Evaluation of the VISITAG SURPOINT™ Module with External Processing Unit (EPU) when used with the THERMOCOOL SMARTTOUCH® SF and the THERMOCOOL SMARTTOUCH® Catheters for Pulmonary Vein Isolation (PVI) (SURPOINT COA)

Clinical Study Protocol

Protocol# BWI_2017_06

Version 4.0
March 8, 2019

[redacted]

Table of Contents

Protocol Agreement Form

Study Title: Evaluation of the VISITAG SURPOINT™ Module with External Processing Unit (EPU) when used with the THERMOCOOL SMARTTOUCH® SF and the THERMOCOOL SMARTTOUCH® Catheters for Pulmonary Vein Isolation (PVI)

(SURPOINT COA)

I have read this protocol and agree to conduct this clinical investigation in accordance with the design and specific provisions outlined herein. I understand the protocol, and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practices (GCP), applicable country regulations the Declaration of Helsinki, the signed clinical study contract with Sponsor and with the protocol outlined herein. I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by the Sponsor.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

I will fulfill the requirements of my Institutional Review Board (IRB)/Ethics Committee (EC), or other oversight committee, to ensure complete and continual oversight of this clinical investigation. I will use an Informed Consent Document approved by the Sponsor and my reviewing IRB/EC (where required).

I agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events, device related adverse events, or procedure related adverse events as defined in this protocol to the Sponsor, and comply with all adverse event reporting requirements of my reviewing IRB/EC. I agree to permit the Sponsor, its authorized representatives, my reviewing IRB/EC, and any regulatory authority/body access to all records relating to the clinical investigation.

The below signature confirms I have read and understood this protocol and its associated amendments or attachments, and will accept respective revisions or amendments provided by the Sponsor.

Principal Investigator	Signature	Date
Name (PRINT)		

Protocol Summary

Evaluation of the VISITAG SURPOINT™ Module with External Processing Unit (EPU) when used with the THERMOCOOL SMARTTOUCH® SF and THERMOCOOL SMARTTOUCH® Catheters for Pulmonary Vein Isolation (PVI)

(SURPOINT COA)

Full Title & Protocol Number	Evaluation of VISITAG SURPOINT™ Module with External Processing Unit (EPU) when used with the THERMOCOOL SMARTTOUCH® SF and THERMOCOOL SMARTTOUCH® Catheters for pulmonary vein isolation (PVI) #: BWI_2017_06
Short Title	Evaluation of VISITAG SURPOINT™ Module and EPU
IDE/IND number	Condition of Approval/Post Market Study
Sponsor	CSS/BWI
Indication	Atrial Fibrillation
Study Article Description	• THERMOCOOL SMARTTOUCH® SF (STSF) Catheter • THERMOCOOL SMARTTOUCH® (ST) Catheter • VISITAG SURPOINT™ Module with External Processing Unit (EPU)
Study Design	Prospective, non-randomized, post market clinical evaluation of the VISITAG SURPOINT™ Module with External Processing Unit (EPU) when used with STSF catheter and ST catheter compared to a historical control performance goal. A maximum of 330 subjects will be enrolled across up to 45 sites. Two hundred eighty (280) enrolled subjects will be treated using the STSF catheter with EPU and 50 subjects will be treated using the ST catheter with EPU. Prior to enrollment, a few sites will be selected to only enroll subjects who will be treated with the ST catheter and the remaining sites will only enroll subjects who will be treated with the STSF catheter. Bayesian adaptive design will be used to assess early success at up to two interims: one after all subjects have completed the 3-month follow-up assessment, and a second to occur after all subjects have completed the 6 months follow-up visit.
Sample Size	N = 330 subjects

<table>
<tr><td></td><td colspan="2">Two hundred eighty (280) enrolled subjects will be treated using the STSF catheter with EPU and 50 subjects will be treated with ST catheter. It is estimated that the attrition rate is no more than 10-15% which means about 30 subjects may be accounted for excluded subjects before receiving treatment.</td></tr>
<tr><td>Study Population</td><td colspan="2">Subjects undergoing electrophysiology mapping and RF ablation with THERMOCOOL SMARTTOUCH® SF (STSF) and THERMOCOOL SMARTTOUCH® (ST) catheters for treatment of Antiarrhythmic Drug Refractory symptomatic paroxysmal AF</td></tr>
<tr><td>Geographic areas to be included</td><td colspan="2">Geographic involvement will include the US.</td></tr>
<tr><td rowspan="2">Study Duration</td><td colspan="2">~24 months (including 12 months enrollment and 12 months follow up from LPI)</td></tr>
<tr><td>Start Date: 3Q18</td><td>End Date:3Q20</td></tr>
<tr><td>Procedure(s) Description</td><td colspan="2">Pulmonary Vein Isolation (PVI)
<u>VISITAG™ parameters</u>
• 2-3mm stability range
• 3-5 sec stability time
• Force Over Time (FOT) 25%,
• 3gr force
• Respiratory Gating Mandatory (unless using Jet Ventilation)
• Tag size – 3mm
• Maximum Inter tag distance 6mm

<u>VISITAG SURPOINT™ Module Tag Index Target Values:</u>
• Anterior, Ridge, Roof segments - target value: 550
• Posterior and inferior segments - target value: 380
Note: All Tag Index target values, especially the posterior wall, are in the absence of safety concerns (i.e. no temperature rise from esophageal probe, pain during conscious sedation, steam pop, etc). In the absence of safety concerns, achieveing target Tag Index values will be the endpoint of RF energy application.
If for safety reasons the ablation needs to be stopped prior to reaching the Tag Index target value, please do so and document accordingly with associated <u>VISITAG ™ location number.</u>
<u>Ablation Parameters</u>:</td></tr>
</table>

	Increases in power and force from previous workflow to hit a specific Tag Index target with a shorter procedure time is not recommended. • RF power range: 15-45 Watts (Investigator discretion) • Contact Force Target range: 5-25 gram (recommended) • RF Time: defined based on above mentioned VISITAG SURPOINT™ Module and Tag Index targets • Flow rate: o STSF Catheter ▪ 8 ml/min for STSF for power ≤ 30W ▪ 15 ml/min for STSF for power > 30W o ST Catheter ▪ 17 ml/min for STSF for power ≤ 30W ▪ 30 ml/min for STSF for power > 30W
Primary Objective	The primary objective of this clinical investigation is to demonstrate the safety and 12-month effectiveness of Tag Index-guided ablation using the VISITAG SURPOINT™ Module with External Processing Unit when used with the THERMOCOOL SMARTTOUCH® SF (STSF) and THERMOCOOL SMARTTOUCH® (ST) catheters for pulmonary vein isolation (PVI) in the treatment of subjects with drug refractory symptomatic paroxysmal atrial fibrillation. Specifically: • To demonstrate the safety based on the proportion of subjects with early-onset (within 7 days of ablation procedure) primary adverse events • To demonstrate the 12-month effectiveness based on the proportion of subject with freedom from documented atrial arrhythmia (atrial fibrillation (AF), atrial tachycardia (AT) or atrial flutter (AFL) episodes during the effectiveness evaluation period (Day 91-365)
Secondary Objectives	The major secondary objectives of this study are: • to evaluate the incidence of (serious) adverse events during and after procedure up to 3 months following procedure. • Acute Procedural Success as defined by: o The % of subjects with ipsilateral PVI (entrance block) at the end of the procedure, and o The % of subjects with ipsilateral PV isolation (entrance block) after first encirclement, after waiting period and adenosine challenge

	• Procedural efficiency gain with the use of VISITAG SURPOINT™ Module with External Processing Unit
Exploratory Objectives	N/A
Primary Endpoints & Follow-up Intervals	**Acute Safety**: o Incidence of early onset primary adverse events (PAE) related to the device or procedure. Occurrence of Primary AEs within 7 days of an ablation procedure. (refer to Table 6-1 for a comprehensive definition list of primary adverse events) **12-Month Effectiveness**: Freedom from documented (Symptomatic and asymptomatic) atrial fibrillation, atrial flutter and atrial tachycardia (AF/AFL/AT) (hereinafter collectively referred to as "atrial tachyarrhythmias") recurrence (episodes ≥ 30 secs on TTM or continuously recorded on the standard 12-leads ECG or 24 Hour Holter monitoring) during the evaluation period (Day 91-365)
Secondary Endpoints & Follow-up Intervals	**Secondary Safety Endpoints**: o 12-Month PAE Rate: Cumulative incidence of primary adverse events occurring within seven (7) days following an AF ablation procedure using study catheters with EPU and any late onset atrio-esophageal fistula or PV stenosis through 12 months o Incidence of Unanticipated Adverse Device Effects (UADEs) o Incidence of Serious Adverse Events (SAEs) within 7 days (early onset), >7 to 30 days (peri-procedural) and >30 days (late onset) of initial ablation o Incidence of bleeding complication: a) major bleeding, b) clinically relevant non-major, and c) minor bleeding as defined in the 2017 HRS/EHRA/ECAS/APHRS /SOLAECE Consensus Statement **Secondary Effectiveness Endpoints**: o *Acute Procedural success*: o % of subjects with ipsilateral PVI (entrance block) at the end of the procedure o % of subjects with ipsilateral PVI (entrance block) after first encirclement (evaluated prior to the 30-minute waiting period and adenosine challenge)

	○ % of subjects with ipsilateral PVI (entrance block) after first encirclement without acute reconnection, after waiting period and adenosine challenge ○ % of touch-up (ablation of acute reconnection) among all targeted veins ○ Anatomical location of acute PV reconnection after first encirclement ○ *Repeat Ablation Procedures*: ○ Incidence (%) of repeat ablation procedures with VISITAG SURPOINT™ module during 12-months period post-procedure ○ % PVs re-isolated among all of the targeted PVs at repeat procedure ○ % repeat ablation procedures requiring new linear lesions and/or identifying new foci outside of initially isolated area among the repeat ablation procedures **Additional Endpoints:** • Procedural data ○ total procedure time, PVI time, RF application time, mapping time ○ fluoroscopy time/dose ○ location of RF applications, number of RF applications ○ RF ablation parameters per application ○ VISITAG SURPOINT™ values (Tag Index) per segment ○ VISITAG™ parameters will be collected in the CARTO® 3 system during the ablation procedures for generation of LA ablation maps • HEMA ○ Incidence of hospitalizations post-index ablation procedure
Inclusion Criteria	Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1. Symptomatic paroxysmal AF who had at least one AF episode electrocardiographically documented within one (1) year prior to enrollment. Documentation may include electrocardiogram (ECG); Transtelephonic monitoring (TTM), Holter monitor or telemetry strip

	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
Exclusion Criteria	Subjects who meet any of the following exclusion criteria are not eligible for enrollment. 1. Previous surgical or catheter ablation for atrial fibrillation 2. Previous cardiac surgery (including CABG) within the past 6 months (180 days) 3. Valvular cardiac surgical/percutaneous procedure (i.e., ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve) 4. Any carotid stenting or endarterectomy 5. Documented LA thrombus on imaging 6. LA size > 50 mm on imaging 7. LVEF < 40% 8. Contraindication to anticoagulation (heparin or warfarin) 9. History of blood clotting or bleeding abnormalities 10. PCI/MI within the past 2 months (60 days) 11. Documented thromboembolic event (including TIA) within the past 12 months (365 days) 12. Rheumatic Heart Disease 13. Uncontrolled heart failure or NYHA function class III or IV 14. Severe mitral regurgitation (Regurgitant volume ≥ 60 mL/beat, Regurgitant fraction ≥ 50%, and/or Effective regurgitant orifice area ≥ 0.40cm2) 15. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months (365 days) 16. Unstable angina 17. Acute illness or active systemic infection or sepsis 18. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.

