF.⁴ However, some of the electrical atrial remodeling may be reversible by destroying the foci.⁸ Studies that included a persistent AF sample have shown some improvement with PV isolation, although the rates of clinical efficacy were found to be lower in subjects with persistent AF than in those with paroxysmal AF at five,⁹ ten,⁸ or twelve^{10,11} months post ablation. A recent meta-analysis corroborated these findings with even longer follow-up times after a single ablation procedure, although due to between-study heterogeneity, the difference between AF types did not reach significance.¹² Many of the non-paroxysmal subjects among the included studies required multiple procedures to achieve long-term rhythm control.¹²

The 2012 HRS/EHRA/ECAS Consensus Statement states that electrical isolation of the pulmonary veins (PVs) from the left atrium is “the cornerstone for most AF ablation procedures.”⁴ However, in patients with persistent AF, more extensive ablation, based on linear lesions or complex fractionated electrograms, should be considered.⁴ In such patients, inclusion of the atrial myocardium becomes more important, as atrial remodeling occurs, augmenting the number of AF drivers and shifting their locations away from the PV ostia⁴ so that the PVs become less important as AF progresses from paroxysmal to persistent.⁹ The current study will utilize a “PVI + Triggers” approach, where isolation of all PVs will be performed, followed by ablation of “non-PV triggers” and triggers induced by isoproterenol. Additional ablation sites will be allowed at the discretion of the investigator but will be limited to certain parameters. All linear lesions will require confirmation of block by mapping or pacing maneuvers and prophylactic ablation of empirical sites is not recommended.

[REDACTED]

Animal studies have demonstrated that, during RF application at high power, saline irrigation maintains a low electrode-tissue interface temperature resulting in deeper and larger lesions.¹³ However, the first catheters that were introduced did not provide the same irrigation flow for any orientation of the catheter, and required increasing volumes of saline to be delivered with increasing number of RF applications. [REDACTED]

[REDACTED]

There have been several studies showing that there is a correlation between electrode-tissue contact and RF lesion generation.¹⁸⁻²⁰ Until recently, there has been no reliable mechanism

to provide a measurement of the direct CF between the tip of the RF ablation catheter and the endocardial tissue. [REDACTED]

[REDACTED]

1.2 Rationale

The theoretical benefits of catheters with CF sensing technology include feedback to the user of adequate degree of tissue contact to prevent inappropriate RF power application. The data have shown when investigators stay within their pre-selected contact force range > 80% of the time the 12-month effectiveness success rate is consistently above 80%. Additional benefits of confirmed tissue contact may include efficient creation of 3-D anatomical maps with the CARTO® 3 Navigation System(s), and may translate to a reduction in mapping, fluoroscopy, and procedure times. Catheters with THERMOCOOL SMARTTOUCH® technology have been used safely in the paroxysmal AF population.^{23,24}

[REDACTED]

As noted, there are few controlled studies on the effectiveness of RF ablation specifically in the persistent AF population,⁴ but studies which included persistent AF patients in their study sample showed promising results for long-term freedom from AF recurrence in this subset.^{8-11,16} The results of the current study will be compared to a pre-determined performance goal of 40% for primary effectiveness, defined as freedom from atrial tachycardias through 12 months post procedure. This is in line with recommendations in the 2012 HRS/EHRA/ECAS Consensus Statement for success rate in persistent AF and longstanding persistent AF.⁴

In patients with AF, elimination or amelioration of symptoms is a major driving force for therapy. The primary clinical benefit of catheter ablation of AF is an improvement in quality of life resulting from the elimination of arrhythmia-related symptoms such as palpitations, fatigue, or effort intolerance.⁴ The 2012 HRS/EHRA/ECAS Consensus Statement underscores the value of AF-specific QOL assessment tools.⁴ The Canadian Cardiovascular Society Severity of Atrial Fibrillation (CCS-SAF) Scale was validated in

484 patients with documented AF (62% paroxysmal and 38% persistent/permanent).²⁷ As the CCS-SAF class increases from 0 to 4, symptom severity increases.

1.3 Risk Analysis

RF catheter ablation has been used for over 15 years, and the risks and complications are well understood. A summary of risks associated with catheter ablation, including analysis of and plans to minimize these risks is provided below:

1.3.1 Description and Analysis of Risks

Risks associated with catheter ablation

The risk of pulmonary adverse events (e.g. PV stenosis, thrombus and hypertension) associated with an AF ablation procedure targeting the pulmonary veins is considered small (<4%).^{8,9,28-32}

Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels can occur (risk <1%).^{33,34} These types of injuries may cause hemorrhage, hematoma or ischemic injury to an extremity or major organ.

Risks associated with RF application

RF current may cause occlusion of a coronary artery, either by direct thermal damage, spasm, or thrombosis. Experience at numerous centers suggests that the risk of coronary occlusion is less than 0.5%.^{33,34} Coronary arterial occlusion could produce myocardial infarction, angina or death.

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

A thrombus may form on the ablation electrode during the application of RF current, usually indicated by an impedance rise; however, thrombus may also occur in the absence of an impedance rise. Thrombus may become dislodged and embolize to produce a stroke, myocardial infarction, or other ischemic injuries. Risk of embolus is reduced by quickly terminating the application of current after an impedance rise, which limits the size of the coagulum on the electrode. An important feature of the THERMOCOOL® family of catheters is the absence or very low likelihood of thrombus formation during RF.

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 other anticoagulant therapy, at the discretion of the investigator.

Cardiac perforation may result from catheter manipulation or application of RF. Published risks of cardiac perforation range from <1% to 2.5%.^{33,34,56,57} This potentially life-threatening injury may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. In the SMART-AF study using the THERMOCOOL SMARTTOUCH® Catheter with contact force sensing technology, there were 4 (2.48%, 4/161) reported incidents of tamponade.⁵¹ Additionally, in the SMART-SF study using a new investigational catheter with contact force sensing technology the observed incidence

of tamponade was 1.3% (2/159). Significant hemodynamic compromise can result in neurologic injury or death. An increased risk of cardiac perforation during ablation may be associated with the use of saline-irrigated electrode catheter due to its ability to create a larger, deeper lesion. This risk is greatest in a thin walled chamber (i.e., right or left atria or right ventricle). However, the risk of perforation related to a deep steam pop is reduced if RF energy is not delivered perpendicular to the wall at power above 35 or 40 watts. If the lesion is deeper the risk of steam pop is higher above 35-40 watts.

Injury to a cardiac valve may result from catheter manipulation or the application of RF current (risk <1%).^{33,34} This may produce valvular insufficiency and possibly require surgical valve replacement.

The application of RF energy along the posterior left atrium can result in thermal injury to the esophagus and the formation of an atrio-esophageal fistula. This is a rare (0.04%) but severe complication of RF ablation requiring surgical intervention or that may result in permanent impairment.³⁵ Reducing power at sites in close proximity to and/or avoiding sites directly over the esophagus may reduce the risk of thermal injury.

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.^{36,37} Prior to ablation in the region of the right superior pulmonary vein, precautionary measures such as pacing maneuvers are recommended to evaluate proximity to the phrenic nerve.

Periesophageal vagal nerve injury or pyloric spasm after left atrial catheter ablation of AF can occur when RF energy is applied to the posterior wall of the LA.⁴ While these complications are rare (approximately < 1%), they can potentially compromise the clinical outcome severely, requiring surgical treatment.⁵⁴⁻⁵⁵ While there is no established method to prevent injury to the vagal nerves, the risk may be reduced by using the same techniques used to avoid an atrial esophageal fistula.⁴

Risks associated with the general procedure

Radiation exposure during the fluoroscopic imaging of the catheters may result in an increase in the lifetime risk of developing a fatal malignancy (0.1%) or a genetic defect in offspring (0.002%).³⁶⁻⁴⁰

A patient could develop an allergic reaction to the local anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure (risk <1%).⁴¹⁻⁴⁵

Hemorrhage could occur as a result of anticoagulation (risk <0.5%), which may require transfusion.^{33,34}

The percutaneous procedure carries risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%).^{33,34} This risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.

1.3.2 Minimization of Risks

The risks associated with performing RF catheter ablation using an ablation catheter with CF sensing technology, such as the THERMOCOOL SMARTTOUCH® SF catheter, are

similar to conventional irrigated catheters that do not include this technology. Similarly, the Surround Flow technology found in the THERMOCOOL SMARTTOUCH® SF catheter confers a decreased risk of volume overflow associated events such as CHF and pulmonary edema in patients with impaired LVEF for kidney dysfunction.^{14,17} Data have shown that both the SF and CF technology allow a decrease in overall procedure time in experienced users; this in turn decreases fluoroscopy exposure.¹⁵

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

Subjects will be screened prior to treatment in the study to ensure compliance with the inclusion and exclusion criteria. The exclusion criteria have been developed to exclude subjects with a medical history or condition that increases their risk of adverse events (refer to Section 3.1.2 Exclusion Criteria). All subjects will have pre-procedure imaging as described in Section 5.3 to exclude subject that may have LA thrombus, which is intended to decrease the potential for thromboembolic complications.

Investigators will undergo training (refer to Sections 5.17.3 and 9.5) on the use of the THERMOCOOL SMARTTOUCH® SF Catheter with Contact Force Sensing Capability technology prior to subject enrollment.

Investigators experienced in intracardiac mapping and ablation of AF with the use of RF ablation catheters containing contact force technology will be selected for participation in the study. AF ablation procedures will be performed in equipped electrophysiology laboratories with the assistance of nurses and technicians trained in electrophysiology and, as applicable, in the requirement of this protocol.

Should occlusion of a coronary artery occur for any reason, the physician will attempt to restore coronary blood flow through pharmacological, catheter and/or surgical intervention as medically indicated.

Additionally, adverse event data will be evaluated periodically during enrollment and follow-up by an unbiased physician review committee functioning as a Global Safety Monitoring Committee (GSMC) for this study.

1.3.3 Precautions

Invasive electrophysiological evaluation and catheter ablation may impart some degree of risk to the subject. The risk of serious complications is generally related to the severity of cardiac disease. The degree of risk of the electrophysiological and catheter ablation procedures versus the potential benefit of the treatment of a persistent or recurrent arrhythmia should be determined by a qualified physician. Cardiac catheterization and electrophysiological procedures should be performed by qualified and appropriately trained personnel in an electrophysiology laboratory. The laboratory should contain sufficient resuscitative equipment and facilities to manage most potential complications. Failure to observe the contraindications, warnings, and precautions in these instructions and the IFU may result in procedural complications. Immediate risks from ablation treatment may include: cardiovascular injury or perforation with or without cardiac tamponade, pulmonary embolus, tricuspid regurgitation, myocardial infarction, bleeding at the catheter insertion site, sepsis, and death.

Contraindications for catheter ablation of arrhythmia include: existing hemodynamic instability, bacteremia, coagulopathy, prosthetic tricuspid valve, intra-atrial or venous thrombosis, and pregnancy.

■ [REDACTED]

[REDACTED]

[REDACTED]

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1.5 Study Catheters

The THERMOCOOL SMARTTOUCH® SF Diagnostic /Ablation Deflectable Tip Catheters with Contact Force Sensing Capability (D-1347-XX-SI and D-1348-XX-SI) are the only study catheters to be used in this study.

