CLINICAL INVESTIGATION PROTOCOL

Clinical study for workflow and acute performance evaluation of the THERMOCOOL SMARTTOUCH® SF-5D system (the THERMOCOOL SMARTTOUCH® SF-5D catheter with temperature sensing capabilities and micro electrodes and CARTO 3 V 6.0 technology) in treatment of patients with Paroxysmal Atrial Fibrillation (QDOT MICRO)

Sponsor: BIOSENSE WEBSTER, INC.
33 Technology Drive
Irvine, California 92618

Protocol number: MQDT-166

Protocol Version Date: Version 2.0 – November, 17th, 2017

History of Changes

Version Date	Description
Version 1.0 – May 26, 2016	Original document
Version 2.0 – November 17th, 2017	Amendment 1

The THERMOCOOL SMARTTOUCH® SF-5D Catheter (D-1395-05-SI) is for investigational device use only and is not commercially available anywhere in the world. '(QDot-MICRO)' is an internal Biosense Webster project name and other than as used in the present clinical investigation, is not intended for any other external use. The final commercial or trade name of the THERMOCOOL SMARTTOUCH® SF-5D catheter may be different.

Clinical study for workflow and acute performance evaluation of the THERMOCOOL SMARTTOUCH® SF-5D system (the THERMOCOOL SMARTTOUCH® SF-5D catheter with temperature sensing capabilities and micro electrodes and CARTO 3 V 6.0 technology) in treatment of patients with Paroxysmal Atrial Fibrillation (QDOT MICRO)

(Protocol # -MQDT-166)

Clinical investigation Number	MQDT-166
Clinical investigation Name	QDOT MICRO
Revision	Version 2.0
Date	17 November 2017
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	Clinical Franchise Leader CSS, EMEA Authorized Legal Representative Nathalie Macours Biosense Webster, EMEA part of the Johnson & Johnson family of companies

	Leonardo Da Vincilaan 15 1831 Diegem – Belgium Tel: +32 2 746 35 27 Email: nmacours1@its.jnj.com Whereas, the Clinical Study is sponsored by Biosense Webster Inc., Johnson and Johnson Medical NV/SA with registered offices at Leonardo Da Vincilaan 15, 1831 Diegem, Belgium, has been duly appointed by the Sponsor to conduct the Clinical Study on its behalf.

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

INVESTIGATOR SIGNATURE PAGE

I have read the protocol and agree:

- To conduct this clinical trial in accordance with the design and specific provisions of this protocol.
- To await EC-positive opinion for the protocol and informed consent as well as approval from the relevant Competent Authorities before initiating enrollment into the clinical trial.
- To ensure that the requirements for obtaining informed consent are met and to obtain informed consent from subjects before their enrollment in the clinical trial.
- To adhere to the content of the Investigator Brochure/ Instructions For Use
- To provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study.
- To provide sufficient and accurate financial disclosure and update information if any relevant changes occur during the investigation and for 1 year following the completion of the clinical trial.
- To collect and record data as required by this protocol and case report forms.
- To maintain the confidentiality of all information received or developed in connection with this protocol.
- To conduct this trial in accordance with ISO: 14155-2011 Standards and any other applicable local laws and regulations.
- To permit trial-related monitoring, audits, EC review, and regulatory inspection(s) by providing direct access to source data/documents.
- To prepare annual, final adverse effect reports as required by this protocol.
- To maintain clinical trial documentation for the period of time required.
- To report all adverse events/incidents within the specified timeframe to Biosense Webster.
- To report all serious adverse events/incidents to Sponsor immediately upon awareness of event but no later than 72 hours enter them into the EDC system.
- To adhere to the publication policy of Biosense Webster for data collected during this clinical trial.