	19. Presence of implanted ICD/CRT-D. 20. 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. 21. Gastroesophageal Reflux Disease (GERD; active requiring significant intervention not including OTC medication) 22. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study. 23. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal) 24. Concurrent enrollment in an investigational study evaluating another device, biologic, or drug. 25. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes vascular access, or manipulation of the catheter. 26. Life expectancy less than 12 months
Statistical Analysis and Power Calculation	The Final analyses for primary safety and effectiveness endpoints will apply Bayesian methods and use a beta-binomial model. Under the assumption of 65% success rate for effectiveness and 8% rate for primary safety, with 330 subjects, assuming a 10-15% attrition rate, we will have more than 90% power for declaring success for each of the primary endpoints controlling the type-I error at 5%.
Interim Analysis	Two interim analyses are planned to evaluate declaration of early success.
Determination if DMC/CEC required	CEC will be convened to adjudicate the primary safety endpoint. No DMC is required. The product will be commercially available.
Time and Events Schedule	• Baseline o Demographics o Medical History o Quality of Life Assessment (SF-12) o AAD Medication History o Arrhythmia History

	○ Device Interrogation (if applicable) • Ablation Procedure ○ Ablation procedure strategy (AF, AFL, & AT) will utilize Investigator's Standard of Care **Data Collection**: ○ EPU and Catheter Information (Serial #, Lot #) ○ Target sites for RF lesion application ▪ Target Sites ▪ Number of RF Applications per target ▪ total RF duration per application (sec) ▪ Fluoroscopy time/dose ▪ Procedure Times ○ Total procedure time ○ Total mapping time ○ Total RF time ○ Time to PVI ▪ Fluid delivered ○ From the Study Catheter ○ From IV (if applicable) ○ CARTO and modified RF Generator download for offline analysis ▪ Segmentation of LA ablation maps based on chosen CARTO tags ▪ Full Case backup [including complete VISITAG export] and CARTO Case recording ▪ RF Ablation parameters per application: Power, Impedance, Flow Rate, Temperature, and Time ▪ Contact force measurements and RF ablation parameters ▪ VISITAG SURPOINT™ value per application ▪ Localized ECG Electrodes measurements for offline analysis ○ Acute Success (entrance and exit block PVI) ○ Adverse Events • Discharge

	○ Recurrence of arrhythmia prior to discharge ○ Device Interrogation (if applicable) ○ HEMA Billing information ○ Adverse Events • Follow-up Assessments Post Ablation* ○ 7 Day phone Call ○ 1-month ○ 3-month ○ 6-month ○ 12-month Data to be collected during the study visits will include: • Adverse Events (since last visit) • Medication update/changes • Quality of Life Assessment (SF-12) • Billing Information for all hospitalizations, ER visits and outpatient visits for economic analyses • Recurrence of Study Arrhythmia (each patient will be provided a TTM event monitor and Holter monitor) ○ Repeat ablation procedures/subject during the follow-up period, repeat ablation procedure will be at the discretion of the investigator ○ Throughout the 12-month effectiveness follow-up period, arrhythmia status will be assessed by symptom-initiated event monitoring. ▪ Device Interrogation (if applicable) ▪ All symptomatic cardiac episodes will be documented *based on the initial ablation procedure
QUALIFICATION AND ACTIVATION OF OPERATORS	• ST or STSF experience – ≥20 cases • Experience with VISITAG™ – ≥20 cases • All operators– require training as specified in physician training plan • Retrospectively provide 5 PAF cases with segmented (9 regions) VISITAG™ with standard workflow

List of Abbreviations

AAD	Antiarrhythmic drug	ICF	Informed consent form
ACC	American College of Cardiology		
ACT	Activated clotting time	IEC	Independent Ethics Committee
AE	Adverse event	IFU	Instructions for use
AF	Atrial fibrillation	IRB	Institutional Review Board
AFL	Atrial flutter	ITT	Intent-to-treat
AHA	American Heart Association	HIPAA	Health Insurance Portability and Accountability Act
ANOVA	Analysis of variance		
AT	Atrial tachycardia	LA	Left atrium
AV	Atrioventricular	MI	Myocardial infarction
BP	Blood pressure	MRI	Magnetic resonance imaging
CABG	Coronary Artery Bypass Grafting	MV	Mitral valve
CEC	Clinical Events Committee		
CHF	Congestive heart failure	PAF	Paroxysmal atrial fibrillation
CF	Contact force	PCI	Percutaneous coronary intervention
CFAE	Complex fractionated atrial electrogram	PIU	Patient Interface Unit
CHADS	Congestive heart failure, High blood pressure, Age 75+, Diabetes, previous Stroke or transient ischemic attack	PP	Per protocol
		PV	Pulmonary vein
CPVI	Complete pulmonary vein isolation	PVI	Pulmonary vein isolation
CRF	Case Report Form		
CRT-D	Cardiac Resynchronization Therapy Defibrillator	QOL	Quality of life
CS	Coronary sinus	RA	Right atrium
CT	Computed tomography	RF	Radiofrequency
CTI	Cavotricuspid isthmus	SADE	Serious adverse device effect
CVA	Cerebrovascular accident	SAE	Serious adverse event
ECAS	European Cardiac Arrhythmia Society	SAP	Statistical analysis plan
EPU	External processing unit	SF	Surround Flow
ESC	European Society of Cardiology	SVC	Superior vena cava
FDA	Food Drug Administration	TIA	Transient ischemic attack
GCP	Good Clinical Practice	TEE	Transesophageal echocardiogram
ECG	Electrocardiogram	TTE	Transthoracic echocardiogram
EHRA	European Heart Rhythm Association	TTM	Transtelephonic monitoring
HRS	Heart Rhythm Society	UADE	Unanticipated adverse device effect
ICD	Implantable cardioverter defibrillator	USADE	Unanticipated serious adverse device effect
ICE	Intracardiac echocardiography	VT	Ventricular tachycardia

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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.[1-4] AF is a complex, progressive disease that results in structural and electrical remodeling in the heart.

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.**Error! Reference source not found.,Error! Reference source not found.** 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.**Error! Reference source not found.**

The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Consensus Statement states that electrical isolation of the pulmonary veins (PVs) from the left atrium is "the cornerstone for most AF ablation procedures."[4] 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.

The Biosense Webster THERMOCOOL SMARTTOUCH® SF and THERMOCOOL SMARTTOUCH® catheters feature improvements over standard irrigated RF catheters. They provide real-time measurement of contact force (CF) between the catheter tip and heart wall, as well as location information, when used with CARTO® 3 Navigation System. A small spring connects the ablation tip electrode to the catheter shaft with a magnetic transmitter and sensors to measure deflection of the spring. The catheter has a high-torque shaft with a uni-directional or bi-directional deflectable tip section containing an array of electrodes which may be used for recording and stimulation purposes. The tip electrode serves to deliver RF current from the RF generator to the desired ablation site.The THERMOCOOL SMARTTOUCH® SF catheter incorporates "surround flow" technology. A temperature sensor is embedded in the 3.5 mm tip dome electrode, which features a 56-hole irrigation pattern. At the proximal end of the catheter, a saline input port with a standard Luer fitting terminates from the open lumen. This saline port serves to permit the injection of normal saline to irrigate the tip electrode. During ablation, heparinized normal saline is passed through the internal lumen of the catheter and through the tip electrode, to irrigate and cool the ablation site as well as the electrode tip.

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.[6] 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. The THERMOCOOL SMARTTOUCH® SF catheter features a porous electrode tip (56 very small holes) in contrast to the predecessor device, which featured 6 larger holes at the distal electrode tip. In subjects with paroxysmal AF, the THERMOCOOL® catheter with Surround Flow (SF) technology was as successful as the predecessor THERMOCOOL® catheter in achieving PV isolation, even though both treatment groups received similar amounts of RF energy. Moreover, the saline volume administered was reduced[7] due to the tip design. Procedural efficiency was also enhanced; time to PV isolation and total RF duration,[8,9] as well as saline irrigation volume,[9,10] were diminished in paroxysmal AF subjects who underwent ablation with the THERMOCOOL® SF catheter compared to the THERMOCOOL® catheter without SF.

There have been several studies showing that there is a correlation between electrode-tissue contact and RF lesion generation.[11-13] 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. The addition of a CF sensor at the distal tip of an irrigated RF catheter allows measurement of CF in real time during the ablation procedure. Initial studies in a clinical setting have suggested that CF measurement allows identification of the use of inappropriately high CF during ablation as well as catheter manipulation[14], and that CF measurement during ablation correlates with clinical outcome in AF patients.[15] Subsequent studies with the THERMOCOOL SMARTTOUCH® catheters showed the ability to know CF in real time to be associated with decreased procedure time and fluoroscopy time,[16] and increased acute and long-term procedural success in the paroxysmal AF population.[16,17] There is *ex vivo* evidence that a higher contact force may result in an increased incidence of serious adverse events.[18] Therefore, a catheter with the capability to provide real-time electrode-tissue contact force may have the potential to better control RF energy application resulting in a more optimal lesion and reducing the incidence of serious injury to the patient.

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 from carefully controled studies 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.[16,17]

While irrigation of the RF catheter tip has been found to effectively reduce temperature at ablation sites and associated adverse events (e.g., thrombus, steam pop),[6] there is a risk of volume overload from high volumes of perfused saline. The “surround flow” technology

of the THERMOCOOL SMARTTOUCH® SF catheters allow a reduction in intraprocedural saline perfusion[7,9,10] as well as in procedure time.[8,9]

Real world reports utilizing CF ablation strategies have produced variable results for 12-month outcomes.[19,20] PV reconnection is common and believed to be the result of catheter instability, tissue edema, and a reversible non-transmural injury. These studies demonstrated a need for better tools to facilitate ablation strategy in a way that allows the operator to reproduce consistent success with a personalized PVI strategy.

The VISITAG SURPOINT™ Tag Index is a novel lesion quality marker that utilizes contact force, time, and power. The formula (a weighted Force-Power-Time Integral) was developed as a marker of ablation outcome and has been evaluated extensively in animal studies.[21,22]

After commercialization of the VISITAG SURPOINT™, early retrospective analysis examined the hypothesis that a minimum Tag Index value was necessary to avoid reconnection after PVI.[25] Early results demonstrated a relationship between a minimum Tag Index value and acute PV reconnection. No acute PV reconnections were seen when the calculated minimum Tag Index value was 380 for posterior/inferior segments and 550 for anterior/roof segments.[25] This study established that different Tag Index values were required for the variety of tissue thickness that are found between different anatomical regions in the left atrium. In a retrospective analysis of the SMART-SF study data, lower Tag Index average values were also used to achieve a successful radiofrequency ablation at the posterior anatomical location compared with other locations while the average contact force applied at each PV anatomical segment was not significantly different.[26]

A study comparing acute success of Tag Index to another lesion quality tool, the Force Time Integral (FTI), [26,27] investigators again demonstrated the requirement for a minimum Tag Index value to have a successful RF application. In this study patients returned for an electrophysiology procedure 2 month after a PVI procedure to examine the success of the PVI. It was observed that a low Tag Index value within an ablation segment was independently predictive of PV reconnection. No reconnections were seen when the minimum Tag Index values per segment were ≥370 for posterior/inferior segments and ≥480 for anterior/roof segments.[29]

In this study both lesion quality assessment tools analyzed, demonstrated good acute success, however, the VISITAG SURPOINT™ Tag index is believed to be superior to FTI.[29] As a marker of lesion quality FTI has two significant limitations; 1) it does not include the role of power delivery in lesion creation and 2) it relies on simple multiplication of contact force and application time.[29] The relationship between contact force and time is dynamic, with both making differing contributions to lesion formation. Using FTI ignores the contribution of power to lesion formation. With a fixed FTI (300gs) an increase in power application from 20W to 35W results in an almost three-fold increase in lesion volume. This introduces an unnecessary element of risk when applying RF to the thin tissue on the posterior wall.