For the remainder of this protocol, “study catheter” will refer to the THERMOCOOL SMARTTOUCH® SF Diagnostic/Ablation Deflectable Tip Catheters with Contact Force Sensing Capability.

Instructions for Use (IFU)

A copy of the IFU for the study catheters and interface cable is included in each product package.

1.6 Supply and Support of Study Catheter

Prior to initiating subject enrollment, Biosense Webster or a representative will provide training to the study site personnel. Investigators selected to participate in the study will have prior experience with the THERMOCOOL SMARTTOUCH® Catheters and received training on the use of the THERMOCOOL SMARTTOUCH® SF Catheter (see Section 5.17.1). The study sites will not be released investigational devices until after receiving IRB approval, signing the clinical study agreement, completing training (may be conducted in parallel with the Site Initiation Visit), and after all other required study start up activities are complete.

2.0 STUDY OBJECTIVE

The purpose of this study is to demonstrate the safety and effectiveness of the THERMOCOOL SMARTTOUCH® SF catheters in the treatment of drug refractory symptomatic persistent atrial fibrillation (PsAF) during standard electrophysiology mapping and RF ablation procedures.

3.0 STUDY DESIGN

The PRECEPT study is a prospective, multicenter, non-randomized clinical evaluation utilizing the THERMOCOOL SMARTTOUCH® SF catheters in treating subjects with symptomatic PsAF who have failed at least one antiarrhythmia drug. Up to 367 subjects will be enrolled at up to 35 sites (approximately 30 US and 5 OUS). Effectiveness and safety endpoints have been defined, and will be compared to predetermined performance goals. Subjects who sign the PRECEPT informed consent are considered enrolled in the study. Enrolled subjects who satisfy all eligibility criteria will then undergo the ablation procedure with the study catheter. After the study ablation procedure, subjects will enter a 3-Month Medication Adjustment Period followed by a 3-Month Therapy Consolidation Period (Day 0-180).

The first 3 months after the ablation procedure, (Medication Adjustment Period; Day 0-90) is intended to allow for modifications to the subject’s medication and allow substrate remodeling to occur. Medication adjustment includes dose modification of currently used AAD or adding new AAD. The following 3-month period (Therapy Consolidation Period; Day 91-180), is to assess the status of the Medication Adjustment Period and perform repeat ablations as necessary. Cardioversion is allowed if the AF recurrence persists during the Therapy Consolidation Period.

After the Therapy Consolidation Period, subjects will enter the Evaluation Period (Days 181-450). Subjects having AF recurrence and/or receiving therapeutic interventions during the evaluation period will be considered effectiveness failures (refer to Section 4.1.1 for all effectiveness failure modes).

All subjects will undergo follow up visits at defined intervals (refer to Table 5-1 Schedule of Treatments and Evaluations). Subjects complete the PRECEPT study after the 15-month follow up visit.

3.1 Subject Selection

3.1.1 Inclusion Criteria

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

1. Documented symptomatic persistent AF, which is defined as continuous AF sustains beyond 7 days and less than 1 year and is documented by the following:
 - a. Physician's note indicating continuous AF \geq 7 days but no more than 1 year;
AND
 - b. Two electrocardiograms (from any forms of rhythm monitoring) showing continuous AF, with electrocardiogram taken at least 7 days apart⁴ (electrograms cannot be >365 days prior to enrollment)
OR
 - c. 24-hour Holter within 90 days of the ablation procedure showing continuous AF
2. Failed at least one antiarrhythmic drug (AAD) (class I or III) as evidenced by recurrent symptomatic AF, or intolerable to the AAD.
3. Age 18 years or older.
4. Signed Patient Informed Consent Form (ICF).
5. Able and willing to comply with all pre-, post-, and follow-up testing and requirements.

3.1.2 Exclusion Criteria

Candidates for this study will be EXCLUDED from the study if ANY of the following conditions apply:

1. Continuous AF > 12 months (1-Year) (Longstanding Persistent AF)
2. Previous surgical or catheter ablation for atrial fibrillation
3. Any cardiac surgery within the past 2 months (60 days) (includes PCI)
4. CABG surgery within the past 6 months (180 days)
5. Valvular cardiac surgical/percutaneous procedure (i.e., ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve)
6. Any carotid stenting or endarterectomy
7. Documented LA thrombus on imaging
8. LA size > 50 mm (parasternal long axis view)
9. LVEF < 40%
10. Contraindication to anticoagulation (heparin or warfarin)
11. History of blood clotting or bleeding abnormalities
12. MI within the past 2 months (60 days)
13. Documented thromboembolic event (including TIA) within the past 12 months (365 days)
14. Rheumatic Heart Disease
15. Uncontrolled heart failure or NYHA function class III or IV
16. Severe mitral regurgitation (Regurgitant volume \geq 60 mL/beat, Regurgitant fraction \geq 50%, and/or Effective regurgitant orifice area \geq 0.40cm²)
17. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months (365 days)
18. Unstable angina
19. Acute illness or active systemic infection or sepsis
20. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
21. Diagnosed atrial myxoma.
22. Presence of implanted ICD/CRT-D.
23. 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.
24. Gastroesophageal Reflux Disease (GERD; active requiring significant intervention not including OTC medication)
25. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study.
26. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal)
27. Enrollment in an investigational study evaluating another device, biologic, or drug.
28. Presence of intramural thrombus, tumor or other abnormality that precludes vascular access, or manipulation of the catheter.
29. Presence of any other condition that precludes appropriate vascular access.
30. Life expectancy less than 12 months

3.2 Subject Disposition

- **Enrolled Subjects:** subjects who sign the informed consent.
- **Excluded Subjects:** subjects who are enrolled but never undergo insertion of the study catheter.
- **Discontinued Subjects:** subjects who have the investigational catheter inserted but do not undergo ablation (i.e., no RF energy is delivered via the study device). These discontinued subjects will be followed up for 30 days.
- **Lost to Follow-up Subjects:** subjects who are enrolled and have study catheter inserted, but contact is lost after most recent follow-up visit (despite 3 documented attempts).
- **Withdrawn / Early Termination Subjects:** subjects who withdraw consent for study participation or are withdrawn by the investigator or are terminated from the study prior to completion of all follow-up visits.
- **Completed Subjects:** enrolled subjects who completed the 15-month follow-up visit.

3.3 Subject Withdrawal/Early Termination

Subjects may withdraw from the clinical investigation at any time. The decision for the subject to withdraw informed consent must be made independently of influence by the investigator or site personnel. The subject's decision will be documented in the source and eCRF. The investigator may also choose to withdraw a subject from the study if there are safety concerns. If a subject withdraws from the study, the date and reason for withdrawal will be recorded on the appropriate electronic case report form (eCRF).

All data will be collected (as available) until the subject is withdrawn. 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.

3.4 Subjects Lost to Follow up

Subjects should be encouraged to return for protocol required, clinic visits for evaluation during the study follow-up period. If a subject is unable to return for an office or clinic visit or unable to be contacted by telephone, 3 separate telephone calls should be made to obtain subject related safety information. All attempts should be documented in the source documents. If the subject does not respond to the 3 telephone calls, then the investigator must send a certified letter requesting the subject's continuation in the study or confirming the subject's desire to terminate from the study.

If the subject does not respond to the phone telephone calls or letter, then the subject will be considered "lost to follow-up."

4.0 STUDY ENDPOINTS

4.1 Primary Endpoints

4.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is defined as the freedom from documented atrial fibrillation, atrial flutter and atrial tachycardia (AF/AFL/AT) (hereinafter collectively referred to as "atrial tachyarrhythmias") recurrence (episodes ≥ 30 secs on Holter recordings/TTM or continuously recorded on the standard 12-leads ECG) during the evaluation period (Day 181-450) and freedom from the following failure modes:

- Acute procedural failure, including:
 - Failure to confirm entrance block in all pulmonary veins post-procedure,
 - Use of a non-study catheter to treat the study arrhythmia for the initial ablation procedure.

Device deficiency of a non-investigational device leading to the use of a non-study catheter (i.e., Stockert 70, SMARTABLATE™ RF Generator and COOLFLOW® Pump, SMARTABLATE™ Irrigation Pump), during the AF procedure will not be considered an acute failure.

- Non-study catheter failure:
 - Use of a non-study catheter to treat the study arrhythmia for repeat ablation procedure during the 3-Month Medication Adjustment or 3-Month Therapy Consolidation Periods.
- Repeat ablation failure, including:
 - > 2 repeat ablation procedures during the 3-Month Medication Adjustment Period / 3-Month Therapy Consolidation Period (Day 0-180) after the index procedure.
 - Any repeat ablation procedure during the Evaluation Period.

Refer to section 5.18 for details.

- AAD failure: Taking a new AAD or a previously failed AAD at a greater than the highest ineffective historical dose for AF during the evaluation period (refer to section 5.14 for details).
- Surgical failure: Undergoing surgical AF ablation or AF surgery any time after the index procedure.

In summary, effectiveness success is defined as freedom from atrial tachyarrhythmia during the Evaluation Period, off or on a previously failed AAD, and not exceeding 2 repeat ablation procedures for an atrial tachyarrhythmia during the 3-Month Medication Adjustment and 3-Month Therapy Consolidation Periods.

This study is designed to compare the primary effectiveness of the investigational device to a pre-determined performance goal of 40%, which is indicated as the minimum acceptable success rate at 12 months for a persistent AF population in the 2012 HRS

consensus statement. The literature relates success rates of ablation with various devices for treating persistent or nonparoxysmal atrial fibrillation ranging from 39.6% to 52.5%.^{10,11,49,50} Anticipated freedom from atrial tachyarrhythmias after ablation is 50%, based on literature review and feedback from BWI's Study Advisory Committee which is comprised of leaders in the electrophysiology field (a list of SAC members appears in section 9.2). With a proposed region of indifference of 10%, the performance goal of the primary effectiveness endpoint for this study will be 40%.

4.1.2 Primary Safety Endpoint

The primary safety endpoint is the incidence of any primary adverse event occurring within 7 days of the AF ablation procedure (including the initial and repeat procedures) using the study catheter per protocol.

Primary adverse events include the following conditions (refer to Table 6-1 Primary Adverse Events for detailed instructions for defining these adverse events):

- Death
- Atrio-esophageal fistula*
- Cardiac Tamponade**+/Perforation⁺
- Myocardial infarction (MI)
- Stroke / Cerebrovascular accident (CVA) †, ††
- Thromboembolism
- Transient Ischemic Attack
- Diaphragmatic paralysis
- Pneumothorax
- Heart block
- PV stenosis*
- Pulmonary edema (Respiratory Insufficiency)
- Pericarditis
- Major vascular access complication / bleeding

* Pulmonary vein (PV) stenosis and atrio-esophageal fistula that occurs greater than one week (7 days) post-procedure shall be deemed Primary AEs.^{47,48}

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

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

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

†† Modified Rankin score assessments should be made by qualified individuals according to a certification process. If there is discordance between the 30 and 90 day Modified Rankin scores, a final determination of major versus minor stroke will be adjudicated by the neurology members of the GSMC.