_____

Signature of Principal Investigator Date

_____

Printed Name of Principal Investigator

PROTOCOL SYNOPSIS

Sponsor	Biosense Webster, Inc. 33 Technology Drive Irvine, California United States of America 92618 Tel +1 800 729 9010
Protocol Title	Clinical study for workflow and acute performance evaluation of the THERMOCOOL SMARTTOUCH® SF-5D system (the THERMOCOOL SMARTTOUCH® SF-5D catheter with temperature sensing capabilities and micro electrodes and CARTO 3 V 6.0 technology) in treatment of patients with Paroxysmal Atrial Fibrillation
Abbreviated Title	QDOT MICRO
Investigational Devices	• THERMOCOOL SMARTTOUCH® SF-5D Catheter (D-1395-05-SI) • nMARQ™ Multi-Channel RF Generator (D-1341-07) with Software V3.0.1
Study Purpose	The purpose of this study is to evaluate the workflow and acute performance, during standard electrophysiology mapping and RF ablation procedures, of the THERMOCOOL SMARTTOUCH® SF-5D catheter with temperature sensing capabilities and micro electrodes used in combination with the CARTO® 3 Navigation System with THERMOCOOL SMARTTOUCH® SF-5D-module.
Study Design	The QDOT MICRO study is a prospective, multi-center, non-randomized, interventional clinical study.
Study Population	Paroxysmal AF subjects who are scheduled to undergo a clinically-indicated ablation procedure for management of their paroxysmal AF will be the target population for screening. Subjects that are consented and meeting all eligibility criteria will undergo ablation with the THERMOCOOL SMARTTOUCH® SF-5D system.
Study Duration & Subject Participation	Approximately 6 months of enrollment, subjects will be followed-up at 7 days and 3-month post-procedure
Primary Outcome	**Acute Device Performance** Acute Device Performance is defined as confirmation of entrance block in all targeted PVs after adenosine and/or isoproterenol challenge.

Secondary Outcomes	• **Safety**
	  ○ Incidence of early onset (within 7 days of ablation procedure) pre-defined primary Adverse Events.
	  ○ Incidence of Serious Adverse Device Effects (SADEs) during follow-up period (3 months)
	• **Procedural data**
	  • Rate for touch-up RF application post adenosine and/ or isoproterenol challenge
	  • Target sites for RF lesion application
	  ○ Target sites
	  ○ Number of RF applications per target
	  ○ Total RF duration per application (sec)
	  • Ablation parameters, including but not limited to:
	  ○ Total RF ablation time
	  ○ Temperature (generator files)
	  ○ Contact Force (CARTO® datafiles)
	  ○ Power (generator files)
	  ○ Impedance
	  • Total Fluoroscopy time/dose
	  • Total procedure time
	  • ECG data
	• **Investigational device performance (rating with survey):**
	  ○ Contact and stability of catheter
	  ○ Signal Quality
	  ○ Temperature visualization
	  ○ Ease of use

Number of Subjects	Approximately 50 evaluable subjects will be enrolled.
Number of study sites	Approximately 5 centers in Europe

Study Inclusion Criteria	Subjects must meet ALL of the following inclusion criteria to be eligible for participation in this clinical investigation: 1. Age 18 or older 2. Patients who have signed the Patient Informed Consent Form (ICF) 3. Subjects diagnosed with symptomatic PAF who are candidates for catheter ablation 4. Able and willing to comply with all pre-, post-, and follow-up testing and requirements (e.g. Patient not confined by a court ruling)
Study Exclusion Criteria	Subjects who meet ANY of the following exclusion criteria are not eligible for enrollment: 1. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause. 2. Previous ablation for atrial fibrillation. 3. Previously diagnosed with persistent AF. 4. Documented Left Atrial thrombus 5. Any carotid stenting or endarterectomy 6. LA size >50mm 7. LVEF <40% 8. Uncontrolled heart failure or NYHA function class III and IV 9. History of blood clotting or bleeding abnormalities or contraindication to anticoagulation (heparin, warfarin, or dabigatran) 10. History of a documented thromboembolic event (including TIA) within the past 12 months.

	11. Previous PCI/MI within the past 3 months 12. Previous cardiac surgery (e.g. CABG) in conjunction with valve surgery or any valvular cardiac surgical/percutaneous procedure (e.g. ventriculotomy, atriomy, valve repair or replacement, presence of a prosthetic valve) within the past 6 months. 13. Awaiting cardiac transplantation or other cardiac surgery within the next 6 months. 14. Unstable angina 15. Significant pulmonary disease (eg, 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. 16. Acute illness, active systemic infection, or sepsis. 17. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation. 18. Presence of a condition that precludes vascular access. 19. Presence of implantable cardioverter-defibrillator (ICD) 20. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this trial. 21. Currently enrolled in an investigational study evaluating another device, biologics, or drug. 22. Women of child bearing potential whom are pregnant, lactating, or planning to become pregnant during the course of the clinical investigation (as evidenced by pregnancy test if of child bearing potential). 23. Life expectancy less than 12 months. 24. Presenting contra-indication for the devices used in the study, as indicated in the respective instructions for use.