Two recent prospective publications, including 12-month effectiveness outcomes, the success of tailored Tag Index values was demonstrated. Hussein et al, compared Tag Index value guided ablation to CF-guided propensity-matched controls. When targeting Tag Index values of 550 anterior/roof and 400 posterior/inferior segments, they demonstrated;

a) better procedural outcomes, with both a much higher rate of first-pass isolation (97% vs 84%) and lower incidence of acute PV reconnection (6% VS 13%), b) the AI group experienced significantly improved freedom from AT at 12 months (83% vs 63%), and c) Tag Index-guided ablation was associated with a significantly higher impedance drop (13.7 Ω vs 8.8 Ω), suggesting creation of better quality lesions. They concluded that the Tag Index value guided ablation may provide a more tailored approach to LA ablation, balancing ablation effectiveness with avoidance of unnecessarily excessive ablation in thin-walled, higher-risk regions.[28]

Recently, Taghji et al in a large single center study (n=130), demonstrated that a PVI ablation strategy using inter-lesion distance ≤6 mm and Tag Index values ≥400 at posterior wall and ≥550 at anterior wall resulted in improved acute and 12-month effectiveness success. Acute success was found to be 98% first-pass PVI and 98% adenosine-proof isolation. At 12 months, the single-procedure freedom from AF/AT/AFL was 91.3% in a subset (104/130) of the patients who were off antiarrhythmic drug therapy. Single-procedure freedom from both AF/AT/AFL and off antiarrhythmic drug therapy was 73.1%.[29]

Efficiency gains using the Tag index values (anterior=550; posterior=400) have also been observed. De Potter et al, reported the PVI success rate after first encirclement was 96%. This was associated with acute procedural efficiency when compare to the SMART-AF study (94.6 min. vs 222.7 min.). The authors concluded that using Tag Index target values increased the predictability of procedures. The efficiency gains observed, did not compromise safety or long-term effectiveness.[30]

To further delineate the utility of using tag index values and inter lesion distance (≤6mm) for PVI during AF ablation procedures, Phlips et al[58] designed the single center "Close" study to provide comparative data to conventional contact force guided PVI. In the 100-patient study (CLOSE group – 50 VISITAG SURPOINT and CONV-AF group – 50 conventional CF), the authors demonstrated superiority in effectiveness and efficiency while maintaining an acceptable safety profile. Ablation procedure time was significantly shorter for the CLOSE group when compare to CONV-CF group (149±33 min vs. 192±42 min.; $p<0.0001$). No complications were observed in the CLOSE group, one tamponade was reported in the CONV-CF group. Kaplan-Meier analysis also demonstrated 12-months effectiveness superiority (freedom from atrial tachyarrhythmias) when the CLOSE group was compared to the CONV-CF group (94% vs. 80%; $p=0.039$). With the limitations inherent in a single center study, this study provides additional evidence for the uniform application of RF energy at different anatomical location within the left atrium when a physician adds the tag index to his standard technique for PVI the cornerstone of successful AF ablation therapy. [58]

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%).[31-35]

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%).[36,37] 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%.[36,37] 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%.[36,37,54,56] 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%).[36,37] 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.[38] 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.[39,40] 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.[52,53] 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%).[41-43]

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%).[44-48]

Hemorrhage could occur as a result of anticoagulation (risk <0.5%), which may require transfusion.[36,37]

The percutaneous procedure carries risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%).[36,37] This risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.

Risks associated with the VISITAG SURPOINT™ module

The use of the VISITAG SURPOINT™ module carries the risk that a physician may misread the Tag index value information or the CARTO EPU may give incorrect information (false high tag index values or false low tag value). The outcome of these risks are similar to the risks associated with RF application and have been addressed in *Risks associated with RF application* above.

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 and THERMOCOOL SMARTTOUCH® catheters, 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.[7,10] 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.[8]

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) on the use of the THERMOCOOL SMARTTOUCH® SF Catheter THERMOCOOL SMARTTOUCH® catheter with Contact Force Sensing Capability technology prior to subject enrollment and the VISITAG SURPOINT™ Module.

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.

The VISITAG SURPOINT™ module is not intended to replace the current practice of clinical judgment for safe RF application including monitoring changes in power, contact force, catheter stability and lesion contiguity.

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 the Sponsor's Medical Safety Officer and an unbiased physician review committee functioning as a Clinical Events Committee (CEC) 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 paroxysmal 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.

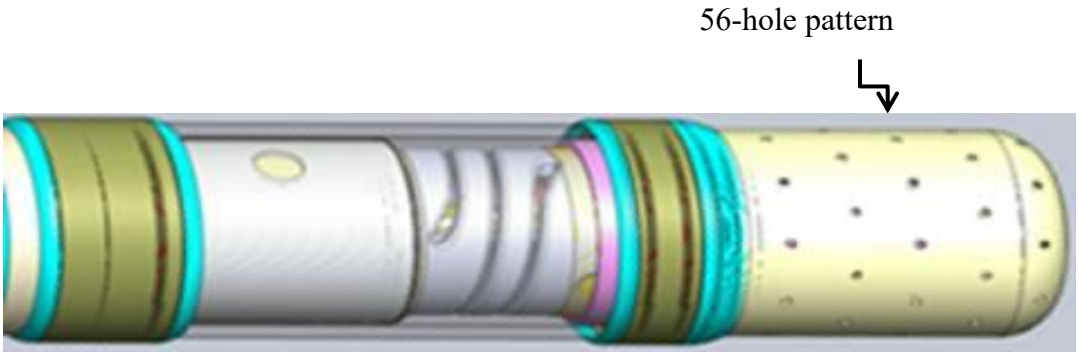
1.4 Device Description

The Biosense Webster THERMOCOOL SMARTTOUCH® family of catheters are steerable, multi-electrode, luminal catheters with a deflectable tip designed to facilitate electrophysiological mapping of the heart and to transmit RF current to the catheter tip dome electrode for ablation purposes. The catheter shaft measures 7.5 F with 8 F ring electrodes. For ablation, the catheter is used in conjunction with an RF generator and a dispersive pad (indifferent electrode). The catheter has force sensing technology that provides a real-time measurement of contact force between the catheter tip and the heart wall.

1.4.1 THERMOCOOL SMARTTOUCH® SF catheter

The catheter has a high-torque shaft, with either a uni-directional or bi-directional braided deflectable tip section, containing an array of ring electrodes. The high-torque shaft allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site. All ring electrodes are manufactured from platinum-iridium. The tip dome electrode is manufactured from palladium-platinum and serves to deliver RF current from the RF generator to the desired ablation site. The catheter incorporates a temperature sensor that is embedded in the 3.5 mm tip dome electrode. The 3.5 mm tip dome features a 56-hole irrigation pattern as shown below in Figure 1-1.

Figure 1-1 Catheter Tip



1.4.1.1 Bi-directional Catheter Description (D-1348-XX-S)

The catheter has a high-torque shaft with a bi-directional deflectable tip section containing an array of electrodes which includes a 3.5 mm tip dome. All of the electrodes may be used for recording and stimulation purposes. The tip electrode serves to deliver RF current from

the RF generator to the desired ablation site. The tip electrode and ring electrodes are made from a noble metal. The catheter incorporates a thermocouple temperature sensor that is embedded in the 3.5 mm tip electrode. A Rocker Lever is used to deflect the tip. The high torque shaft also allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site. Additionally, a variety of curve types are available in symmetric or asymmetric combinations, providing two 180° opposed, single planed curves. Currently, the available curves for the Biosense Webster THERMOCOOL SMARTTOUCH® SF Bi-Directional Navigation Catheter include the following: DF, FF, and FJ.

1.4.1.2 Uni-directional Catheter Description (D-1347-XX-S)

The catheter has a high-torque shaft with a Uni-Directional deflectable tip section containing an array of electrodes which includes a 3.5 mm tip dome. All of the electrodes may be used for recording and stimulation purposes. The tip electrode serves to deliver RF current from the RF generator to the desired ablation site. The tip electrode and ring electrodes are made from a noble metal. The catheter incorporates a thermocouple temperature sensor that is embedded in the 3.5 mm tip electrode. Tip deflection is controlled at the proximal end by a handpiece in which a piston slides; a thumbknob on the piston controls piston travel. When the thumbknob is pushed forward, the tip is deflected (curved). When the thumbknob is pulled back, the tip straightens. The high torque shaft also allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site.

1.4.2 THERMOCOOL SMARTTOUCH® catheter

1.4.2.1 Bi-directional Catheter Description (D-1327-0X-S)

The bi-directional catheter has a high-torque shaft with a bi-directional deflectable tip section containing an array of electrodes, which includes a 3.5 mm tip dome. All of the electrodes may be used for recording and stimulation purposes. The tip electrode serves

to deliver RF current from the RF generator to the desired ablation site. The tip electrode and ring electrodes are made from platinum-iridium. The catheter incorporates a thermocouple temperature sensor that is embedded in the 3.5 mm tip electrode. A rocker lever is used to deflect a tip with an asymmetrical DF curve, providing two 180° opposed, single planed curves. The high-torque shaft also allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site.

1.4.2.2 Uni-directional Catheter Description (D-1336-0X-S)

The unidirectional catheter has a high-torque shaft with a uni-directional deflectable tip section containing an array of electrodes, which includes a 3.5 mm tip dome. All of the electrodes may be used for recording and stimulation purposes. The tip electrode serves to deliver RF current from the RF generator to the desired ablation site. The tip electrode and ring electrodes are made from platinum-iridium. The catheter incorporates a thermocouple temperature sensor that is embedded in the 3.5mm tip electrode. Tip deflection is controlled at the proximal end by a hand piece in which a piston slides; a thumb knob on the piston controls piston travel. When the thumb knob is pushed forward, the tip is deflected (curved). When the thumb knob is pulled back, the tip straightens. The high-torque shaft also allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site.

At the proximal end of the STSF/ST catheters, a saline input port with a standard luer fitting terminates from the open lumen. This saline port serves to permit the injection of normal saline to irrigate the tip electrode. During ablation, heparinized normal saline is passed through the internal lumen of the catheter and and through the irrigated, tip electrode. A compatible irrigation pump is used to control the saline irrigation.The catheter connects to the CARTO 3 Navigation System through an interface box called the Patient Interface Unit (PIU). The catheter interfaces with standard recording equipment and a compatible RF generator via accessory extension cables with the appropriate connectors.

The THERMOCOOL SMARTTOUCH family of catheters feature a location sensor embedded in the tip section that transmits location information to the CARTO 3 Navigation System. An appropriate reference device is required for location reference position purposes. A sensor in the tip section transmits contact force information that is displayed on the CARTO 3 Navigation System. For use in mapping procedures, for information on appropriate reference devices, and for further description of the operation of the CARTO 3 Navigation System, refer to the CARTO 3 Navigation System User Manual.

For further information on the irrigation pump (COOLFLOW® Irrigation Pump, SMARTABLATE™ Irrigation Pump) RF Generator (Stockert 70, SMARTABLATE™ RF Generator), and required cables, refer to the respective Instructions for Use and/or User Manual.

Refer to Section 5.17 (Study Equipment) for details on additional equipment required for this study.

1.5 Approved Catheters

The THERMOCOOL SMARTTOUCH® Diagnostic /Ablation Deflectable Tip Catheters with Contact Force Sensing Capability (D-1327-0X-S and D-1336-0X-S) and the THERMOCOOL SMARTTOUCH® SF Diagnostic /Ablation Deflectable Tip Catheters with Contact Force Sensing Capability (D-1347-XX-S and D-1348-XX-S) are the only approved catheters to be used in this study.

For the remainder of this protocol, "STSF" will refer to the THERMOCOOL SMARTTOUCH® SF Diagnostic/Ablation Deflectable Tip Catheters with Contact Force Sensing Capability and "ST" will refer to the THERMOCOOL SMARTTOUCH ®Diagnostic/ Ablation Deflectable Tip Catheters with Contact Force Sensing Capability

Instructions for Use (IFU)

A copy of the IFU for the THERMOCOOL SMARTTOUCH® SF and The THERMOCOOL SMARTTOUCH® catheters and interface cable is included in each product package.

1.6 Supply of Approved Catheter

The THERMOCOOL SMARTTOUCH® SF and the THERMOCOOL SMARTTOUCH® Catheters have been approved for the treatment of drug refractory PAF. Catheters used in this study can be taken from commercial stock.

1.7 VISITAG SURPOINT™ Module (Tag Index)

The VISITAG SURPOINT™ module is a lesion quality marker that utilizes contact force, time, and power to calculates Tag Index values that are displayed on the CARTO 3 system screen. The formula (a weighted Force-Power-Time Integral) was developed as a marker of ablation outcome and has been evaluated extensively in animal studies.[21,22]

Tag Index is based on the hypothesis that there is an Index that represents a dimension (e.g. depth, diameter) of a single lesion generated on the cardiac tissue. Tag Index is calculated via integration of the ablation parameters used during the cardiac ablation.