Based upon the data reported in the BW THERMOCOOL SMARTTOUCH® IDE study (#G110030) and publications cited in Calkins⁵⁹, the expected primary safety event rate is 8% in the current study. The meta-analysis reported by Calkins⁵⁹ combined safety events in patients with persistent and paroxysmal AF, comprising roughly 15% and 85% of the series respectively. The individual studies in the meta-analysis were therefore reviewed to identify those that included patients with persistent AF^{8, 9, 60-74}. Event rates reported in these studies together with the event rates observed in the SMART-AF were used to derive the expected event rates listed in Table 4-1 for persistent AF subjects in the current study. Since many subjects in the current study are expected to be in AF at the time of the procedure, the anticipated event rate for stroke/TIA is 1.5%. Following the strict definitions of the 2012 HRS Consensus Statement, the expected pericarditis rate is 0.6% while the expected rate of cardiac tamponade/cardiac perforation is 2.00%. The expected event rate

for the composite derived additively from the components is 8% (see Table 4-1 Estimated Safety Event Rate for Persistent AF Subjects).

The table is a large grid with a blue header row. Below the header are several rows of redacted text. The rows alternate between light blue and white backgrounds. The redaction consists of solid black boxes covering the text. The table appears to be a continuation of Table 4-1 mentioned in the text above.

The performance goal for the primary safety endpoint is set at 16% assuming an expected composite event rate of 8% with an 8% region of indifference.

4.2 Secondary Endpoints

4.2.1 Secondary Effectiveness Endpoints

- Acute Procedural Success
 - Acute procedural success is defined as confirmation of entrance block in all PVs.
- 15-Month Single Procedure Success
 - The 15-month single procedure success is defined as freedom from documented AF/AFL/AT recurrence (episodes ≥ 30 secs) during the Evaluation Period after a single ablation procedure. Any repeat ablation procedure during the Evaluation Period will be deemed effectiveness failure for this analysis.
 - The 15-month single procedure success is defined as freedom from documented symptomatic AF/AFL/AT recurrence (episodes ≥ 30 secs) during the Evaluation Period after a single ablation procedure. Any repeat ablation procedure during the Evaluation Period will be deemed effectiveness failure for this analysis.

4.2.2 Secondary Safety Endpoints

- Occurrence of Early Onset (within 7 days of initial ablation) Serious Adverse Event
- Occurrence of Peri-Procedural (>7 to 30 days) Serious Adverse Event
- Occurrence of Late Onset (>30 days) Serious Adverse Event

Refer to section 6.3 for the definition of Serious Adverse Event.

4.3 Additional Endpoints

- 15-Month Effectiveness Success – Post Medication Adjustment Period (Day 91-450):
 - All AF Success: Clinical success is defined as freedom from documented all-cause (symptomatic and asymptomatic) AF/AFL/AT recurrence (episodes ≥ 30 secs) between the end of the 3-Month Medication Adjustment Period and the 15-month follow-up visit (Day 91-450) excluding other protocol effectiveness failure modes.
 - Symptomatic AF Success: Clinical success is defined as freedom from documented symptomatic AF/AFL/AT recurrence (episodes ≥ 30 secs) between the end of the 3-Month Medication Adjustment Period and the 15-month follow-up visit (Day 91-450) excluding other protocol effectiveness failure modes.
- 15-Month Effectiveness Success – Post Therapy Consolidation Period (Day 181-450):
 - All AF Success: Clinical success is defined as freedom from documented all-cause (symptomatic and asymptomatic) AF/AFL/AT recurrence (episodes ≥ 30 secs) during the evaluation period (Day 181-450) excluding other protocol effectiveness failure modes.
 - Symptomatic AF Success: Clinical success is defined as freedom from documented symptomatic AF/AFL/AT recurrence (episodes ≥ 30 secs) during the evaluation period (Day 181-450) excluding other protocol effectiveness failure modes.
- Procedural Data:
 - % PV isolation with the study device(s) by PV
 - Repeat Ablation Rate
 - Total Fluoroscopy Time
 - Overall Procedure Time
 - Duration of RF application time
 - RF Ablation parameters per application
 - Device(s) utilized (per ablation)
 - Duration of mapping time
 - VISITAG® Settings
 - CF range
 - Power range
 - Ablation index Assessment per anatomical region

Ablation index data (Force, Power, and Time) will be collected in the CARTO® 3 system during the ablation procedures. The data will be processed to generate the ablation index.

- Quality of Life:
Quality of Life (QOL) status will be evaluated by assessing AFEQT and arrhythmia-specific Symptom Frequency and Severity Checklist outcomes
 - Quality of Life – AFEQT
 - AF Symptom Frequency and Severity Checklist
- Ablation Strategies Post-PVI:
Ablation strategies post PVI will be recorded during the AF ablation procedure. Safety and effectiveness of the ablation strategies employed post PVI will be characterized.

4.4 Health Economic Data

The cost and frequency of health care utilization during hospitalization for the study index ablation procedure, as well as any additional hospitalizations during the study period will be collected. Because this data does not support the safety and efficacy of the investigational device, it will not be provided to the Food and Drug Administration (FDA) as part of the IDE reporting.

The hospitalization health care data to be collected may include but is not limited to: copies of the subject's hospital bills (UB04) and/or itemized hospital bills. Subject's admission date, discharge date, procedure date, ICD-9 and procedure code, DRG assignment and total cost for the hospitalization will be extracted from the forms.

In addition, the sponsor will also collect health economic data associated with follow up care, including any repeat ablation procedure for treating arrhythmia, necessary procedures/surgeries resulting from procedure, ER visits, and outpatient visits to address issues related to arrhythmia or cardiovascular conditions.

5.0 TREATMENT DESCRIPTION

The Sponsor's intention is for the enrolled subject population to be as representative as possible of the well-defined study population. Investigators will be encouraged to consecutively evaluate all persistent AF candidates for ablation for participation in the study, and to offer enrollment to all who meet preliminary eligibility criteria.

Centers will be selected for participation in the study based on experience with THERMOCOOL SMARTTOUCH® technology, ablation experience, their capacity to screen and enroll a reasonable number of eligible patients, and ability to 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 possibly other regions. The trial may include up to 30% of subjects enrolled at OUS sites and approximately 70% of subjects enrolled at US sites. To ensure generalizability of results and minimize the influence of any single site, no more than approximately 15% of the total enrollment will be allowed at a single site.

Historically, women have been underrepresented in or excluded from many clinical studies, leading to lack of information for women and their physicians regarding the risks and benefits of many medical treatments and diagnostic procedures. It is the Sponsor's intent to apply the principles from FDA's guidance titled Evaluation of Sex-Specific Data in Medical Device Clinical Studies in this clinical trial to ensure adequate representation of women and minorities. The Sponsor will take feasibility steps to ensure adequate representation of women and racial or ethnic minorities in this clinical trial:

In order to reflect the gender ratio of the intended population, Sponsor plans to enroll approximately 70% males and 30% females in the study. The gender ratio (male: female = 7:3) undergoing ablation procedures in the AF population is estimated based on previous studies.⁷⁵

5.1 Patient Screening

All patients considered for RF ablation procedure for drug refractory recurrent symptomatic PsAF should be evaluated by the investigator or designated member of the research team for study eligibility per the protocol inclusion and exclusion criteria.

Subjects are enrolled upon signing the informed consent form. No subject may undergo any protocol required tests or examinations falling outside the standard of care without first signing the Informed Consent form for this clinical investigation.

5.2 Informed Consent

Signing of an approved Informed Consent form (ICF) or Patient Information/Informed Consent form (PI/ICF) by the study candidate documents the patient's acceptance and enrollment in the study. Prior to signing, the investigator or authorized member of the research team should discuss the background, potential risks and benefits, and expectations of the study with the candidate. The candidate should have any questions answered to his or her satisfaction and should have access to an investigator for technical or medical questions as requested. Sufficient time must be given for this process. The subject or legal representative must sign the consent form prior to conducting any study-specific exams or tests that fall outside of the standard of care. The consent form used must have prior approval from a duly-constituted Institutional Review Board, Regional Ethics Board, or Ethics Committee. Failure to obtain informed consent renders the subject ineligible for participation in the study.

The informed consent will include an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) or as required per local regulations. Subject confidentiality will be maintained throughout the clinical trial in a way that assures that individual subject data can be tracked back to the source data. For this purpose, a unique subject identification code will be used that allows identification of all data reported for each subject. Data relating to the trial may be made available to third parties, provided the data are treated as confidential and that the subject's privacy is guaranteed.

The informed consent will also request authorization for release of billing information specific to the subject's participation in the study. Specifically, the subject's UB04 (an itemized bill for the study procedure), the explanation of benefits (EOB) and any other

hospitalizations or ER visits that occur during the study will be requested for each procedure and/or hospitalization.

5.3 Pre-Procedure Assessments

Pre-procedure assessments should be performed within 30 days prior to the index AF ablation procedure unless otherwise noted. Some assessments (listed below) have a shorter window prior to the AF ablation procedure.

- Transthoracic Echocardiogram (TTE) – Imaging to determine the atrial size prior to the AF procedure. If the subject has undergone an imaging procedure within the last 6-months where the atrial size (parasternal long axis view) was assessed and documented, the pre-procedure imaging assessment is not required.
- Imaging for detection of LA thrombus – performed day before procedure or day of ablation procedure. The following are allowable imaging modalities:
 - TEE
 - CT/MRI
 - Intracardiac Echocardiography (ICE)
- Pregnancy Test – Pre-menopausal women only, performed within 24 hours prior to the procedure.
- Electrocardiogram (12-Lead ECG)
- Baseline 24-Hour Holter monitor (optional)
- Baseline medical history
- NIH Stroke Scale (NIHSS) assessment (within 72 hours prior to the ablation procedure)
- Arrhythmias history (including findings from TTM, ECG, Holter monitor, etc.)
- Concomitant cardiac medications (including anticoagulation regimen and failed AADs)
- Baseline Quality of Life (QOL) assessment; AFEQT and Symptoms Severity and Frequency Checklist

5.4 General AF Procedure Guidelines

The AF ablation procedures for this study should follow the sequence below:

- Diagnostic catheter placement
- Electrophysiology study (discretion of investigator)
- Transseptal puncture
- Cardioversion if subject is in AF (discretion of investigator)
- A left atrial anatomical map is required prior to an ablation procedure in the LA.

- An anatomical map is not required of triggers outside of the left atrium e.g. SVC/CS etc.
- Introduction of the Study Catheter
 - Minimize the amount of power, contact force and time when ablating the posterior wall.
 - To minimize the risk of PV stenosis, it is recommended that RF energy applications are at least 1 to 2 cm outside the PV ostia to isolate the left and right-sided PVs.
 - Use caution when ablating near the esophagus (along the posterior wall of the left atrium), including but not limited to appropriately reducing RF power
 - For ablation in the region of the right superior PV, precautionary measures such as pacing maneuvers are recommended to evaluate proximity to the phrenic nerve.
- Post ablation pacing procedure(s) and/or infusion of cardiac medications to induce AF/reconnection (e.g., Adenosine, Isoproterenol 2-20 mcg/min)

5.5

[REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

- [REDACTED]
- [REDACTED]

■ [REDACTED]

■ [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

■ [REDACTED]

- [REDACTED]
- [REDACTED]
- [REDACTED]

■ [REDACTED]

- [REDACTED]
- [REDACTED]

- Clinical Investigator judgment and monitoring of ablation effectiveness parameters commonly used such as EGM reduction and/or impedance changes, and/or
- Esophageal monitoring as described in section 5.8.
 - Ablation within the CS:
 - If ablation is required in the CS, power may not exceed 35 W.
 - Duration of ablation is limited to 20 seconds per location in the CS.

■ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

■ [REDACTED]

[REDACTED]

[REDACTED]

■ [REDACTED]

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[REDACTED]

■ [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- Contact force data and individual procedure working ranges will be collected for each RF application during a study ablation procedure for offline analysis.

5.7 [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]
[REDACTED]

5.8 Esophageal Monitoring

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.**

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

5.9 Ablation Procedure

The ablation procedure includes PVI, ablation of non-PV triggers and substrate modification. Study procedure requirements are outlined below:

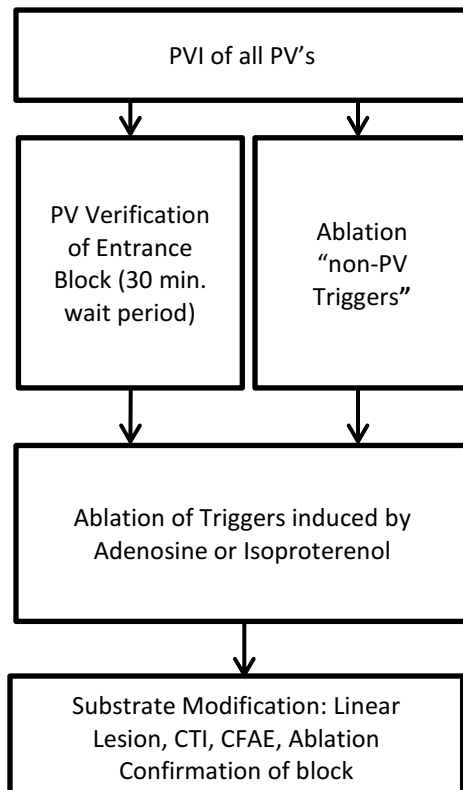
- PVI of all PV's are required (acute success)
- Linear ablation lines are only required to treat documented macro-reentry atrial tachycardia's and limited to the following targets only:
 - LA roof line
 - MV isthmus line
 - LA floor line
 - CTI
- A right atrial CTI linear ablation is **REQUIRED** in cases with documented typical atrial flutter either prior to or during the procedure.
- Ablation of spontaneous non-PV triggers

- CFAE ablation (left atrial, right atrial and CS) will ONLY be considered if normal sinus rhythm is not spontaneously restored after ablation of PV/non-PV triggers & substrate modification with linear ablation
- Ablation of non-PV triggers induced by adenosine or isoproterenol

Prophylactic ablation of empirical sites is not allowed.

All linear lesions require confirmation of bidirectional conduction block by pacing and/or mapping maneuvers.

Figure 5-1 Study Ablation Flow Diagram



5.10 Post Ablation

- Verification of entrance block is required for all PVs.
 - **A 30-minute waiting period is REQUIRED from the last RF application at a PV before verification may be confirmed.** 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 may 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.
 - Administration of adenosine or isoproterenol after a 30-minute waiting period is **REQUIRED** to rule out dormant conduction.

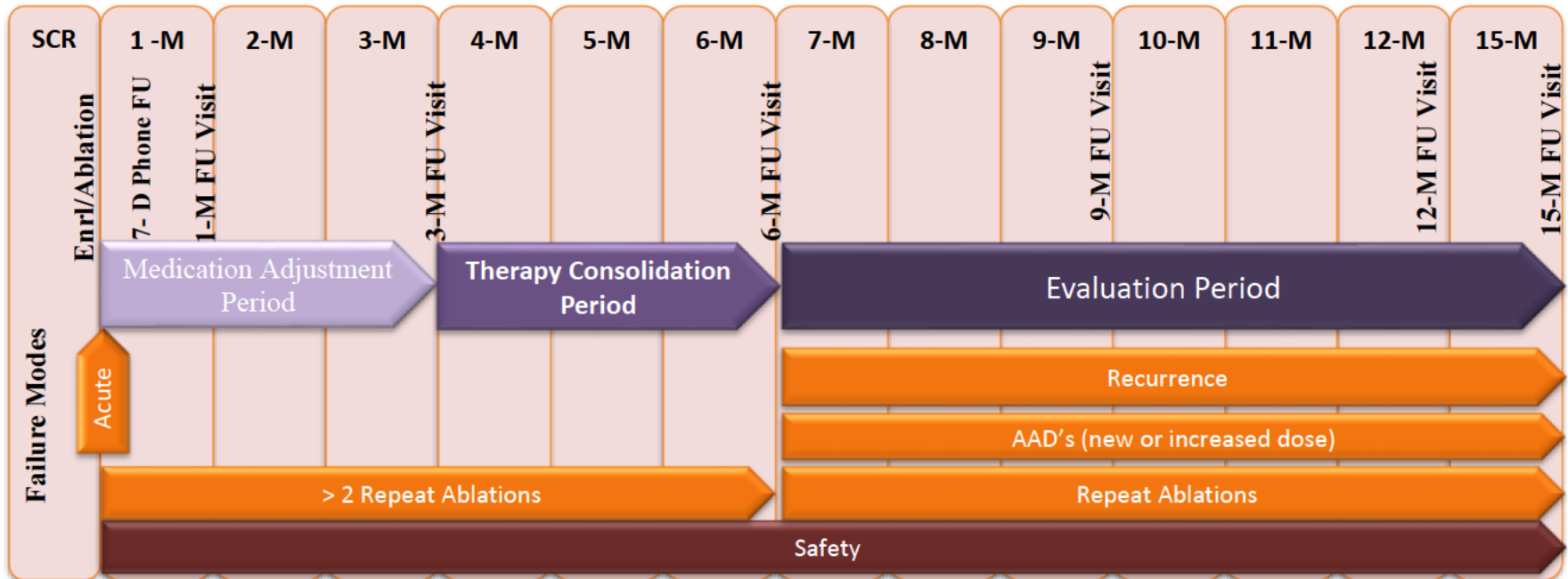
- Demonstration of entrance block **MUST** be confirmed and documented by the LASSO® Circular Mapping Catheter or PENTARAY® NAV Catheter.
- **Linear ablation lines** may only be performed to treat documented macro-reentry atrial tachycardia's (LA roof line, MV isthmus line, LA floor line, CTI).
 - Bidirectional block must be confirmed and documented
- The ablation procedure is considered complete when confirmation of block is confirmed and documented.
- In addition to the data collected on the CRFs, a CARTO backup file identified with the subject's study number will be made for each case and sent to the sponsor as part of the data collection.

5.11 Post Procedure Assessments

- Before hospital discharge:
 - Occurrence of arrhythmias, if any
 - Electrocardiogram (12-Lead ECG)
 - NIH Stroke Scale (NIHSS) assessment prior to hospital discharge
 - Transthoracic Echocardiogram (TTE), if necessary. Subjects who develop symptoms suggestive of pericardial effusion and/or pericarditis should undergo a transthoracic echocardiogram (TTE) to assess the pericardium, before hospital discharge. In the event significant pericardial effusion is identified, subjects should be followed until the condition resolves.
 - Cardiac-related concomitant medications (such as AADs, anticoagulation regimen, etc.)
 - Adverse events, if any
 - Collect Subject Hospitalization Billing information (including UB04 and EOB)
- Follow-up measurements at **7-9 Days (telephone), 1-Month (30 +/- 7 days, telephone or office visit)** and **3-Month (90 +/- 7 days; office visit)**:
 - Adverse events, if any
 - Subjects who have symptoms suggestive of PV stenosis should undergo imaging (CT/MRI)
 - Health Economic Data for hospitalizations, ER visits and outpatient visits, if any
 - At all visits, health economic data to be collected may include, but is not limited to: hospitalization charge (UB04), repeat ablation procedure and/or procedures resulting from the ablation procedure, outpatient visits, and ER visits

- **Follow-up measurements at 6-Month (180 +/- 14 days), 9-Month (270 +/- 28 days), 12-Month (360 +/- 28 days) and 15-Month (450 +/- 28 days) Clinic Visits:**
 - Medical / Hospitalization History
 - Occurrence of arrhythmias, if any
 - Electrocardiogram (12-Lead ECG)
 - QOL Assessments (AFEQT and AF Symptom Frequency and Severity Checklist)
 - 24 Hour Holter Monitor (6, 12 and 15-Month)
 - TTM Monitor (monthly transmissions starting 7 months post procedure and when symptomatic cardiac episodes occur)
 - Concomitant medications only cardiac related (AADs, anticoagulation regimen, etc.)
 - Adverse events, if any
 - Subjects who have symptoms suggestive of PV Stenosis should undergo imaging (CT/MRI)
 - AF Recurrence
 - Health Economic Data for hospitalizations, ER visits and outpatient visits, if any
 - At each follow-up visit, health economic data to be collected may include, but is not limited to: hospitalization charge (UB04), repeat ablation procedure and/or procedures resulting from the ablation procedure, outpatient visits, and ER visits
 - End of Study Report (15-Month)

Figure 5-2 Study Flow Diagram



5.12 Standard Tests and Procedures

The required schedule for subject treatments and evaluations is summarized in Table 5-1.

Table 5-1 Schedule of Treatments and Evaluations

	Pre-Procedure		Ablation Procedure ¹	Discharge	Phone Call	Phone/ Office visit	Follow-Up Visits					Unscheduled Visit
	Screening / Baseline				7-9 Days	1 Month +/- 1 wks.	3 Month +/- 1 wks.	6 Month +/- 2 wks.	9 Month +/- 4 wks.	12 Month +/- 4 wks.	15 Month +/- 4 wks.	
Visit no.	1	2	3	4	5	6	7	8	9	10	11	12
Informed consent ¹	X											
Inclusion & exclusion criteria	X											
Demographics	X											
Medical history / Hospitalization history	X				X	X	X	X	X	X	X	X
Arrhythmias	X [history]			X	X	X	X	X	X	X	X	X
NIH Stroke Scale ¹²		X		X ¹²								
ECG		X		X				X	X	X	X	X
NYHA		X										
CCS-SAF		X						X	X	X	X	
QOL assessment ²		X						X	X	X	X	
Pregnancy test ³		X										
LA thrombus Imaging ⁴			X									
TTE ⁵		X ⁵		X ¹⁶								
Ablation assessments			X									
Holter monitor (24 hr)		X optional						X		X	X	
TTM monitoring ^{13,14}								X ^{13,14}	X ^{13,14}	X ^{13,14}	X ^{13,14}	

	Pre-Procedure		Discharge	Phone Call	Phone/Office visit	Follow-Up Visits						Unscheduled Visit
	Screening / Baseline	Ablation Procedure ¹				7-9 Days	1 Month +/- 1 wks.	3 Month +/- 1 wks.	6 Month +/- 2 wks.	9 Month +/- 4 wks.	12 Month +/- 4 wks.	
Visit no.	1	2	3	4	5	6	7	8	9	10	11	12
Device deficiency			X									
Concomitant medications ⁶		X	X	X	X	X	X	X	X	X	X	X
Health Economic Data Collection ⁷				X ⁷	X ⁷	X ⁷	X ⁷	X ⁷	X ⁷	X ⁷	X ⁷	X ⁷
Adverse events ^{8,9}	X	X	X	X	X ¹⁰	X ¹⁰	X	X	X	X	X	X
PV stenosis imaging assessment ¹¹					X ¹¹	X ¹¹	X ¹¹	X ¹¹	X ¹¹	X ¹¹	X ¹¹	X ¹¹
AF recurrence								X	X	X	X	X
End-of study follow-up											X ¹⁵	

¹ Initial ablation procedure should be done within 30 days of consent.