The general mathematical model for the integration of the ablation parameters is:

$$\boldsymbol{Index}(t) = \left(k \int_0^T \boldsymbol{AE}^a(t) \boldsymbol{P}^b(t) dt \right)^c$$

where

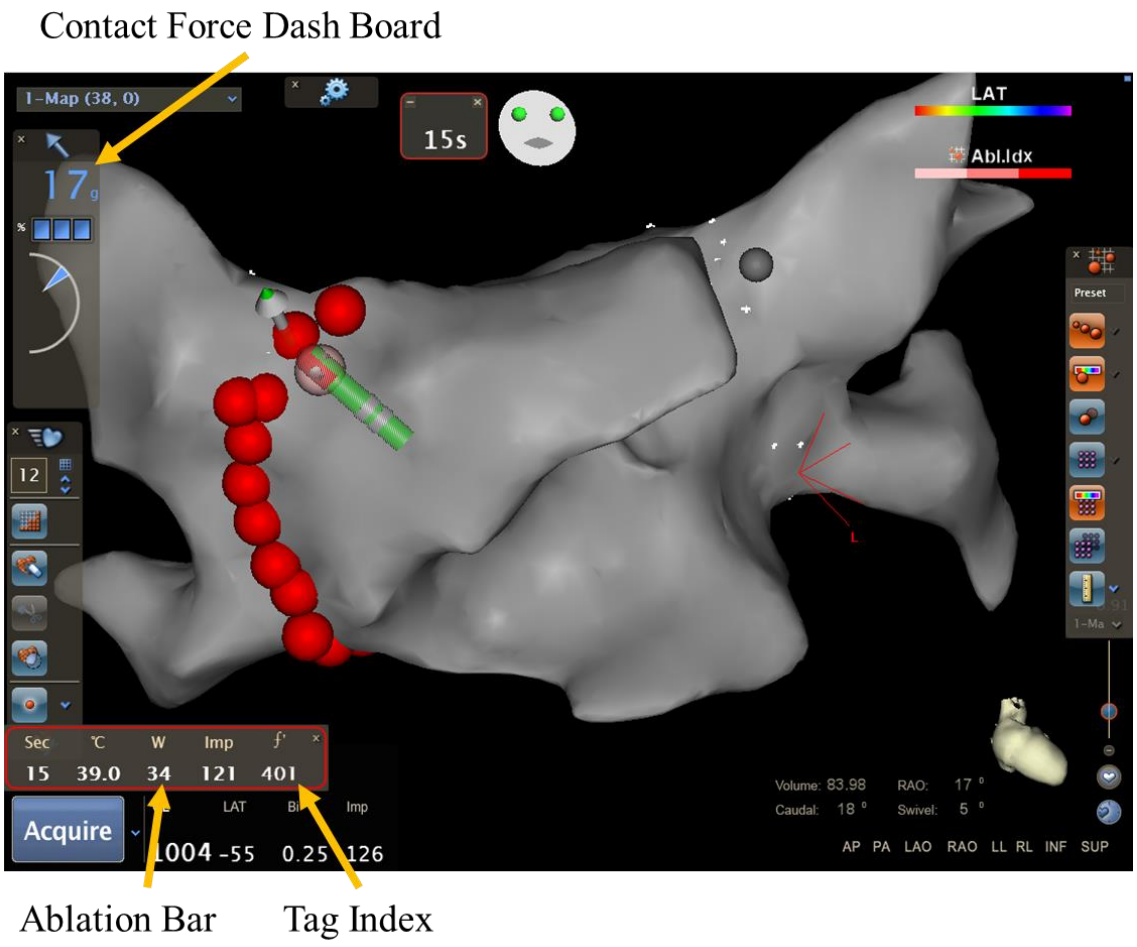
AE: Ablation Efficiency
P: RF Power
t: Application Time
k, a, b, c: user defined coefficients

It is hypothesized that the ablation volume (i.e., formula in parenthesis) correlates with the applied radiofrequency (RF) Power (***P***) and Application Time (***t***), which represents the amount of thermal flux created to produce a cardiac lesion during ablation. Ablation Efficiency (***AE***) reflects the amount of RF Power (***P***) that is transferred to the cardiac tissue. The Exponent coefficient (***c)*** (outside the parenthesis) is anticipated to provide a single dimension of the lesion volume.

By giving a different weight to the power, force, and time parameters the calculated Tag Index value results in a single index number that is cumulative over the time of the RF application. The Tag Index value is not intended to indicate the effectiveness of RF energy application and is not intended to replace current practice of clinical judgment. It is intended to provide the operator with a reproducible RF application strategy, that is more uniform at specified anatomical location of the LA.

During an RF application, the CARTO 3 system displays the contact force dash board and the ablation bar (refer to figure 1-2 below). The Ablation Bar displays the cumulative Tag Index value next to the clinically accepted endpoints for RF applications (e.g. time, temperature, power changes, impedance changes and CF). The Tag Index values are calculated in the EPU and communicated to the CARTO Screen for display.

Figure 1-2: CARTO GUI with Contact Force dash board and CARTO Ablation Bar



1.8 VISITAG SURPOINT™ EPU Description

The EPU is an external hardware designed to perform Tag Index calculations. The EPU receives ablation data (power, contact force, and duration) from the CARTO® 3 System, computes the Tag Index values, and then returns the computed results for display in the CARTO® 3 System. A picture of the EPU is provided in Figure 1.

Figure 1-3: VISITAG SURPOINT™ EPU with Attached Docking Plate

1.8.1 VISITAG SURPOINT™ EPU indication for Use

The VISITAG SURPOINT™ EPU is intended to perform Tag Index calculations combining parameters of power, contact force, and duration during electrophysiology procedures. The EPU is intended for use with the CARTO® 3 System (software version 6.0.60 or higher) with the CARTO VISITAG™ Module and the VISITAG SURPOINT™ Module installed.

Equivalent Tag index values do not represent equivalentRF lesion size. The clinical utility of Tag Index value has not been evaluated. For information on the application of RF energy, refer to the instructions for use for the ablation catheter.

The VISITAG SURPOINT™ EPU is intended for use with a compatible contact force sensing catheter including the THERMOCOOL SMARTTOUCH® or THERMOCOOL SMARTTOUCH® SF Catheter.

1.8.2 Principles of Operation

The EPU is an external processing unit connected to the CARTO® 3 System Workstation through a USB cable. The EPU receives ablation data from the CARTO® 3 System Workstation, namely data streams of ablation power, contact force, and duration. The EPU operates automatically whenever the CARTO® 3 System Workstation is on, provided that

the VISITAG SURPOINT™ Module has been installed and activated. During an AF ablation procedure conducted with the VISITAG SURPOINT™ Module, data automatically flows to and from the EPU. Upon request from the VISITAG SURPOINT™ Module, the EPU will calculate the Tag Index value according to a pre-installed Tag Index formula. The calculated results are sent back to the CARTO® 3 System Workstation to be displayed for the user.

2. STUDY OBJECTIVE

The purpose of this study is to assess the safety and 12-month effectiveness of Tag Index-guided ablation using the THERMOCOOL SMARTTOUCH® SF (STSF) and the THERMOCOOL SMARTTOUCH® (ST) Catheters with VISITAG SURPOINT™ Module with External Processing Unit(EPU) for pulmonary vein isolation in the treatment of drug refractory symptomatic paroxysmal atrial fibrillation.

3. STUDY DESIGN

The SURPOINT COA study is a prospective, multicenter, non-randomized post-market clinical evaluation of the VISITAG SURPOINT™ Module with EPU when used with the STSF/ST catheters in treating subjects with symptomatic PAF who have failed at least one antiarrhythmic drug. A total of 330 subjects will be enrolled at up to 45 sites. Two hundred eighty (280) enrolled subjects will be treated using the STSF catheter with EPU and fifty (50) subjects will be treated with ST catheter. Prior to enrollment, a few sites will be selected to only enroll subjects who will be treated with the ST catheter and the remaining sites will only enroll subjects who will be treated with the STSF catheter. Effectiveness and safety endpoints have been defined, and will be compared to predetermined performance goals. Subjects who sign the SURPOINT COA informed consent are considered enrolled in the study. Enrolled subjects who satisfy all eligibility criteria will then undergo the ablation procedure with the catheter and VISITAG SURPOINT™ Module. After the study ablation procedure, subjects will enter a 3-Month blanking period (Day 0-90).

After the Blanking Period, subjects will enter the Evaluation Period (Days 91-365). 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 SURPOINT COA study after the 12-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. Symptomatic paroxysmal AF who had at least one AF episode electrocardiographically documented within one (1) year prior to enrollment. Documentation may include electrocardiogram (ECG); Transtelephonic monitoring (TTM), Holter monitor or telemetry strip.

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. Previous surgical or catheter ablation for atrial fibrillation
2. Previous cardiac surgery (including CABG) within the past 6 months (180 days)
3. Valvular cardiac surgical/percutaneous procedure (i.e., ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve)
4. Any carotid stenting or endarterectomy
5. Documented LA thrombus on imaging
6. LA size > 50 mm on imaging
7. LVEF < 40%
8. Contraindication to anticoagulation (heparin or warfarin)
9. History of blood clotting or bleeding abnormalities
10. PCI/MI within the past 2 months (60 days)
11. Documented thromboembolic event (including TIA) within the past 12 months (365 days)
12. Rheumatic Heart Disease
13. Uncontrolled heart failure or NYHA function class III or IV
14. Severe mitral regurgitation (Regurgitant volume ≥ 60 mL/beat, Regurgitant fraction ≥ 50%, and/or Effective regurgitant orifice area ≥ 0.40cm2)
15. Awaiting cardiac transplantation or other cardiac surgery within the next 12 months (365 days)
16. Unstable angina
17. Acute illness or active systemic infection or sepsis
18. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
19. Presence of implanted ICD/CRT-D.
20. 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.

21. Gastroesophageal Reflux Disease (GERD; active requiring significant intervention not including OTC medication)
22. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study.
23. Women who are pregnant (as evidenced by pregnancy test if pre-menopausal)
24. Concurrent enrollment in an investigational study evaluating another device, biologic, or drug.
25. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes vascular access, or manipulation of the catheter.
26. Life expectancy less than 12 months

3.2 Subject Disposition

- **Enrolled Subjects**: subjects who sign the informed consent.
- **Excluded Subjects:** subjects who do not have the STSF/ST catheter inserted or have the STSF/ST catheter inserted but do not undergo ablation with VISITAG SURPOINT™ Module. Subjects who have the STSF/ST catheter inserted but do not undergo ablation with VISITAG SURPOINT™ Module will be followed for 12-months.
- **Lost to Follow-up Subjects:** subjects who are enrolled and have STSF/ST catheter inserted and undergo ablation with VISITAG SURPOINT™ Module, 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 12-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. STUDY ENDPOINTS

4.1 Primary Endpoints

4.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is defined as the freedom from documented (Symptomatic and asymptomatic) atrial fibrillation, atrial flutter and atrial tachycardia (AF/AFL/AT) (hereinafter collectively referred to as "atrial tachyarrhythmias") recurrence (episodes ≥ 30 secs on TTM or continuously recorded on the standard 12-leads ECG or 24 Hour Holter monitoring) during the evaluation period (Day 91-365) and freedom from the following failure modes:

- Acute procedural failure, including:
  - Failure to confirm entrance block in all pulmonary veins post-procedure,
- Repeat ablation failure, including:
  - > 1 repeat ablation procedures during the 3-Month Blanking Period (Day 0-90) after the index ablation procedure.
  - Any repeat ablation procedure during the Evaluation Period.
- DC cardioversion for AF/AFL/AT following the 3-month blanking period
- Surgical treatment for AF/AFL/AT after the index ablation procedure.
- AAD failure: Taking a new AAD, a previously failed AAD at a greater than the highest ineffective historical dose or starting an AAD for AF during the evaluation period (refer to section 5.14 for details).

In summary, effectiveness success is defined as freedom from atrial tachyarrhthmia during the Evaluation Period, off or on a previously failed AAD, and not exceeding 1 repeat ablation procedures for an atrial tachyarrhthmia during the 3-Month Blanking Period.

This study is designed to compare the primary effectiveness of the VISITAG SURPOINT™ Module with EPU to a pre-determined performance goal of 50%, which is indicated as the minimum acceptable success rate at 12 months for a paroxysmal AF population in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE consensus statement.

4.1.2 Primary Safety Endpoint

The primary safety endpoint is the incidence of any primary adverse event occurring within 7 days following an AF ablation procedure (including the initial and repeat procedures) using the STSF/ST catheter with the EPU per protocol, except atrio-esophageal fistula and PV stenosis, which may also be considered as primary adverse events if occurring greater than seven (7) days post the ablation procedure [49,50].

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 Insuffciency)
- Vagal Nerve Injury
- Pericarditis
- Major vascular access complication / bleeding

* 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 certified individuals.

4.2 Secondary Endpoints

4.2.1 Secondary Effectiveness Endpoints

- Acute Procedural Success
  - % of subjects with ipsilateral PVI (entrance block) at the end of the procedure
  - % of subjects with ipsilateral PV isolation (entrance block) after first encirclement (evaluated prior to the 30-minute waiting period and adenosine challenge)
  - % of touch-up (ablation of acute reconnection) among all targeted veins
  - Anatomical location of acute PV reconnection after first encirclement
- Repeat ablation procedures during 12-month period post-procedure
  - Incidence (%) of repeat ablation procedures
  - % PVs re-isolated among all of the targeted PVs at repeat procedure
  - % repeat ablation procedures requiring new linear lesions and/or identifying new foci outside of initially isolated area among the repeat ablation procedures

- 12-Month Single Procedure Success
    - The 12-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 and off AADs. Any repeat ablation procedure or AAD therapy will be deemed effectiveness failure for this analysis.

4.2.2 Secondary Safety Endpoints

- 12-Month PAE Rate: Cumulative incidence of primary adverse events occurring within seven (7) days following an AF ablation procedure using study catheters with EPU and any late onset atrio-esophageal fistula or PV stenosis through 12 months
- Incidence of Unanticipated Adverse Device Effects (UADEs)
- Incidence of Serious Adverse Events (SAEs) within 7 days (early onset), >7 to 30 days (peri-procedural) and >30 days (late onset) of initial ablation
- Incidence of bleeding complication (ISTH definitions): a) major, b) clinically relevant non-major and c) minor bleeding

Refer to section 6.3 for the definition of Serious Adverse Event. Refer to Appendix A: Study Definitions for the ISTH beeding complications definitions.

4.3 Additional Endpoints

No formal statistical hypothesis and inferential statistics will be formulated and performed for the additional endpoints.

- Procedural Data:
    - Total procedure time, PVI time, RF application time, mapping time and RF application time per lesion
    - Total Fluoroscopy Time/dose
    - Fluid delivered from the study catheter
    - Location of RF applications, number of RF applications
    - Repeat Ablation Rate
    - RF Ablation parameters per application (e.g. temperature, power, impedance, CF etc.)
    - Device(s) utilized (per ablation)
    - VISITAG™ Settings
    - CF range
    - Power range
    - Tag Index Assessment per anatomical region

NOTE: Tag 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 Tag Index.

- Quality of Life:
  - Quality of Life (QOL) status will be evaluated by assessing SF-12

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 effectiveness of the STSF/ST Catheter and the VISITAG SURPOINT™ module, 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-10 and procedure code, Diagnosis Related Group (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, any inpatient or outpatient visit (including ER admissions) to address post-procedural complications or any procedure related condition and any inpatient or outpatient visit (including ER admissions) related to arrhythmia and cardiovascular conditions.

5. 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 paroxysmal AF candidates for ablation for participation in the study, and to offer enrollment to all who meet preliminary eligibility criteria. Screening log will be maintained at the research sites.

Sponsor will attempt to include a diversified group of research sites engaging a variety of academic and private institutions geographically located throughout the US. 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. Prior to enrollment, a few sites will be selected to only enroll subjects who will be treated with the ST catheter and the remaining sites will only enroll subjects who will be treated with the STSF catheter.

Potential clinical sites and investigators will be screened on the following criteria:

- Experience and qualifications- Electrophysiologists with Catheter ablation experience, Previous clinical research study experience, performance and reporting,
- Previous experience with hosting and responding to FDA inspections and sponsor audits and their outcomes if applicable
- Study specific: THERMOCOOL SMARTTOUCH® and THERMOCOOL SMARTTOUCH® SF catheter use and past experience, VISITAG module experience

- Patient population: number of patients with Paroxysmal atrial fibrillation, monthly PAF ablation volume.
- Time and resources to commit to the study- Number of ongoing PAF trails, Number of other studies being conducted, number of dedicated study coordinators, number of operators (EPs performing catheter ablation at a site), number of research managers.
- Previous experience with the site enrollment, if any
- Assess if potential Investigators are disqualified, debarred or restricted from performing research by regulatory bodies and/or health authorities.
- Assess financial conflict of interest assessment for investigators and sites
- Certifications and training- GCP, HIPAA, Safe harbor, use of human subjects for research
- IRB processes:
    - Is the site using a central or local IRB?
    - Average turnaround time for full IRB approval?
- Facilities: Esophageal temperature monitoring, equipped to handle emergency situation
- Geographic location: to ensure generalizability

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 reasonable 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.[5757] In order to ensure that an appropriate gender ratio is maintained at our sites the sponsor may choose to do the following:

- Target investigational sites where recruitment of needed populations can be more easily facilitated (e.g., women's clinics).
- Alternative communication strategies for study recruitment to reach women through social media ads, study related flyers and brochures may be done.
- The sites will maintain screening logs that can be evaluated to ensure appropriate enrollment of women.
- The investigational sites will be encouraged to increase recruitment by communicating the study information with primary care and family practitioners.
- The subjects may be provided compensation to cover transportation costs and child care costs.

- The investigational sites will be encouraged to consider flexibility in follow-up visit scheduling to match subjects' schedules, which may include evenings and weekends, as long as the visits fall within visit window.
- The sponsor will ensure collection, analysis and reporting of gender demographics in interim post-approval study status reports and clinical study reports.

5.1 Patient Screening

All patients considered for RF ablation procedure for drug refractory recurrent symptomatic PAF 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 within 48 hours of ablation procedure. The following are allowable imaging modalities:
    - TEE
    - CT/MRI
    - Intracardiac Echocardography (ICE)
- Pregnancy Test – Pre-menopausal women only, performed within 24 hours prior to the procedure.
- New York Heart Association (NYHA) Classification
- Electrocardiogram (12-Lead ECG)
- Baseline medical history
- 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; SF-12 Health Survey

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.
- CARTO® Respiratory Gating Mandatory (unless using Jet Ventilation)
- Introduction of the STSF/ST 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 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**.

Power reduction data and clinical practice associated with posterior wall RF applications will be collected in the CRFs and CARTO® data files for analysis.

NOTE 1: The recommendations provided are based on data obtained from animal and clinical studies. Use clinical judgment when using this catheter paying careful attention to impedance drop, electrogram reduction, time of RF application, and with consideration of individual subject conditions when selecting settings.

NOTE 2: Power and contact force should both be reduced when creating RF lesions on the posterior wall of the left atrium.

NOTE 3: Reduce Power when high contact forces are observed during creation of RF lesions in the left atrium. For CF ≥ 20g power should be ≤ 35 watts.

5.6 Recommended RF Power:

- A RF power range of 15-45 Watts (W) is recommended for atrial ablation.[7-10]
- Do not rely on the catheter tip temperature response to guide ablation. If the temperature increases rapidly, stop RF application immediately.
- At anatomical locations **other than** the LA posterior wall or CS:
  - Maximum power should not exceed 45 W, and

  - Duration of ablation should not exceed 60 seconds of continuous ablation at a given location.

- RF energy delivery can be interrupted at any time when there is a safety concern (e.g., esophageal temperature rise, pain during conscious sedation, and steam pop).
- LA posterior wall close to the esophagus:
  - Start ablation at ≤ 25 W.
  - Move/drag the catheter to a new location if clinically effective ablation is not achieved within 20 seconds, as denoted by EGM reduction and/or impedance drop.
  - Power can be increased if clinically effective ablation isn't achieved within 20 seconds, as demonstrated by absence of EGM reduction and/or impedance drop). Maximum power used SHOULD NOT exceed 35 W.
  - RF energy delivery can be interrupted at any time when there is a safety concern (e.g., esophageal temperature rise, pain during conscious sedation, and steam pop).
- 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.
- Power reduction data and clinical practice associated with posterior wall RF applications will be collected in the CRFs and CARTO® data files for analysis.

5.7 Contact Force (CF) Settings

Operators should select individualized CF target ranges based on their case experience and the prior results from the THERMOCOOL SMARTTOUCH® SF catheter IDE trial.[24]

- Contact Force settings:
  - Contact Force Target range: 5-25 gram (recommended)
  - Minimum CF of 3-5 grams
- Risk of cardiac tamponade and perforation may correlate with higher CF (≥ 40 g) used during RF ablation.
  - For CF ≥ 20g, power should be ≤ 35 watts.
- Contact force data and individual procedure working ranges will be collected for each RF application during a study ablation procedure for offline analysis.

5.8 VISITAG™ Settings

- Stability Settings:
  - Range: 2-3 mm
  - Time: 3-5 seconds

- Filter (FOT) Settings:
    - If an FOT filter is desired, the percentage of time of the chosen gram force should be 25%.
- Tag size – 3mm
- Maximum Inter tag distance 6mm

5.9 VISITAG SURPOINT™ Tag Index Targets

VISITAG SURPOINT™ Module Tag Index target values for specified anatomical locations:

- Anterior, Ridge, Roof segments - target value: 550
- Posterior and inferior segments - target value: 380

NOTE 1: All Tag Index target values, especially the posterior wall, are in the absence of safety concerns (i.e. no temperature rise from esophageal probe, pain during conscious sedation or steam pop, etc). In the absence of safety concerns, achieveing target Tag Index values will be the endpoint of RF energy application.

NOTE 2: If for safety reasons the ablation needs to be stopped prior to reaching the Tag Index target value, please do so and document accordingly with associated VISITAG™ location number.

NOTE 3: Increases in power and force from previous workflow to hit a specific Tag Index target with a shorter procedure time is not recommended

5.10 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) is not recommended
- Ablation of non-PV triggers induced by adenosine or isoproterenol

NOTE 4: Tag Index target values for non-PV targets are not provided. The operator should follow the catheter IFU, use clinical judgment and their standard of care while ablating non-PV targets.

Prophylactic ablation of empirical sites is not allowed.

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

5.11 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.

5.12 Post Procedure Assessments

- Before hospital discharge:
    - Occurrence of arrhythmias, if any
    - Electrocardiogram (12-Lead ECG)
    - 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)**
  - Medical History – any change from previous
  - Occurrence of arrhythmias, if any
  - Cardiac-related concomitant medications (such as AADs, anticoagulation regimen, etc.)
  - 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 1-Month (+/-7days)**:
  - Medical history- any change from previous
  - Physical Exam including standardized neurological assessment and cardiovascular/ pulmonary examination.
  - Occurrence of arrhythmias, if any
  - Electrocardiogram (12-Lead ECG)
  - Concomitant medications only cardiac related (AADs, anticoagulation regimen, etc.)
  - TTM Monitor (refer to section 5.16 for transmission schedules)
  - 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 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

- **Follow-up measurements at, 3-Month (+/- 7 days), 6 (+/-14 days), 12-Month (+/- 28 days) and Unscheduled Clinic Visits**:
  - Medical History – any change from previousOccurrence of arrhythmias, if any
  - Occurrence of arrhythmias, if any
  - Electrocardiogram (12-Lead ECG)
  - QOL Assessments (SF-12 Health Survey) (Only collected at 3, 6 and 12 months visit)
  - TTM Monitor (refer to section 5.16 for transmission schedules)
  - 24 hour Holter monitoring (12-month visit)
  - 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)
  - 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 – Subject completion/discontinuation form (12-Month or last completed visit)

  Note: For follow-up visit schedules defined in this protocol, 1 month = 30 days, 1 week =7 days.

5.13 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				Phone Call	Follow-Up Visits				
	Screening / Baseline		Ablation Procedure[1]	Discharge	7-9 Days	1 Month +/- 1 wks	3 Month +/- 1 wks	6 Month +/- 2 wks	12 Month +/- 4 wks	Unscheduled Visit
Visit no.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Informed consent[1]	X									
Inclusion & exclusion criteria	X									
Demographics	X									
Medical history	X				X[10]	X[10]	X[10]	X[10]	X[10]	X[10]
Physical Exam						X				
Arrhythmias	X [history]			X	X	X	X	X	X	X
ECG		X		X		X	X	X	X	X
NYHA		X								
QOL assessment[2]		X					X	X	X	
Pregnancy test[3]		X								
LA thrombus Imaging[4]			X[4]							
TTE[5,13]		X[5]		X[13]						
Ablation assessments			X							
Device deficiency			X							
Concomitant medications[6]		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]
Adverse events[8,9]	X	X	X	X	X	X	X	X	X	X

	Pre-Procedure				Phone Call	Follow-Up Visits				
	Screening / Baseline		Ablation Procedure[1]	Discharge	7-9 Days	1 Month +/- 1 wks	3 Month +/- 1 wks	6 Month +/- 2 wks	12 Month +/- 4 wks	Unscheduled Visit
Visit no.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
TTM monitoring[11]						X[11]	X[11]	X[11]	X[11]	
24 Hour Holter									X	
PV stenosis imaging assessment[12]					X[12]	X[12]	X[12]	X[12]	X[12]	X[12]
Subject Completion/ discontinuation form									X[14]	

[1] Initial ablation procedure should be done within 30 days of consent.
[2] Quality of life tools (SF-12 Health Survey)
[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 to confirm no changes in medical history since last visit
[11] TTM: all symptomatic cardiac episodes should be recorded and transmitted at the time the event occurs. Asymptomatic transmissions should be recorded as scheduled (weekly: months 2-5 and monthly: months 6, 7, 8, 9, 10, 11, 12) and transmitted to the Core Lab. Refer to section 5.16.
[12] PV imaging (CT/MRI) for subjects who have symptoms suggestive of PV stenosis
[13] Subjects who develop symptoms suggestive of pericardial effusion and/or pericarditis should undergo a transthoracic echocardiogram (TTE) to assess the pericardium
[14] 12-month visit or last completed visit

5.14 Study Medications

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

5.14.1 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**: 12 mg to 24 mg 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 2017 HRS/EHRA/ECAS/APHRS/SOLAECE 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 3-5 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 thromo-embolism. Systemic oral anticoagulation is strongly encouraged to be continued beyond 2 months post ablation in subjects with $CHADS_2$ score > 1.