² Quality of life tools (AFEQT and Symptom and Severity Checklist)

³ Pregnancy test must be done on pre-menopausal women only, within 24 hours of the procedure.

⁴ Section 5.3 of the protocol should be followed when determining if a subject should undergo imaging for the presence of LA Thrombus.

⁵ Imaging TTE to determine the atrial size (if the subject has undergone an imaging procedure within the last 6 months where the atrial size was assessed, the pre-procedure imaging assessment is not required)

⁶ Concomitant medications: only cardiac related (anti-arrhythmia drugs, anticoagulation regimen, etc.)

⁷ Health Economic Data for hospitalizations (UB04), ER visits and outpatient visits, if any

⁸ AEs collected once consent has been signed

⁹ If AE results in Hospitalization health economic data collection is required

¹⁰ Collected via phone follow-up

¹¹ PV imaging (CT/MRI) for subjects who have symptoms suggestive of PV stenosis

¹² Performed prior to hospital discharge or 24 hours after the procedure, whichever is later or any time after the subject experiences a CVA/Stroke, perform Neuro consult as needed Refer to section 6.2.1 for additional details.

¹³ Asymptomatic TTM: should be recorded monthly (i.e. at months 7, 8, 9, 10, 11, 12, 13, 14, 15) and transmitted to the Core Lab. Refer to section 5.15.

¹⁴ TTM: all symptomatic cardiac episodes should be recorded and transmitted at the time the event occurs. Refer to section 5.15.

¹⁵ 15-month visit or last completed visit

¹⁶ Subjects who develop symptoms suggestive of pericardial effusion and/or pericarditis should undergo a transthoracic echocardiogram (TTE) to assess the pericardium

5.13 Study Medications

The following medications are recommended/required (as indicated) for subjects undergoing a study catheter ablation for AF.

5.13.1 Anticoagulation Medications

- **Medication Prior to AF Ablation Procedure**
 - Subject should be placed on systemic anticoagulation therapy for at least 3 weeks prior to the AF ablation procedure.
- **Medication During AF Ablation Procedure**
 - **Heparin:** to achieve an activated clotting time (ACT) of ≥ 325 seconds during the AF ablation procedure in the left atrium.
 - ACT levels **MUST** be checked prior to administering RF energy and rechecked every 15-30 minutes during the ablation procedure in the left atrium to ensure ACT ≥ 325 seconds. All recordings must be documented in the medical records as source documentation.
 - **Adenosine:** 20mg bolus to confirm PV isolation; rule out dormant conduction
 - **Isoproterenol:** recommended if pacing maneuvers are not performed, to achieve a ≥ 20 beats per minute increase in heart rate to induce AF upon completion of the ablation procedure is (recommended dose range is 2-20 mcg/min).
- **Medication Following AF Ablation Procedure**
 - 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.⁴ All anticoagulation therapy will be recorded on the appropriate case report form.
 - All subjects **MUST** be maintained on systemic oral anticoagulation therapy for 2 months post-procedure. Reinitiate oral anticoagulation therapy within 6 hours post procedure).
 - Systemic oral anticoagulation is achieved using INR- dose adjusted warfarin (INR should be maintained between 2.0 and 3.0, inclusive), direct thrombin inhibitor, or factor Xa inhibitor.
 - At 2 months post-procedure, decision regarding continuation of systemic anti-coagulation agents is based on the subject risk for thrombo-embolism. Systemic oral anticoagulation is strongly encouraged to be continued beyond 2 months post ablation in subjects with CHADS₂ score > 1 .

5.14 Antiarrhythmic Drug (AAD) Management

5.14.1 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.)

- **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 both 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 AF

- **New AAD**

ANY AAD that was never taken for the treatment of AF prior to enrollment is considered a “new AAD” if the drug is administered to treat an “atrial tachyarrhythmia” post-enrollment.

5.14.2 AAD Usage and Primary Effectiveness Classification

- **AAD Therapy in the 3-Month Medication Adjustment Period (Day 0-90) and 3-Month Therapy Consolidation Period (Day 91-180):**

During this interval, subjects may receive new AADs or previously failed AADs without affecting their primary effectiveness classification.

- **AAD Therapy in the Effectiveness Evaluation Period (Day 181-450):**

- New AADs:

- Continued beyond the 3-Month Medication Adjustment Period / 3-Month Therapy Consolidation Period for treating “atrial tachyarrhythmia” will result in the subject being classified as a primary effectiveness failure.

- A new AAD for an “atrial tachyarrhythmia” started in the evaluation period will result in the affected subject being classified as a primary effectiveness failure.

- Previously failed AADs:

- Started in or continued from the 3-Month Medication Adjustment Period / 3-Month Therapy Consolidation Period and remaining at the same or lower dose than the highest ineffective historical dose will not result in the affected subject being classified as a primary effectiveness failure.

- Taking a previously failed AAD at a dose greater than the highest ineffective historical dose for AF during the evaluation period will result in the affected subject being classified as a primary effectiveness failure.

Table 5-2 illustrates the corresponding classifications based on AAD therapy administered in the 3-Month Medication Adjustment Period / 3-Month Therapy Consolidation Period and the evaluation period.

Table 5-2 AAD Usage and Impact on Primary Effectiveness Classification

AAD Medication		
	Medication Adjustment / Therapy Consolidation Period: (Day 0-180):	Evaluation Period: (Day 181-450)
New AAD	if initiated but stopped by Day 180; subject <i>will not</i> be classified as a primary effectiveness failure.	if initiated; subject <i>will</i> be classified as a primary effectiveness failure. if initiated during Medication Adjustment/Therapy Consolidation period and continued past 180-days post-ablation; subject <i>will</i> be classified as a primary effectiveness failure.
Previously failed AAD*	if initiated at same or lower dose as previous prescription; subject <i>will not</i> be classified as a primary effectiveness failure. if continued (from prior to study enrollment); subject <i>will not</i> be classified as a primary effectiveness failure.	if initiated and prescribed at the same or a lower than the highest ineffective historical dose; subject <i>will not</i> be classified as a primary effectiveness failure. if continued (after initiation in medication adjustment/therapy consolidation period) and prescribed at the same or a lower than the highest ineffective historical dose after 180 days of the initial ablation. Subject <i>will not</i> be classified as a primary effectiveness failure if increased to dose greater than the highest ineffective historical dose, subject <i>will</i> be classified as primary effectiveness failure

5.15 Heart Rhythm Monitoring

Holter Monitors, ECG, and Trans telephonic monitors (TTM) will be used to monitor the subjects' heart rhythm post-treatment.

Holter Monitor:

- 24-hour Holter monitors are required at the baseline, 6, 12 and 15-month visits.

As part of the 6- and 12 and 15-month follow up visit assessment, all subjects will undergo 24-hour Holter Monitoring to assess their heart rhythm. Holter Monitor data will be sent to the Core Laboratory for independent interrogation and analysis.

Trans telephonic Monitors (TTM):

Trans telephonic monitors (TTM) will be provided to each subject at the 6-month follow-up visit for scheduled transmissions of heart rhythm status. Subjects will be instructed to transmit all emergent symptomatic cardiac events and follow a detailed schedule if the subject remains asymptomatic post ablation during the Evaluation Period (Day 181-450).

The TTM transmission schedule:

- Each subject will be provided with a TTM device at the 6-month visit.

- Subjects will complete a test transmission upon receipt of the TTM device to demonstrate a working understanding of the device.
- Transmission will be performed monthly during the Evaluation Period, starting at day 181 (i.e. at months 7, 8, 9, 10, 11, 12, 13, 14, 15) post index AF ablation procedure. Monthly TTM transmissions are sent directly to the Core Lab.
- All symptomatic cardiac episodes should be recorded and transmitted soon after the event occurs.

5.16 Neurological Assessment (NIHSS)

The NIH Stroke Scale (NIHSS) assessment will be used for neurologic evaluation pre and post ablation procedures. The NIHSS will be administered by a certified person at baseline and hospital discharge, or 24 hours after the procedure, whichever is later. The NIHSS results will be recorded in the study case report forms. Subjects that demonstrated an increase in NIHSS post ablation should have a formal neurology consult and exam, with appropriate imaging used to corroborate any diagnosis.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

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[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

[REDACTED]
 [REDACTED]
 [REDACTED]

5.17.3 Investigator Training

Each investigator will be trained on the use of the Biosense Webster THERMOCOOL SMARTTOUCH® SF Diagnostic/Ablation Deflectable Tip Catheter (“study catheter”). This training will include contact force reference ranges that were used in the pre-clinical (animal), prior clinical (human) studies (EZCF-125, SMART-AF IDE, and SMART-SF IDE clinical trials) and published literature. This will acquaint the investigator with ranges selected by other operators.

5.18 Repeat AF Ablation Procedures

Repeat AF ablations(s) may be performed at the discretion of the physician. Repeat ablations performed during the Medication Adjustment and Therapy Consolidation Periods should utilize the study catheter. The follow-up schedule (Medication Adjustment and Therapy Consolidation periods and exam intervals) will continue based on the initial AF ablation procedure performed, regardless of repeat ablations.

The following assessments should be performed before each procedure utilizing the study catheter:

- Transesophageal Echocardiogram (TEE) – performed within 24 hours prior to the procedure.
- Pregnancy Test – Pre-menopausal women only, performed within 24 hours prior to the procedure.

5.18.1 Repeat Ablation and Primary Effectiveness Classification

- Repeat Ablations in Day 0-180:
 - **Medication Adjustment Period** (Day 0-90): is intended to allow for the patient to receive medication and to allow remodeling to occur. Repeat ablations are discouraged, but subjects requiring a repeat ablation during this period will not be classified as primary effectiveness failures.
 - **Therapy Consolidation Period** (Day 91-180): During this interval, subjects undergoing up to 2 repeat ablations will not be classified as primary effectiveness failures. Circumstances associated with the repeat ablation(s) must be documented in the medical records and recorded in the eCRFs.

During the Medication Adjustment and Therapy Consolidation Periods, a subject may undergo up to 2 repeat ablations. More than 2 repeat ablations during these periods will result in classification as a primary effectiveness failure. Using non-study catheters in repeat ablation procedures during these periods will also be classified as a primary effectiveness failure.

- Repeat Ablation in Day 181-450:
 - During the **Evaluation Period** (Day 181-450), all subjects who have a repeat ablation will be classified as a primary effectiveness failure.
 - The study catheter may NOT be used to perform repeat ablations during the Evaluation Period (Day 181-450)

Table 5-5 illustrates the corresponding primary effectiveness classifications based on the number of repeat ablations in the 3-Month Medication Adjustment Period and 3-Month Therapy Consolidation Period and Evaluation Periods.