5.15 Antiarrhythmic Drug (AAD) Management

5.15.1 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.

5.16 Heart Rhythm Monitoring

ECG, Transtelephonic monitors (TTM) and 24 Hour Holter Monitoring will be used to monitor the subjects' heart rhythm post-treatment.

Electrocardiogram (12-lead ECG):

ECG device will be provided to each site. Sites will be instructed to record and transmit for every subject per the schedule of treatment and evaluations summarized in Table 5-1.

Transtelephonic Monitors (TTM):

Transtelephonic monitors (TTM) will be provided to each subject at the 1-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 last 2 months of the blanking period and the Evaluation Period (Day 91-365).

The TTM transmission schedule:

- Each subject will be provided with a TTM device at the 1-month visit.
- Subjects will complete a test transmission upon receipt of the TTM device to demonstrate a working understanding of the device.
- The TTM schedule will include 2 months of TTMs during the blanking period. At the 1-month office visit or during discharge, subjects will be provided a TTM for event monitoring during the follow-up period. The first transmission will be at the 1- month office visit. TTM schedule will be every week for months 2, 3, 4 and 5 . After the weekly transmissions, subjects will be asked to record and transmit a minimum of 1 transmission (60 seconds) per month until the effectiveness

assessment period is completed (12 months post index procedure). In addition, subjects will also be asked to transmit any symptom-triggered episode that occurs during the 12-month follow-up period.

Months (post-procedure)	TTM schedule (asymptomatic)
Month 2, 3, 4, 5	1 per week
Month 6, 7, 8, 9, 10, 11, 12	1 per month

- All symptomatic cardiac episodes should be recorded and transmitted soon after the event occurs. A core lab will be used to evaluate and assess the TTM tracings.

Holter Monitoring:

- A 24 Hour Holter will be used at the 12 month follow-up visit to monitor the subjects' heart rhythm. A core lab will be utilized to evaluate and assess the 24-hour Holter recordings.

5.17 Study Equipment

5.17.1 Required Catheters and Equipment

The following devices are required for the AF ablation procedure during this study:

Table 5-2 Required Study Equipment

Equipment	Function or Specifics
VISITAG SURPOINT™ Module Activation Kit (KT5400163)	Activiation of Software that the EPU uses to compute Tag Index values and communicate with the CARTO 3 System
VISITAG SURPOINT™ External Processing Unit (EPU) (D-1608-01)	EPU is a device that receives ablation data from the CARTO® 3 System Workstation (power, contact force, and duration), computes Tag Index values, and then returns the computed results for display in the CARTO® 3 System
Approved Catheter(s) • THERMOCOOL SMARTTOUCH® Catheter: ○ Uni-directional Catheter Description (D-1336-OX-S) ○ Bi-directional Catheter Description (D-1327-OX-S) • THERMOCOOL SMARTTOUCH® SF Catheter: ○ Uni-directional Catheter Description (D-1347-XX-S) ○ Bi-directional Catheter Description (D-1348-XX-S)	Used to map, navigate, and deliver RF energy to the target tissue while providing the contact force measurement feedback.
SMARTABLATE RF Generator	Transmits radiofrequency energy to the THERMOCOOL SMARTTOUCH® SF and THERMOCOOL SMARTTOUCH® Mapping & Ablation Catheters
CARTO® 3 V 6.0 System	For mapping and visualization information. Version 6.0.54.x or higher

5.17.2 Recommendation for Irrigation Pump Setting and RF Power Delivery

The Irrigation Pump will deliver a continuous infusion of 2 ml/min of room temperature heparinized saline (1 u heparin/1 ml saline) when not delivering RF current. Operators should increase the irrigation to high flow rate starting up to 5 seconds before the onset of RF energy delivery and maintain this higher flow rate until 5 seconds after termination of the energy application. For THERMOCOOL SMARTTOUCH®SF Catheter, for power levels up to 30 W, a high flow rate of 8 ml/min should be used. For power levels between 31 and 45 W, a high flow rate of 15 ml/min should be used. Do not use this catheter without irrigation flow. For THERMOCOOL SMARTTOUCH® Catheter, for power levels up to 30 W, a high flow rate of 17 ml/min should be used. For power levels between 31 and 45 W, a high flow rate of 30 ml/min should be used.

Treatment of AF: It is recommended that power not exceed 45 W and 35 W if the catheter is perpendicular to the tissue. Refer to the IFU Summary of Clinical Studies for lesion recommendations.

Table 5-3 Recommended RF Energy Delivery Parameters

Power*	Irrigation Flow Rate
Maintenance Flow	**2 ml/min**
≤ 30 W	**8 ml/min**
31-45 W	**15 ml/min**

* Reduce power at start of ablation. Power titration should be used for all applications of RF to achieve the desired result. Refer to the IFU or THERMOCOOL SMARTTOUCH® SF AND THERMOCOOL SMARTTOUCH® training slides for usage of catheters.

5.17.3 Investigator Training

SMARTTOUCH SF Catheter Training:

Investigators selected to participate in the study will be skilled in intracardiac mapping and AF ablation with THERMOCOOL SMARTTOUCH® and THERMOCOOL SMARTTOUCH® SF catheters (>20 cases). They will provide 5 Retrospective PAF cases with segmented VISITAG™ (9 regions) with their standard workflow. Investigators will undergo device training in accordance with the documented physician training plan.

VISITAG SURPOINT™ Module:

The purpose of the individual training process is to identify the Tag index value which best represents the physician's ablation strategy, per anatomical ablation segment.

- The process:
  - Is individual,
  - Maintains the physician's ablation strategy – catheter, force, power, time, etc.
  - Optimizes the system settings to have exactly one tag per RF application and location,
  - displaying the tag as early as possible, emphasizing on catheter tip stability.
  - Requires at least 5 retrospective cases, blinded to the Tag Index
  - Provides descriptive statistical analysis of Tag Index values, per segment.
  - Ends with the physician selecting his/hers own Tag index values.
- Based on literature review, we recommend the following Tag Index target Values:
  - 380 on the posterior and inferior
  - 550 on the anterior, roof and ridge

FIGURE 5.17.3A: An example of retrospective analysis:

Anatomical Segment Locations VISITAG SURPOINT Tag Index Values

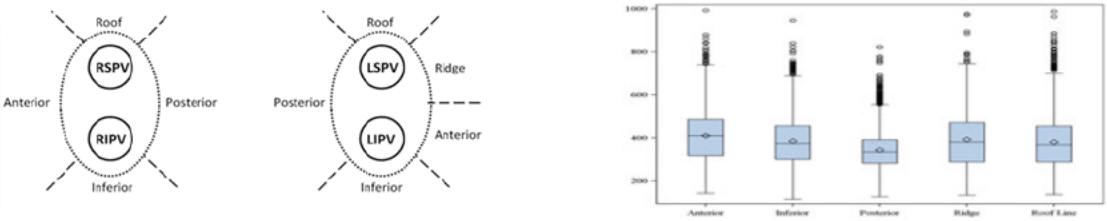


TABLE 5-5: An Example of Retrospective VISITAG SURPOINT Tag Index Values

Segment	Posterior	Inferior	Anterior	Roof	Ridge
Count	47	23	23	21	6
Mean	**244**	**278**	**351**	**307**	**385**
StdDev	56	55	73	89	100
Min	155	181	231	155	188
Median	246	280	350	310	423
Max	356	359	501	464	468
Q1	196	235	293	258	381
Q3	288	324	409	369	428

5.18 Repeat AF Ablation Procedures

Repeat AF ablations(s) may be performed at the discretion of the physician. 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:

- Imaging for detection of LA thrombus – performed within 48 hours prior to the procedure (refer to Section 5.3 for details).
- Pregnancy Test – Pre-menopausal women only, performed within 24 hours prior to the procedure.

5.19 Core Laboratory

A core laboratory will be used for objective evaluation of the TTMs and 24 Hr Holter 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. 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 or not 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 are 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 STSF/ST catheter and VISITAG SURPOINT™ module with EPU, except atrio-esophageal fistula and PV stenosis, which may also be considered as primary adverse events if occurring greater than seven (7) days post the ablation procedure [49,50].

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: • 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

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Stroke[56] / Cerebrovascular Accident	Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. Duration of a focal or global neurological deficit ≥24 h; or <24 h, if therapeutic intervention(s) were performed (e.g. thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; or the neurological deficit results in death. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences)† Confirmation of the diagnosis by at least one of the following: • Neurology or neurosurgical specialist • Neuroimaging procedure (MR or CT scan or cerebral angiography) • Lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage) Stroke: (diagnosis as above, preferably with positive neuroimaging study) • Minor—Modified Rankin score <2 at 30 and 90 days†† • Major—Modified Rankin score ≥2 at 30 and 90 days
Thromboembolism	Formation of a clot (thrombus) inside a blood vessel causing obstruction to blood flow. The thrombus can migrate (embolus) and obstruct distal vascular sites. Diagnostic tests to help detect thromboembolisms may include but are not limited to angiography (pulmonary or distal), ventilation-perfusion (V/Q) scans, venography, Doppler ultrasonography, spiral CT, and echocardiography.
Transient Ischemic Attack[56]	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24h. Neuroimaging without tissue injury.
Phrenic Nerve Injury / Diaphragmatic Paralysis	Absent phrenic nerve function as assessed by a sniff test. A phrenic nerve paralysis is considered to be permanent when it is documented to be present 12 months or longer following ablation.
Pneumothorax	Introduction of air into the intrapleural cavity necessitating chest tube placement or surgical intervention.

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: • Pneumonia – infiltrate, fever and leukocytosis • Acute Respiratory Distress Syndrome
Vagal Nerve Injury	Injury to the vagal nerve that results in esophageal dysmotility or gastroparesis. Vagal nerve injury is considered to be a major complication if it prolongs hospitalization, requires hospitalization, or results in ongoing symptoms for more than 30 days following an ablation procedure.
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	**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. **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.

* 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 certified individuals.

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 (NSAEs)

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.	Typical Atrial flutter
19.	Atypical left atrial flutter
20.	Atypical right atrial flutter
21.	AV fistula
22.	Bleeding complications
23.	Bleeding requiring transfusion
24.	Cardiac arrest
25.	Cardiac perforation
26.	Tamponade
27.	Cardiac thrombo-embolism
28.	Cerebro-vascular accident (CVA) / stroke
29.	Chest pain/discomfort
30.	Complete heart block, temporary or permanent
31.	Conduction block: ongoing / resolved
32.	Congestive Heart Failure
33.	Coronary artery dissection
34.	Coronary artery occlusion
35.	Coronary artery spasm
36.	Coronary artery Thrombosis
37.	Death
38.	Deep venous thrombosis
39.	Dislodgement of ICD (Implantable Cardioverter Defibrillator)
40.	Dislodgement of permanent pacing leads
41.	Disseminated Intravascular Coagulation
42.	Dyspnoea

Anticipated Adverse Events	
43.	Endocarditis
44.	Epistaxis
45.	Esophageal perforation
46.	Expressive aphasia
47.	Fainting
48.	Fatigue
49.	Gastro-intestinal NOS
50.	Gastric reflux
51.	Nausea
52.	Gastrointestinal diverticulosis
53.	Heart Failure
54.	Hematoma (local) /ecchymosis
55.	Hemorrhage
56.	Hemothorax
57.	High / increased creatine phosphokinase (CPK)
58.	Hypotension
59.	Hypertension
60.	Hypoxia
61.	Infection, localized
62.	Infection, systemic
63.	Laceration
64.	Leakage of air or blood into the lungs or other organs due to perforation
65.	Liver toxicity
66.	Mobile strands in Inferior Vena Cava
67.	Myocardial Infarction
68.	Neurological disorders (tremor)
69.	Neurological disorders (poor coordination)
70.	Neurological disorders (headache)
71.	Obstruction to the vascular system
72.	Perforation of the vascular system
73.	Damage to the vascular system
74.	Pericardial effusion resulting in tamponade
75.	Pericardial effusion without tamponade
76.	Pericarditis
77.	Peripheral embolus
78.	Peripheral nerve injury
79.	Peripheral thromboembolism
80.	Phlebitis
81.	Phrenic nerve damage
82.	Diaphragmatic paralysis
83.	Pleural effusion
84.	Acute Respiratory Distress Syndrome (ARDS)

Anticipated Adverse Events	
85.	Pneumothorax
86.	Pseudoaneurysm
87.	Pulmonary edema
88.	Heart failure
89.	Pulmonary embolism
90.	Pulmonary hypertension
91.	Pulmonary toxicity, like acute pulmonary syndrome
92.	Pulmonary vein dissection
93.	Pulmonary vein Stenosis
94.	Pulmonary vein thrombus
95.	Pump failure
96.	Renal failure
97.	Respiratory depression
98.	Respiratory failure
99.	Retroperitoneal hematoma
100.	Rhabdomyolysis, including produced by body position or propofol
101.	Sedation induced CO2 retention with lethargy and cholecystitis
102.	Seizure
103.	Sepsis
104.	Skin burns (due to cardioversion, tape, etc)
105.	Skin discoloration
106.	Skin injury / muscle or connective tissue injury due to body position, electrical cardioversion
107.	Skin rash
108.	Thrombocytopenia
109.	Thromboembolism
110.	Thrombosis
111.	Thyroid disorders
112.	Transient extremity numbness
113.	Extremity numbness
114.	Transient ischemic attack (TIA)
115.	Unintended complete or incomplete AV, Sinus node, or other heart block or damage
116.	Urinary retention
117.	Urinary tract infection
118.	Urinary tract injury or infection related to the urinary catheter
119.	Vagal Nerve injury
120.	Valvular damage/insufficiency
121.	Vasovagal reactions
122.	Vision change
123.	Volume overload
124.	Worsening obstructive, restrictive, or other form of pulmonary disease
125.	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 study 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 serious AEs, 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 Primary AEs, Serious AEs, UADE/SADE/USADE, and Study device failure/malfunction/deficiency immediately upon their awareness of the event as soon as possible but no longer than 72 hours* from when the study site becomes aware of SAEs and UADEs. For all other non-serious Adverse Events, the Study Site has 2 weeks from when the study site becomes aware to inform the Johnson and Johnson Study Sponsor. Failure to report any event requiring expedited reporting within this interval will be classified as a protocol deviation.

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 dos 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

Recovered/ Resolved without Sequelae	Subject fully recovered with no observable residual effects.
Recovering/ Resolving	Subject has not fully recovered
Recovered/ Resolved with Sequelae	Subject recovered with observable residual effects.
Ongoing/ Not recovered	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.
Unknown	The outcome of the adverse event is unknown

6.11 Causality

Cause of AEs is defined as follows:

Table 6-5 Adverse Event Causality Classifications

Device Relationship	
Definitely Device-Related	The VISITAG SURPOINT™ Module when used with THERMOCOOL SMARTTOUCH® SF or THERMOCOOL SMARTTOUCH® catheter directly caused or contributed to the AE.
Possibly Device-Related	The VISITAG SURPOINT™ Module when used with THERMOCOOL SMARTTOUCH® SF or THERMOCOOL SMARTTOUCH® catheter may have caused or contributed to the AE.
Not Device-Related	The AE is not associated with the THERMOCOOL SMARTTOUCH® SF or THERMOCOOL SMARTTOUCH® catheter and VISITAG SURPOINT™ Module.
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 Clinical Events Committee (CEC)

Primary Adverse Events and Serious Adverse Events of cardiac origin occurring throughout the study period (1-year) will be reviewed by Biosense Webster clinical staff with Medical Safety Officer or designee, and submitted to the independent Clinical Events Committee (CEC) for review.

7. STATISTICAL ANALYSIS METHODS

7.1 Study Design

The SURPOINT COA study is a prospective, multicenter, non-randomized clinical evaluation of the VISITAG SURPOINT™ Module with EPU when used with the STSF and ST catheters in treating subjects with symptomatic PAF who have failed at least one antiarrhythmic drug. A maximum of 330 subjects will be enrolled at up to 45 sites. Two hundred eighty (280) subjects will be treated using the STSF catheter with EPU and 50 subjects will be treated using the ST catheter with EPU. Prior to enrollment, a few sites will be selected to only enroll subjects who will be treated with the ST catheter and the remaining sites will only enroll subjects who will be treated with the STSF catheter. Two interim analyses are planned to take place after all subjects who are treated using STSF catheter with EPU have completed their 3-month and 6-month follow-up visits for the evaluation of early success. The planned interim analysis will be based on data collected only in the subjects who are treated using STSF catheter with EPU. The final analysis of the primary effectiveness and safety endpoints will be based on all subjects's full 12-month follow-up data. Effectiveness and safety endpoints defined in association with the primary study objectives will be compared to the predetermined performance goals.

Enrolled subjects who satisfy all eligibility criteria will then undergo the ablation procedure with the catheter and VISITAG SURPOINT™ Module. After the study ablation procedure, subjects will enter a 3-Month blanking period (Day 0-90). After the Blanking Period, subjects will enter the Evaluation Period (Days 91-365). Subjects having AF recurrence and/or receiving therapeutic interventions during the evaluation period will be considered effectiveness failures.

All subjects will undergo follow up visits at defined intervals (refer to Table 5-1 Schedule of Treatments and Evaluations in protocol). Subjects complete the SURPOINT COA study after the 12-month follow up visit.

7.2 Treatment Assignment

This is a single-arm study. The only treatment assigned is the THERMOCOOL SMARTTOUCH® SF (STSF) and THERMOCOOL SMARTTOUCH® (ST) catheters using VISITAG SURPOINT™ Module with External Processing Unit (EPU).

7.3 Randomization and Blinding Procedures

This study is a non-randomized single-arm study. An independent group will perform the Bayesian interim analyses. The sponsor is not blinded to individual or aggregated data.

7.4 Interval Windows

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

7.5 Primary and Secondary Endpoint(s) and Associated Hypotheses

7.5.1 Primary Endpoints and Associated Hypotheses

7.5.1.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint of this study is the effectiveness success rate at Month 12, defined as the proportion of subjects who are freedom from documented (symptomatic and asymptomatic) atrial fibrillation, atrial flutter and atrial tachycardia (AF/AFL/AT) (hereinafter collectively referred to as “atrial tachyarrhythmias") recurrence (episodes ≥ 30 secs on TTM or continuously recorded on the standard 12-leads ECG or holter) during the evaluation period (Day 91-365) and freedom from the following failure modes:

- Acute procedural failure, including:
  - Failure to confirm entrance block in all pulmonary veins at the end of procedure
- Repeat ablation failure, including:
  - > 1 repeat ablation procedures during the 3-Month Blanking Period (Day 0-90) after the index ablation procedure.
  - Any repeat ablation procedure during the evaluation period.
- DC cardioversion for AF/AFL/AT following the 3-month blanking period
- Surgical treatment for AF/AFL/AT after the index ablation procedure.
- AAD failure: Taking a new AAD for AF, a previously failed AAD at a greater than the highest ineffective historical dose during the evaluation period.

This study is designed to compare the primary effectiveness of the VISITAG SURPOINT™ Module with EPU to a pre-determined performance goal of 50%, which is indicated as the minimum acceptable success rate at 12 months for a paroxysmal AF population in the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE consensus statement.

The hypotheses to be tested for this evaluation are:

$$H_0: p \leq 0.50 \qquad \text{vs.} \qquad H_A: p > 0.50,$$

where p is the effectiveness success rate.

7.5.1.2 Primary Safety Endpoint

The primary safety endpoint is the proportion of subjects with any primary adverse event (PAE) occurring within 7 days following the AF ablation procedure (including the initial and repeat procedures) using the STSF catheter with EPU, except atrio-esophageal fistula and PV stenosis, which may also be considered as primary adverse events if occurring greater than seven (7) days post the ablation procedure [49,50].

The PAE rate will be compared against the performance goal of 14% by testing the following hypotheses:

$$H_0: q \geq 0.14 \qquad \text{vs.} \qquad H_A: q < 0.14$$

where q is the PAE rate.

7.5.2 Secondary Endpoints

No formal statistical hypothesis and inferential statistics will be formulated and performed for the secondary effectiveness and safety endpoints.

7.5.2.1 Secondary Effectiveness Endpoints

- Acute Procedural Success
  - % of subjects with ipsilateral PVI (entrance block) at the end of the procedure
  - % of subjects with ipsilateral PVI (entrance block) after first encirclement (evaluated prior to the 30-minute waiting period and adenosine challenge)
  - % of touch-up (ablation of acute reconnection) among all targeted veins
  - Anatomical location of acute PV reconnection after first encirclement
- Repeat ablation procedures during 12-month period post-procedure
  - Incidence (%) of repeat ablation procedures
  - % PVs re-isolated among all of the targeted PVs at repeat procedure
  - % repeat ablation procedures requiring new linear lesions and/or identifying new foci outside of initially isolated area among the repeat ablation procedures
- 12-Month Single Procedure Success
  - The 12-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 and off AADs. Any repeat ablation procedure or AAD therapy will be deemed effectiveness failure for this analysis.

7.5.2.2 Secondary Safety Endpoints

- 12-Month PAE Rate: Cumulative incidence of primary adverse events occurring within seven (7) days following an AF ablation procedure using study catheters with EPU and any late onset atrio-esophageal fistula or PV stenosis through 12 months
- Incidence of Unanticipated Adverse Device Effects (UADEs)
- Incidence of Serious Adverse Events (SAEs) within 7 days (early onset), >7 to 30 days (peri-procedural) and >30 days (late onset) of initial ablation
- Incidence of bleeding complication (ISTH definitions): a) major, b) clinically relevant non-major and c) minor bleeding

7.5.3 Additional Endpoints

No formal statistical hypothesis and inferential statistics will be formulated and performed for the additional endpoints.

- Procedural Data:
  - Total procedure time, PVI time, RF application time, mapping time and RF application time per lesion
  - Total Fluoroscopy Time
  - Fluid delivered from the study catheter
  - Location of RF applications, number of RF applications
  - RF Ablation parameters per application (e.g. temperature, power, impedance, CF etc.)
  - Device(s) utilized (per ablation)
  - VISITAG™ Settings
  - CF range
  - Power range
  - Tag Index Assessment per anatomical region
- Quality of Life (QOL): SF-12

7.5.4 Health Economic Data

The primary health economic data will include the cost and frequency of hospitalization for the study index ablation procedure, as well as any additional hospitalizations during the study period. The health care utilization during hospitalizations will be assessed by utilizing all data available for this study such as copies of the subject's hospital bills (UB04) and/or itemized hospital bills.

The health economic data associated with follow up care will include any repeat ablation procedure for treating arrhythmia, any inpatient or outpatient visit (including ER admissions) to address post-procedural complications or any procedure related condition and any inpatient or outpatient visit (including ER admissions) related to arrhythmia and cardiovascular conditions.

7.6 Level of Significance

The type I error for the interim and final analyses of the primary endpoints is controlled at one-sided 5%. Please refer to Appendix C for the operating characteristics of the Bayesian adaptive design including the type-I error simulation results.

7.7 Analysis Sets

For the analysis of study endpoints, the analysis populations defined in the following will be used:

- Safety Population: The SP will consist of all enrolled subjects who have undergone insertion of the STSF/ST catheters and use of the VISITAG SURPOINT™ Module with EPU. The safety population (SP) will be used to analyze safety endpoints.