Table 5-5 Repeat Ablations and Impact on Primary Effectiveness Classification

Repeat Ablations		
Medication Adjustment Period: (Day 0-90)	Therapy Consolidation Period: (Day 91-180)	Evaluation Period: (Day 181-450)
<ul style="list-style-type: none"> ● ≤ 2 repeat ablations are allowed ● Using non-study catheter will be classified as a primary effectiveness failure 		If subject undergoes any repeat ablation; Subject will be classified as a primary effectiveness failure. Use of study catheter not allowed
Repeat Ablations are discouraged Subject will <u>NOT</u> be classified as a primary effectiveness failure.	Subject will <u>NOT</u> be classified as a primary effectiveness failure.	

5.19 Core Laboratory

A core laboratory will be used for objective evaluation of the 24-Hour Holter Monitors, ECGs, and TTMs for the evaluation of recurrence of atrial tachyarrhythmias. Evaluations will be reviewed by a physician. AF episodes will be evaluated per the definition included in this protocol.

6.0 ADVERSE EVENTS

6.1 Adverse Event Recording

An Adverse Event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) occurring during a clinical study, whether related to the study device or ablation procedure.

Adverse events will be collected from signing of informed consent throughout study follow-up, at each evaluation and whenever the physician becomes aware of an event. Investigators will determine, at each encounter, whether any adverse events (AE) have occurred, and judge their seriousness and relationship to the study device and procedure.

All adverse events, regardless of classification, seriousness, intensity, outcome, or causality, must be recorded in the electronic CRF(s) in a timely manner throughout the study. Onset date of the event, its treatment, current status (resolved, stabilized, or ongoing), and assessment of its seriousness and relationship to the device should be provided when available. All AEs will be monitored until they are resolved or stabilized (no further changes anticipated).

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 not an AE.

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

- Minor pericarditis attributable to the ablation procedure defined as pleuritic chest discomfort with or without pericardial rub and ECG changes.
- A trace / trivial / minor pericardial effusion that is asymptomatic, requires no medical intervention, and does not extend hospitalization will not be considered an adverse event.
- 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.
- Reablation for AF or pre-existing AFL/AT.

6.2 Classification

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

6.2.1 Primary Adverse Event

A Primary AE is one of the following events occurring within seven (7) days following an AF ablation procedure with the study catheter:

Table 6-1 Primary Adverse Events

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Death	Patient death directly related to the device or procedure and occurs at any time during or after the procedure.
Atrio-Esophageal Fistula*	Is defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophagus erosion combined with evidence of a fistulous connection to the atrium such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT or MRI scan is the most common method of documentation of an atrio-esophageal fistula.
Cardiac Tamponade***/Perforation⁺	The development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure. A significant pericardial effusion is one which results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1 cm or more pericardial effusion as documented by echocardiography. Cardiac tamponade should also be classified as "early" or "late" depending on whether it is diagnosed during or following initial discharge from the hospital.
Myocardial Infarction	The presence of any one of the following criteria: <ul style="list-style-type: none"> • Detection of ECG changes indicative of new ischemia (new ST-T changes or new LBBB) which persists for more than 1 h • Development of a new pathological Q waves on an ECG, and • Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Stroke⁵⁸	

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Cerebrovascular Accident	<p>Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke.</p> <p>Duration of a focal or global neurological deficit ≥ 24 h; or < 24 h, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death.</p> <p>No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences) †</p> <p>Confirmation of the diagnosis by at least one of the following:</p> <ul style="list-style-type: none"> • Neurology or neurosurgical specialist • Neuroimaging procedure (MR or CT scan or cerebral angiography) • Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) <p>Stroke: (diagnosis as above, preferably with positive neuroimaging study)</p> <ul style="list-style-type: none"> • Minor—Modified Rankin score < 2 at 30 and 90 days†† • Major—Modified Rankin score ≥ 2 at 30 and 90 days
Thromboembolism	<p>Formation of a clot (thrombus) inside a blood vessel causing obstruction to blood flow. The thrombus can migrate (embolus) and obstruct distal vascular sites. Diagnostic tests to help detect thromboembolisms may include but are not limited to angiography (pulmonary or distal), ventilation-perfusion (V/Q) scans, venography, Doppler ultrasonography, spiral CT, and echocardiography.</p>
Transient Ischemic Attack⁵⁸	<p>New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h, always within 24h. Neuroimaging without tissue injury.</p>
Diaphragmatic Paralysis	<p>Absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis is considered to be permanent when it is documented to be present 12 months or longer following ablation.</p>
Pneumothorax	<p>Introduction of air into the intrapleural cavity necessitating chest tube placement or surgical intervention.</p>

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Heart Block	Impairment of AV conduction requiring intervention (e.g. temporary or permanent pacemaker) due to iatrogenic cause (e.g. inappropriate RF application, traumatic maneuvering of catheter or other intracardiac devices).
Pulmonary Vein Stenosis*	A reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as mild <50%, moderate 50-70%, and severe 70% reduction in the diameter of the PV or PV branch. Severe PV stenosis and symptomatic PV stenosis with any degree of PV narrowing will be considered a primary adverse event and major complication of AF ablation.
Pulmonary Edema (Respiratory Insufficiency)	Respiratory insufficiency resulting in pulmonary complications necessitating intubation or other significant intervention (including diuretics administered specifically for treating pulmonary edema or ICU hospitalization requiring oxygen administration but not intubation) Exclusion criteria include: <ul style="list-style-type: none"> • Pneumonia – infiltrate, fever and leukocytosis • Acute Respiratory Distress Syndrome
Pericarditis	Should be considered a major complication following ablation if it results in effusion which leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 h, requires hospitalization, or persists for more than 30 days following the ablation procedure.
Major Vascular Access Complication / Bleeding	<p>Major Bleeding: A major complication of AF ablation if it requires and/or treated with transfusion or results in a 20% or greater fall in HCT.</p> <p>Major Vascular Access Complication: Defined as hematoma, an AV fistula, or a pseudoaneurysm which requires intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.</p>

* Pulmonary vein (PV) stenosis and atrio-esophageal fistula that occurs greater than one week (7 days) post-procedure shall be deemed Primary AEs.^{47,48}

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

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

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

†† Modified Rankin score assessments should be made by qualified individuals according to a certification process. If there is discordance between the 30 and 90 day Modified Rankin scores, a final determination of major versus minor stroke will be adjudicated by the Global Safety Monitoring Committee.

All reported Primary AEs will be monitored until they are adequately resolved or explained.

6.3 Serious AEs

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

- Lead to a death
- Lead to a serious deterioration in the health of a subject that:
 - Resulted in a life-threatening illness or injury
 - Resulted in a permanent impairment of a body structure or a body function;
 - Required in-patient hospitalization or prolongation of existing hospitalization*
 - Resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
- Lead to fetal distress, fetal death or a congenital abnormality or birth defect.

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

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

6.4 Non-Serious AEs

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

6.5 Anticipated AEs

An anticipated AE is one that has been reported in previous studies of RF ablation and can be anticipated in this current study as per the risk analysis. Table 6-2 provides a comprehensive list of anticipated AEs.

Table 6-2 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

Anticipated Adverse Events	
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

Anticipated Adverse Events	
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

6.6 Unanticipated Serious Adverse Device Effect

A (serious) adverse device effect (ADE/SADE) is any (serious) adverse effect on subjects' health, safety, rights, welfare, and life-threatening problems including death, which is caused by, or associated with the study device. Accordingly, relationship to device or study is crucial assessment by investigators. An unanticipated adverse device

effect (UADE) or unanticipated serious adverse device effect (USADE) is any ADE or SADE that has not been previously identified in nature, severity, or degree of incidence in the investigational plan or risk analysis report.

6.7 Clinical Investigation Device Failure/Malfunction/Deficiency

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.). If a device failure is detected or suspected, it should be documented on the appropriate CRF and **the device must be promptly returned** according to the Sponsor's instructions. If the device failure is associated with an AE, **both** the device failure and AE must be reported to the Sponsor **immediately** upon awareness (refer to section 6.8).

6.8 Reporting Requirements

All SAEs, UADE/SADE/USADE, and Study device failure/malfunction/deficiency, whether or not they are related to the device or procedure, **must be reported by eCRF** to the Sponsor (**Biosense Webster Clinical Operations**). Investigators/sites are expected to report any SAEs, UADE/SADE/USADE, and Study device failure/malfunction/deficiency immediately upon their awareness of the event, or in any event no later than 72 hours from the time of awareness. Failure to report any event requiring expedited reporting within this interval will be classified as a protocol deviation.

For all other non-serious AEs, the Study Site has 14 calendar days from when the site becomes aware to inform the Johnson and Johnson Study Sponsor by entering the AE into the eCRF.

6.9 Intensity or Severity

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

Table 6-3 Intensity or Severity Definitions

Mild	Events that result in minimal transient impairment of a body function or damage to a body structure, and/or does not require intervention other than monitoring.
Moderate	Events that result in moderate transient impairment of a body function or damage to a body structure, or that require intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure.
Severe	Events that are life threatening and/or result in permanent impairment of body functions or damage to body structures, or that require significant intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

Intermittent AEs should be classified according to their greatest severity. A continuous AE that changes severity should be reported as a new AE.

6.10 Outcome

AE outcomes are assessed according to the following classifications:

Table 6-4 Adverse Event Outcome Classifications

Resolved without Sequelae	Subject fully recovered with no observable residual effects.
Resolved with Sequelae	Subject recovered with observable residual effects.
Ongoing	Adverse event has not resolved and additional change in condition is possible
Death	Subject died as a result of the adverse event, whether or not the AE is related to the device or procedure. Note; deaths from any cause occurring on this study are to follow expedited reporting.

6.11 Causality

Cause of AEs is defined as follows:

Table 6-5 Adverse Event Causality Classifications

Device Relationship	
Definitely Device-Related	The THERMOCOOL SMARTTOUCH® SF catheter directly caused or contributed to the AE.
Possibly Device-Related	The THERMOCOOL SMARTTOUCH® SF catheter may have caused or contributed to the AE.
Not Device-Related	The AE is not associated with the THERMOCOOL SMARTTOUCH® SF catheter.
Procedure Relationship	
Definitely Procedure-Related	The AE is directly associated by timing and/or pathophysiology with the standard electrophysiology or AF ablation procedure described in this protocol.
Possibly Procedure-Related	The AE may be associated by timing and/or pathophysiologic with the standard electrophysiology procedure described in this protocol.
Not Procedure Related	The AE is not associated with the AF procedure described in this protocol.

6.12 Documentation

All AEs must be documented on the appropriate eCRF. All AEs must be monitored until they are adequately resolved or stabilized, with follow-up reports submitted to the Sponsor or designee as soon as new information becomes available. Additional documentation may be requested by the Sponsor or designee, such as a written event narrative detailing the

clinical course, copies of correspondence with the local IRB/EC, hospital records, death certificates, and autopsy reports, if applicable.

6.13 Global Safety Monitoring Committee (GSMC)

In order to minimize risks to subjects enrolled in the study, the sponsor will convene a formal independent Global Safety Monitoring Committee (GSMC) at pre-determined intervals to review the adverse event reports and recommend appropriate action(s) to ensure subject safety.

Primary Adverse Events and Serious Adverse Events occurring within 30 days of the ablation procedure and of cardiac origin will be reviewed by Biosense Webster clinical staff with Medical Safety Officer or designee, and submitted to the independent GSMC for review.

7.0 STATISTICAL ANALYSIS METHODS

7.1 Analysis Population

- **Modified Intent-To-Treat (mITT) Population:** the modified Intent-To-Treat (mITT) population will consist of all enrolled subjects who meet all eligibility criteria **AND** in whom
 - (1) RF energy was delivered with study catheter **OR**
 - (2) Study catheter was inserted but no RF energy was delivered.
- **Safety Population (SP):** The safety population will consist of all enrolled subjects who have undergone insertion of the study catheter.
- **Per Protocol (PP) Population:** The PP population will include subjects who satisfy the following criteria:
 - are enrolled and meet all eligibility criteria
 - have undergone RF ablation
 - are treated with the study catheters, and have been treated for the study-related arrhythmia

7.2 Analyses for Primary Endpoints

7.2.1 Analyses for Primary Effectiveness Endpoint

The null and alternative hypotheses are:

Hypothesis $H_0: P_E \leq 0.40$

$H_a: P_E > 0.40$

P_E : the freedom from documented atrial fibrillation, atrial flutter and atrial tachycardia recurrence at 15 months follow-up

Null hypothesis: The freedom from documented AF/AFL/AT at 15 months is less than or equal to the pre-determined performance goal of 40%.

Alternative hypothesis: The freedom from documented AF/ATL/AT at 15 months is greater than the pre-determined performance goal of 40%.

Analysis Population: The per-protocol population will be used as the primary analysis population. Subjects with missing effectiveness endpoints data during 15 months follow-up period will be excluded from the primary analysis. The subjects who have failed the primary effectiveness endpoint before 15 months will be included in the analysis. Analyses of the primary effectiveness endpoint will be repeated in the mITT population. Sensitivity analyses for missing data will be performed in the PP and mITT populations to assess the impact of missingness on the primary effectiveness outcome and are described in the Statistical Analysis Plan (SAP).

Analysis Method: The primary effectiveness endpoint will be evaluated using the exact test for a binomial proportion at a two-sided significance level of 5%. If the lower bound of the exact two-sided 95% confidence interval of the primary effectiveness endpoint rate is greater than the performance goal of 40%, the study will be considered to have demonstrated effectiveness.

7.2.2 Analyses for Primary Safety Endpoint

The null and alternative hypotheses are:

Hypothesis $H_0: P_S \geq 0.16$

$H_a: P_S < 0.16$

P_S : the rate of early onset (within seven days of the ablation procedure) primary AE

Null hypothesis: The rate of early onset primary AE is greater than or equal to the pre-determined performance goal of 16%.

Alternative hypothesis: The rate of early onset primary AE is less than the pre-determined performance goal of 16%.

Analysis Population: The safety population (SP) will be used as the primary analysis population. Subjects with missing primary safety data will be excluded in the primary analysis. Sensitivity analyses for missing data will be performed in the SP and are described in the Statistical Analysis Plan (SAP).

Analysis Method: The primary safety endpoint will be evaluated using the exact test for a binomial proportion at a two-sided significance level of 5%. If the upper bound of the exact two-sided 95% confidence interval of the primary safety endpoint rate is less than the performance goal of 16%, the study will be considered to have demonstrated safety.

7.3 Site Heterogeneity

Each site should enroll no more than 15% of the total enrollment to minimize the possibility that the study results could be highly influenced by a few sites. Sites with less than five

subjects will be combined according to geographic regions. Using this pre-determined criterion, sites with less than five subjects within the same geographic region will be combined such that the combined center(s) would have five or more subjects and no more than 5 sites combined.

A Chi-square statistic will be used to examine the homogeneity across sites for the primary effectiveness and safety endpoints. A p-value less than 0.15 will be considered statistically significant for an assessment of homogeneity across sites. A non-significant result will support pooling of sites for the primary analyses.

If the sites are not poolable, logistic regression models treating site as a random effect will be fit to examine the impact of site heterogeneity on the primary endpoints. The claim of trial success will be based upon the totality of the data.

7.4 Primary Effectiveness Endpoint

Based on a performance goal of 40% and an anticipated freedom from AF recurrence of 50%, 330 subjects will be required to obtain at least 90% power at a two-sided significance level of 0.05 using the exact binomial method.

7.5 Primary Safety Endpoint

Based on a performance goal of 16% and an anticipated rate of 8% for the primary safety endpoint, 232 subjects will be required to obtain at least 90% power at a two-sided significance level of 0.05 using the exact binomial method.

7.6 Total Sample Size

It is estimated that the attrition rate is no more than 10%. In order to obtain 330 subjects, Biosense Webster proposes to enroll 367 ($=330/0.90$) subjects to account for this potential subject attrition.

7.7 Analyses for Secondary and Additional Endpoints

Descriptive statistics will be presented for the secondary and additional endpoints. No formal statistical hypotheses and inferential statistics will be formulated and performed for the secondary and additional effectiveness and safety endpoints. Details of analyses methods for secondary and additional endpoints will be provided in SAP.

8.0 ADMINISTRATIVE RESPONSIBILITIES

8.1 Ethics Review

Study materials including informed consent must be reviewed and approved by an appropriately-constituted IRB/IEC/REB before enrollment of subjects. Biosense Webster and the IRB must approve in writing any changes to the protocol.

Proof of IRB/IEC/REB review and approval must be obtained prior to subject enrollment. Investigators are responsible for submitting and obtaining initial and continuing review (per local regulations) of the study by their IRB/IEC/REB.

8.2 Patient Informed Consent

Biosense Webster and the reviewing IRB/IEC/REB must approve any modifications to the ICF or PI/ICF. The ICF may be translated as appropriate. Certification of accurate translation will be required.

Informed consent is mandatory and must be obtained from all subjects prior to their participation in this study. Copies of all signed consents must be retained in the records of the study, and an unsigned sample copy of the approved ICF must also be in the study file. Subjects must each receive a copy of the ICF.

8.3 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, or representatives of Health Authorities (HA) or Regulatory Authorities (RA) acting in their official capacities will have access to these confidential files. No data transmitted to Sponsor for evaluation and reporting will contain identifiable references to individual subjects.

8.4 Data Management

8.4.1 Case Report Forms (CRFs)

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

8.4.2 Data Reporting

The investigator, or a designated individual, is responsible for recording data from the trial on the eCRFs supplied by Biosense Webster. The investigator or a delegated individual is required to electronically sign eCRFs 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 remotely and at the investigational site by Biosense Webster personnel or designees throughout the trial. To this end, the investigator and institution must permit inspection of trial files including original (source) records and subject eCRFs by sponsor representatives and responsible government agencies.

8.4.3 Data Review

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

8.5 Records and Reports

8.5.1 Records

Records to be maintained by the investigator include:

- Study protocol/Investigational Plan and all amendments with signature pages
- Signed clinical study agreement and Statement of Investigator
- IRB/IEC/REB approval letter, including approved ICF document
- Evidence of IRB/IEC/REB compliance
- Other significant IRB/IEC/REB correspondence
- Significant sponsor correspondence relating to the study
- CVs for all investigator(s)
- Financial Disclosure for key study staff
- Records of protocol and supporting training
- Site personnel delegation of authority/responsibility
- Clinical Monitor/Site Visit sign-in log
- Device accountability log
- 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 electronic CRFs and supporting source documentation
- Supporting documentation of any AEs and/or death

The investigator must retain copies of procedure reports, procedure nursing notes and the results of any interventional procedures that occur while the subject is enrolled in the study. Biosense Webster reserves the right to secure data clarification and additional medical documentation on subjects enrolled in this study.

8.5.2 Record Retention

Records and reports of the study will remain on file at sites for a minimum of two (2) years after its completion/termination. Records for U.S. sites must be maintained in accordance with 21 CFR 812.140 [d], and for OUS sites, according to local requirements.

If the principal investigator plans to leave the study site, he/she is responsible for identification of another individual at site who will assume the obligation for file maintenance and management of any continuing subjects. Biosense Webster and pertinent HA/RA, per its requirements, should be notified of this change.

Records and reports may be discarded upon notification by Biosense Webster to the study site. Site personnel should contact Biosense Webster prior to destruction of any study-related records and reports to ensure appropriate record retention.

8.5.3 Procedural Data

It is the responsibility of the investigator to provide timely completion of CRFs to the sponsor.

8.5.4 Investigator's Final Report

Upon completion or termination of the Biosense Webster study, the principal investigator must submit a final written report to the approving Investigational Review Board/Ethics Committee (as required by the IRB/IEC/REB) and provide a copy to Biosense Webster. The report should contain the information required by the IRB/IEC/REB and be submitted in the time frame required by the IRB/IEC/REB.

8.6 Labeling

THERMOCOOL SMARTTOUCH® SF Diagnostic/Ablation Deflectable Tip Catheter with Contact Force Sensing Capability and interface cable Instructions for Use is included in each product package.

8.7 Deviations from Protocol and Good Clinical Practice

The investigator should not deviate from the protocol except in medical emergencies. In emergencies, prior approval for a protocol deviation will not be required, but the Biosense Webster clinical operations personnel should be notified as soon as possible. IRB/REBs must also be notified promptly of significant protocol deviations as they are defined by the IRB/REBs.

9.0 STUDY MANAGEMENT

9.1 Study Timelines

Study Duration: The study is expected to last Approximately 2.5 years (~1.0 years for enrollment; 15 months of follow-up for primary endpoint).

9.2 Study Advisory Committee (SAC)

The responsibilities of the SAC include:

- Consultation on Study Design and Protocol Development
- FDA Interactions: Reviewing periodic clinical reports prepared by the Sponsor including annual HA/RA reports and the final study report.
- Enrollment Champions (addressing enrollment issues with Clinicians)
- Help to ensure that all investigators comply with the ablation and medical treatments described in the protocol

- Advising the Sponsor of unforeseen medical issues identified during the clinical study.
- Addressing subject 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 / Consultation

Physicians serving on the Study Advisory Committee for this study are:

Andrea Natale, MD
St David's Medical Center
Texas Cardiac Arrhythmia Research
1015 East 32nd Sreet, Suite 500
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9.3 Investigator Responsibilities

The Principal Investigator is responsible for supervision of all study activities and is ultimately responsible for overall compliance with protocol, GCP, local and regional regulations, and IRB/REB requirements. Many study activities may be formally delegated to support staff, but the Principal Investigator retains responsibility for supervision of all study activities.