- Per Protocol (PP) Population: The PP population will be used for the analysis of effectiveness endpoints. 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 STSF/ST catheters with the VISITAG SURPOINT™ Module with EPU, and have been treated for the study-related arrhythmia

- Full Set Effectiveness Population: The full set effectiveness population will be used to analyze the effectiveness endpoints. This population will include those who have met the following criteria:
  - are enrolled
  - have undergone RF ablation
  - are treated with the STSF/ST catheters with the VISITAG SURPOINT™ Module with EPU, and have been treated for the study-related arrhythmia

7.8 Sample Size Justification

The final analyses for primary safety and effectiveness endpoints will apply Bayesian methods and use a beta-binomial model.
The power calculations for the Bayesian adaptive design are presented in the simulation report Appendix C Table 6 (probability of success). Under the assumption of 65% success rate for primary effectiveness and 8% rate for primary safety, with 330 subjects, assuming 10-15% attrition rate, we will provide 90% power for declaring success for each of the primary endpoints controlling the type-I error at 5%.

7.9 Statistical Analysis Methods

7.9.1 General Conventions

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

7.9.2 Subject Disposition

Disposition of the study subjects are defined as the following.

- **Enrolled Subjects**: subjects who sign the informed consent.
- **Excluded Subjects:** subjects who do not have the STSF/ST catheters inserted or have the STSF/ST catheters inserted but do not undergo ablation with VISITAG SURPOINT™ Module.
- **Lost to Follow-up Subjects:** subjects who are enrolled and have STSF/ST catheter inserted and undergo ablation with VISITAG SURPOINT™ Module, 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 12-month follow-up visit.

7.9.3 Demography and Baseline Characteristics

Subject demographics, medical history, AAD medical history and other baseline data will be summarized descriptively for all enrolled subjects as well as the safety and PP populations.

7.9.4 Analysis of Primary Endpoints

The primary effectiveness endpoint is the proportion of patients that are free from primary effectiveness failure at Month 12. The failure modes are defined in the section 7.5.1.1. The effectiveness success rate at Month 12 will be compared against the performance goal of 50%.

The primary safety endpoint is the proportion of subjects who have any primary adverse events occurring within seven (7) days following an AF ablation procedure using study catheters with EPU, except atrio-esophageal fistula and PV stenosis, which may also be considered as primary adverse events if occurring within three (3) months post the ablation procedure.The PAE rate will be compared against the performance goal of 14%. The final analyses will apply the Bayesian methods using a beta-binomial model

7.9.4.1 Final Analysis

The primary goal of the trial is to demonstrate effectiveness and safety. For the trial to be successful, both endpoints must be statistically significant relative to their respective PG goals.

The effectiveness endpoint will be assessed by testing the hypotheses:

$$H_0: \Pr(p > 0.5|x,n) \leq 0.97 \quad \text{vs.} \qquad H_A: \Pr(p > 0.5|x,n) > 0.97$$

where p is the responder rate, x is the observed number of patients that are failure-free through 12 months ("responders"), and n is the number of subjects in the PP population. If the predictive posterior probability of the primary effectiveness endpoint meeting the 50% PG is greater than 97%, then we meet the threshold for primary effectiveness success.

We model the number of responders

$$X \sim \text{Binomial}(n,p),$$

We use a Beta(0.01, 0.01) prior distribution. This prior is centered at 50% and has an effective sample size of 0.02 observations.

Then the posterior distribution is

$$(p|x,n) \sim \text{Beta}(0.01 + x, 0.01 + n - x).$$

Subjects with missing data on the effectiveness endpoint will have their outcomes multiply imputed from a longitudinal model.

Similarly, the hypothesis test for the safety endpoint is:

$$H_0\text{: Pr}(q < 0.14|y,n) \leq 0.95 \qquad \text{vs.} \qquad H_A\text{: Pr}(q < 0.14|y,n) > 0.95$$

where q is the PAE rate, y is the observed number of subjects who had PAE and n is the number of subjects in the safety population. If the predictive posterior probability of the primary safety endpoint meeting the 14% PG is greater than 95%, then we meet the threshold for primary safety success.

We model the number of patients with PAE as

$$Y \sim \text{Binomial}(n, q)$$

with Beta(1, 1) prior distribution on q. No imputation for missing data will be performed for the safety endpoint.

The trial will be considered a success if BOTH

1. $\text{Pr}(p > 0.5|x,n) > 0.97$ AND
2. $\text{Pr}(q < 0.14|y,n) > 0.95$.

These thresholds control the overall Type I error rate for the trial below one-sided 5%. The Type I error for each endpoint individually is also below 5%. The protocol Appendix C contains a detailed description of the statistical methods planned for testing the hypotheses around the primary effectiveness and safety endpoints.

Note that the final analysis will be performed if early success is not declared at either of the two interim looks. If early success is declared at either of the two interim looks, a summary of the primary endpoints based on full 12-month follow-up will be provided. In addition, both safety and effectiveness results will also be descriptively summarized separately for subjects treated with the ST and STSF catheters.

7.9.4.2 Interim Analysis

Two interim analyses are planned. The first will occur once all subjects who are treated using STSF catheter with EPU have completed their 3 months follow-up. The second interim will occur when all subjects who are treated using STSF catheter with EPU have completed their 6 months follow-up. The planned interim analysis will be based on data collected only in subjects treated using STSF with EPU.
For the safety endpoint, among patients with more than 3 months of follow-up at the time of the interim analyses, any atrio-esophageal fistula and PV stenosis occurring post procedure will be deemed PAE.

At each interim analysis, the trial will declare early success if the predictive probability of success at the final analysis is greater than or equal to 99%. Early success will be declared at an interim if:

1. The safety objective has been met, and
2. The effectiveness endpoint has greater than or equal to 99% predictive probability of success.

The predictive probability is the probability of observing the success rate larger than 0.50 if the study continues to the end, given the observed data. If early success is declared, the subjects will be continued to be to be followed up for the remainder of the follow-up period.

7.9.4.3 Handling of Missing Data

At the time of each interim analysis, some subjects will not have completed the full 12-month evaluation period. For example, recently enrolled subjects who are currently failure-free but have only been observed for a portion of the observation period will have "censored" final outcomes. Some subjects may still be within the 13-week blanking period, and have no follow-up time during the observation period. Some subjects may be lost to follow-up. A longitudinal model will be employed to enable final observations to be multiply imputed for those subjects with partial or no follow up. Details are included in the protocol Appendix C.
The model is a piecewise exponential model for the time-to-failure during the 39-week post-blanking period. The model has three distinct segments: (0, 2], (2, 8], and (8, 39] weeks. The probability of failure during each interval is exponentially distributed, with different hazard rates in each segment. The model is:

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

where

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

These intervals are based on the model used in the ThermoCool Pivotal trial.
Noninformative Gamma (1, 1) prior distributions will be used for each λ in the model.

7.9.4.4 Sensitivity Analyses

Provided in detail in the SAP.

7.9.5 Additional Analysis for Primary Effectiveness Endpoint

Provided in detail in the SAP.

7.9.6 Analysis of Secondary Endpoints

Provided in detail in the SAP.

7.9.7 Analysis of Additional Endpoints

Provided in detail in the SAP.

7.9.8 Analysis of Health Economic Data

Provided in detail in the SAP.

7.10 Data Monitoring Committee

No Data Monitoring Committee will be formed for this study.

8. 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 research 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 may include but not limited to:

- Study protocol 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
- Medical licences and 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 log
- Reports (e.g. Interim Post- Approval Study Status 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

- Full Case CARTO backup [including complete VISITAG export] and CARTO Case recording

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.

8.5.5 Interim Post-Approval Study Status Report

An Interim Post-Approval Study Status Report will be provided to the FDA on the status of the post-approval study every 6 months for the first 2 years after the PMA approval and annually, thereafter.

The interim status report will include the following data to be posted by FDA on PAS website:

- Number of study sites enrolled
- Number of patients enrolled per site
- Summary data on subject enrollment and accountability
- Demographic data

- Summary data on SAEs, NSAEs, Device malfunctions, Catheter use, follow-up duration.

8.6 Labeling

THERMOCOOL SMARTTOUCH® and THERMOCOOL SMARTTOUCH® SF Diagnostic/Ablation Deflectable Tip Catheters with Contact Force Sensing Capability 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. STUDY MANAGEMENT

9.1 Study Timelines

Study Duration: The study is expected to last Approximately 2.5 years (~1.0 years for enrollment; 12 months of follow-up for primary endpoint).

Expected date of study initiation	3Q 2018
Expected monthly number of study sites with IRB approvals	1 to 5 sites per month
Expected number of subjects enrolled per month	1.7 subjects per site/month; average 20 subjects per month over 12 months
Expected date of enrollment completion	3Q2019
Expected date of study follow-up completion	3Q2020
Expected date for Final Report submission	4Q2020

9.2 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/REB requirements.
- Notifying Sponsor promptly of withdrawal of IRB/REB approval
- Complying with IRB/REB (as applicable) and Sponsor interim post-approval study status report requirements
- Maintaining accurate and current logs for the study such as Subject log, Device 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/REB updates as required

9.3 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 approval from the FDA
- 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
- Creation and maintenance of eCRF database
- Conducting all communications with Health authorities (HAs)/ Regulatory authorities (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 biannually for the first 2 years followed by annually thereafter, which will be supplied to the FDA and to other HAs/RAs as requested. Interim post-approval study status 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

9.4 Training

9.4.1 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 Clinical Research Coordinator 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 Sponsor Contact Information

9.6 Initiation of the Investigation

Potential research 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.

9.7 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.

9.8 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, 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.

9.9 Device Log

9.9.1 Device Log

The Research sites will use their commercially available STSF/ST catheters per the approved IFU and SURPOINT COA Protocol requirements. The site will keep a device log of the catheter used during the study.

The site Device Log will include the following information:

- Catalog number for catheters
- Serial/lot numbers
- Dates devices were used
- Subject IDs for whom devices were used
- Dates of return (as applicable)

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

All tracking information must be retained. Catheters must be returned to:

9.10 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.

9.11 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.

9.12 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.

9.13 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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APPENDIX A: STUDY DEFINITIONS

Term	Definition
Adverse Event (AE)	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 whether or not related to the sponor's product. This definition includes events related to the medical device and/or the comparator, and events related to the procedure in which the device was used.
Adverse Device Effects (ADE's)	Adverse events related to the use of the 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 medical device. This definition includes any event resulting from use errors or from intentional misuse of the investigation medical device.
AF/AT/AFL Episode	An episode of AF/AT/AFL ≥ 30 seconds in duration.
AF Episode	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
Anticipated AE	An effect which by its nature, incidence, severity or outcome has been identified as possible complications associated with the medical device and/ or intervention procedure.

Term	Definition
Atypical Flutter	Macroreentrant circuits within the atria where activation rotates around large obstacles that does not meet the criteria for Typical Flutter.
Bleeding Complications (ISTH definition):	**Major (ISTH definition):** Fatal bleeding AND/OR symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular, pericardial, or intramuscular with compartment syndrome AND/OR bleeding causing a fall in hemoglobin level of 2 g/dL (1.24 mmol/L) or more, or leading to transfusion of two or more units of blood. **Clinically relevant nonmajor bleed (ISTH definition):** An acute or subacute clinically overt bleed that does not meet the criteria for a major blrrd but ptomps a clinical response such that it leads to one of the following: hospital admission for bleeding; physician guided medical or surgical treatment for bleeding; change in antithrombotic therapy (including interruption or discontinuation). **Minor bleeding (ISTH definition):** All nonmajor bleeds. Minor bleeds are further divided into clinically relevant and not.
Catheter Insertion	Defined as the STSF/ST catheter breaching the sheath and entering the bloodstream.
Device Deficiency	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.
Documented AF/AT/AFL episode	An AF/AT/AFL episode documented by an electrocardiographic monitoring tool. This may include ILR, ECG, TTM, Holter monitor, or telemetry strip. *Reporting of a symptomatic episode by a patient or in a referral letter is not considered a documented AF episode.*
Paroxysmal AF	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.
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.

Term	Definition
Serious adverse event (SAE)	1. Any adverse event that: • Led to a death • Led to a serious deterioration in health that either: o Resulted in a life-threatening illness or injury, or o Resulted in a permanent impairment of a body structure or a body function, or o Required in-patient hospitalization or prolongation of existing hospitalization, or o 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 2. Any Device Deficiency that could have led to an SAE 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. 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.
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.
Unanticipated Serious Adverse Device Effect (USADE)	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. NOTE: Anticipated SADE: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report

Term	Definition
Ventricular Tachycardia (VT)	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).