Specific responsibilities include:

- Obtaining IRB/REB approval and renewals
- Providing Sponsor with:
 - Written IRB/REB approval letters and IRB/REB-approved consent forms,
 - Signed, dated Investigator Agreement,
 - Signed and dated Financial Disclosure form at study outset and any time financial changes occur, for up to one year following completion of the study

- Curriculum vitae for each Investigator and key research staff member
- Maintaining an accurate and current Study Personnel Log which identifies all individuals authorized to perform work for the study at each site
- Completing appropriate training on the study device and the study protocol prior to enrolling and treating subjects
- Obtaining informed consent (including privacy language) from patients
- Performing the ablation procedure
- Complying with the clinical protocol
- Notifying the Sponsor and IRB/REB of adverse events, deaths, and deviations as defined in this protocol and per IRB/EC requirements.
- Notifying Sponsor promptly of withdrawal of IRB/REB approval
- Complying with IRB/REB (as applicable) and Sponsor annual report requirements
- Maintaining accurate and current logs for the study such as Subject log, Device Accountability Log
- Completing eCRFs accurately and as soon as possible after collection of data
- Reviewing and signing designated eCRFs
- Maintaining relevant source documentation to support future verification of data on the eCRFs.
- Complete all subject follow-up visits, including efforts to maintain contact with subjects who fail to comply with the follow-up schedule. Before a subject may be classified as 'lost to follow-up', the Investigator or authorized personnel should document attempts to contact the subject.
- Retaining study records as described in 8.5.2. The Sponsor will notify the Investigator when records may be destroyed.
- Preparing a final report and periodic IRB/EC updates as required

9.4 Sponsor Responsibilities

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

- Preparing of study documents including but not limited to the protocol, eCRFs and template informed consent, if no local template is preferred
- Completing pre-study site assessments and approvals
- Obtaining IDE approval from the FDA and regional HAs/RAs
- Providing protocol training to investigators and research personnel
- Instructing operators and technicians in the proper use and monitoring of study devices

- Monitoring the study throughout the duration of the investigation
- Securing investigator/site compliance with the protocol and applicable regulations
- Shipping investigational devices to each site
- Creation and maintenance of eCRF database
- Conducting all communications with HAs/RAs
- Submitting study supplements for regulatory approval (as necessary), e.g., request for study expansion
- Preparing reports summarizing the status of the clinical study no less often than annually, which will be supplied to the FDA and to other HAs/RAs as requested. Annual reports may also be provided to each HA//RA, and possibly to the Principal Investigator as requested
- Access to clinical study data provides opportunities to conduct further research that may help advance medical science and improve patient care. This helps ensure the data provided by research participants are used in the creation of knowledge and understanding. To this end, the study results on all pre-specified outcomes, including negative outcomes, will be submitted to ClinicalTrials.gov no later than one year after completion of the primary endpoint (unless an extension has been approved via certification from the Secretary of Health and Human Services). Results submission could be delayed if an extension is granted to the results submission deadline; however, the release of all results on pre-specified outcomes will be hastened if the study is terminated early

9.5 Training

9.5.1 Research Team

The training of appropriate clinical site personnel will be the responsibility of the Sponsor or the Sponsor's representative. In some cases, training may be performed by an existing site staff member who has already been trained by the Sponsor (such as assigning a new CRC to the study). To insure uniform data collection and protocol compliance, the Sponsor will present a formal educational session to study site personnel that will include review of the Clinical Study Protocol, techniques for the identification of eligible subjects, instructions on in-hospital data collection, follow-up schedules, and regulatory requirements. Remote as well as on-site contacts will be used to monitor study performance indicators such as enrollment compliance, data submission rate, data errors, protocol questions, and GCP compliance.

9.5.2 Investigator Proctoring

Investigators selected to participate in the study will have prior experience treating patients with the THERMOCOOL SMARTTOUCH® Catheters and/or the THERMOCOOL® SF Catheters. The research sites will not be able to order product until a participating study physician has completed the BWI training program in use of the STSF catheter.

9.6

[REDACTED]

9.7 Initiation of the Investigation

Potential investigational sites will undergo prestudy evaluations to ensure their qualification for supporting the study. Selected sites will be provided with appropriate study-specific training prior to commencement of activities.

9.8 Monitoring the Study

Each site will undergo periodic monitoring of the study, which involves a visit from a trained Sponsor representative. Monitoring visits may include, but will not be limited to, the following:

- Verification of accuracy of study logs such as the Delegation of Responsibility, etc.
- Verification that informed consent is obtained for all subjects
- Verification of completeness of the Regulatory Binder.
- Data source verification with the eCRFs.
- Identification and action to resolve any issues or problems with the study.

Monitoring activities will be documented through such means as contact reports and follow-up summaries of status and action items.

9.9 Termination of the Study

The study may be suspended or terminated early at the discretion of the Sponsor, for reasons such as incidence of unanticipated serious adverse device effects that may pose a risk to other subjects. In any early termination, already enrolled subjects will continue to be followed per the study protocol requirements.

Sponsor may also terminate a site prior to completion if it believes the site is no longer capable of participating (e.g., cannot fulfill subject enrollment or protocol compliance goals, site suspension by IRB/REB).

At termination of the investigation, each active site will undergo closeout monitoring to conclude any outstanding issues, resolve all data discrepancies and make sure any outstanding eCRFs are completed, reconcile disposition of investigational devices, discuss responsibilities with the Principal Investigator, and discuss any other items relevant to the conclusion of the study. The termination process will be documented by a written report.

9.10 Device Accountability

9.10.1 Device Accountability

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 and identity that each device was used in the study, and disposition information regarding return to the Sponsor. The Sponsor will label all devices as “Investigational device” (as applicable for the region) in a prominent location.

The site Device Accountability Log will include the following information:

- Date of receipt
- Individual acknowledging receipt
- Quantity received
- Catalog number for catheters
- Serial/lot numbers
- Dates devices were used
- Subject IDs for whom devices were used
- Dates of return (as applicable)
- Type of disposal (i.e., return to Sponsor for adverse event, complaint, etc.)

9.11 Device Returns

All study catheters will be labeled “**Investigational Device**” and are only to be used for subjects enrolled in this clinical study.

The OUS sites will use their commercially available STSF catheters per the approved IFU and PRECEPT Protocol requirements within the country of use. The allowable curves for use in the study are those listed in the PRECEPT Protocol Section 1.4.1, Section 1.4.2 and commercially approved in the country of use.

Devices suspected of deficiency or device associated with a (device related or possibly related) adverse event should be returned immediately to BWI and will undergo thorough analysis. Returned devices must be decontaminated per hospital policy and labeled with the following:

- Subject identification number, or if unused, site number
- Date of use/event or if applicable, specify “unused”
- Return type (device deficiency related, AE related, etc.)

All tracking information must be retained. All study catheters must be returned to:



9.12 Electronic Case Report Forms

Electronic CRFs (eCRFs) have been developed to capture the information outlined in this Study Protocol. Data on these eCRFs will be monitored, corrected if necessary, and entered into a validated database. All changes made to the data will be tracked in the electronic audit trail, recording the current value, previous value, reason for change, date timestamp of data entry/change, and the name of the person who changed the data. The investigator will electronically sign all subject eCRFs as verification that the data have been reviewed and correctly reflects source documentation. Data from these eCRFs will be used to provide analysis of this study.

9.13 Source Documentation

Data entered into the eCRFs may be taken from source documentation, such as hospital procedure reports, admission and discharge summaries, and other hospital or physician office/clinic documents. If no standard hospital or office document exists to capture some of the information that may be unique to this study, a worksheet may be developed to record this information. Data collection instruments should clearly identify the individual collecting the data and the date of collection. The instrument of original capture of all study data will serve as the source document for future verification of for those data parameters. Privacy regulations will be observed during the use of these source documents during monitoring.

9.14 Subject Confidentiality/Record

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

Site personnel should also be attentive to privacy considerations and should not transmit PHI outside of PI control (e.g., via .pdf or FAX) without redaction of patient identifiers.

Privacy considerations such as above will also be covered in protocol training for both Sponsor representatives and study site personnel.

9.15 Data Management

The Sponsor will be responsible for all data management activities. These activities include development of a database, utilizing validated database software, into which all study data will be entered by the clinical sites. The Sponsor will be responsible for ensuring the overall integrity of the database.

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11.0 APPENDIX A: STUDY DEFINITIONS

Term	Definition
Adverse Event (AE)	<p>Any unfavorable and unintended sign, medical occurrence, disease or injury (including abnormal laboratory findings) in subjects, users or other persons temporally associated with the use of a medicinal product or device (investigational) whether or not related to the investigational product.</p> <p>This definition includes events related to the investigational medical device and/or the comparator, and events related to the procedure in which the investigational device was used.</p>
Adverse Device Effects (ADE's)	<p>Adverse events related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use errors or from intentional misuse of the investigation medical device.</p>
AF/AT/AFL Episode	<p>An episode of AF/AT/AFL ≥ 30 seconds in duration.</p>
AF Episode	<p>An atrial fibrillation episode is defined as AF which is documented by ECG monitoring and has a duration of at least 30 seconds, or if less than 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</p>
Anticipated AE	<p>An effect which by its nature, incidence, severity or outcome has been identified as possible complications associated with the investigational medical device and/ or intervention procedure.</p>
Atypical Flutter	<p>Macroreentrant circuits within the atria where activation rotates around large obstacles that does not meet the criteria for Typical Flutter.</p>
Catheter Insertion	<p>Defined as the study catheter breaching the sheath and entering the bloodstream.</p>
Device Deficiency	<p>Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction (failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol), misuse or use error and inadequate labeling.</p>
Documented AF/AT/AFL episode	<p>An AF/AT/AFL episode documented by an electrocardiographic monitoring tool. This may include ILR, ECG, TTM, Holter monitor, or telemetry strip.</p> <p><i>Reporting of a symptomatic episode by a patient or in a referral letter is not considered a documented AF episode.</i></p>
Longstanding persistent AF	<p>Continuous AF of > 12 months duration</p>
Paroxysmal AF	<p>Paroxysmal AF is defined as recurrent AF (≥ 2 episodes) that terminates spontaneously within 7 days. Episodes of AF of ≤ 48 hours duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.</p>

Term	Definition
Permanent AF	Not appropriate in the context of patients undergoing catheter ablation of AF; refers to a group of patients where a decision has been made not to pursue restoration of sinus rhythm by any means, including catheter or surgical ablation.
Persistent AF (PsAF)	Persistent AF is defined as continuous AF that is sustained beyond 7 days and less than 1 year.
Serious adverse event (SAE)	<p>1. Any adverse event that:</p> <ul style="list-style-type: none"> • Led to a death • Led to a serious deterioration in health that either: <ul style="list-style-type: none"> ○ Resulted in a life-threatening illness or injury, or ○ Resulted in a permanent impairment of a body structure or a body function, or ○ Required in-patient hospitalization or prolongation of existing hospitalization, or ○ Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function • Led to fetal distress, fetal death or a congenital abnormality or birth defect <p>2. Any Device Deficiency that could have led to an SAE</p> <p>A planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event.</p> <p>Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.</p>
Serious Adverse Device Effects (SADE's)	Adverse device effects that has resulted in any of the consequences characteristic of a serious adverse event.
Symptomatic AF/AT/AFL Episode	Symptom(s) which is/are exhibited by the subject which made them seek medical attention, and are concurrent with a documented episode of AF/AT/AFL by either 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.
Typical Flutter	Atrial flutter is caused by a reentrant rhythm in either the right or left atrium. Typically initiated by a premature electrical impulse arising in the atria, atrial flutter is propagated due to differences in refractory periods of atrial tissue. This creates electrical activity that moves in a localized self-perpetuating loop. For each cycle around the loop, there results an electric impulse that propagates through the atria.

Term	Definition
Unanticipated Serious Adverse Device Effect (USADE)	<p>Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.</p> <p>NOTE: Anticipated SADE: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report</p>
Ventricular Tachycardia (VT)	<p>Ventricular tachycardia: a tachycardia (rate ≥ 100/min) with three or more consecutive beats that originates from the ventricles independent of atrial or AV nodal conduction. Continuous VT for ≥ 30 s or that requires an intervention for termination (such as cardioversion).</p>