Table 1 Subject treatment and Follow-up schedule

Assessments	Screening/ Baseline (Clinic Visit)	Study Ablation Procedure	Discharge	Follow-up	
				7 Day (+2d) (Clinic Visit or Phone call)	3 Month (-1w, +2wk) (Clinic Visit)
Patient Information and Consent[1]	✓				
Pregnancy Test[2]	✓				
Demographics	✓				
Medical History[3]	✓				
Transthoracic Echo (TTE)[4]	✓		✓		
12 Lead ECG[5]	✓		✓		✓
Left atrial thrombus detection[6]		✓			
AF Recurrence			✓	✓	✓
Concomitant Medication[7]	✓	✓	✓	✓	✓
Device Deficiencies		✓			
Adverse Events[8]	✓	✓	✓	✓	✓
Cardiac CT/MRI[9]			✓	✓	✓

[1] Procedure must be done within 60 days of consent.
[2] Pregnancy tests must be done on women of child-bearing potential only, within 1 week prior to the procedure.
[3] Medical history-including but not limited to arrhythmia, heart disease and thromboembolic events.
[4] TTE within 30 days prior to procedure to determine the LA size and LVEF%, 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.
[5] Standard of care assessments can be performed before ICF signature.
[6] Performed the day before procedure or day of Ablation Procedure to rule out the presence of atrial thrombus using one of the following modalities TEE, ICE, CT, MRI.
[7] Concomitant medications: only cardiac related (anti-arrhythmia drugs, anticoagulation regimen, etc.).
[8] AEs must be collected from the time the subject signs the informed consent onward.
[9] Subjects who have symptoms suggestive of PV stenosis should undergo imaging (CT/MRI)

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1. ABBREVIATIONS

AAD	Antiarrhythmic Drug
ACT	Activated Clotting Time
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AFL	Atrial Flutter
AT	Atrial Tachycardia
BP	Blood Pressure
CA	Competent Authority
CABG	Coronary Artery Bypass Grafting
CE	Conformité Européen
CFAE	Complex Fractionated Atrial Electrogram
CHF	Congestive Heart Failure
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CT scan	Computerized Tomography scan
DD	Device Deficiency
EC	Ethics Committee
ECG	ElectroCardioGram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EF	Ejection Fraction
EOS	End-Of-Study
EP	Electrophysiology
ER	Emergency Room
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	GastroIntestinal

HCP	Health Care Provider
IB	Investigator Brochure
ICD	Implantable Cardioverter-Defibrillator
ICE	IntraCardiac Echocardiography
ICH	International Conference on Harmonization
ID	IDentification
IFU	Instructions for Use
ISO	International Organization for Standardization
IV	IntraVenous
IVC	Inferior Vena Cava
LA	Left Atrium
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
PAE	Primary Adverse Event
PAF	Paroxysmal Atrial Fibrillation
PE	Primary Endpoint
PE	Physical Examination
PIU	Patient Interface Unit
PV	Pulmonary Vein
QA	Quality Assurance
QoL	Quality of Life
RA	Right Atrium
RBA	Risk-Benefit Analysis
RV	Right Ventricle
RF	RadioFrequency
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SVC	Superior Vena Cava
SW	SoftWare
TEE	TransEsophageal Echo
TIA	Transient Ischaemic Attack
TTE	TransThoracic Echo
UADE	Unanticipated Adverse Device Effect
UAE	Unanticipated Adverse Event
US	United States
USADE	Unanticipated Serious Adverse Device Effect
VT	Ventricular Tachycardia

2. INTRODUCTION

2.1 Background

Atrial fibrillation (AF) is the most common sustained arrhythmia in humans. It affects anywhere from 0.4% to 1% of the general population, and increases in prevalence with age, from < 1% in young adults to 8% in patients over 80 years of age.[1,2] Patients with AF report a considerably impaired quality of life (QOL) that is independent of disease severity. Improvement in health-related QOL is directly correlated with restoration and maintenance of normal sinus rhythm. In addition to the impaired QOL, AF sufferers have been shown to have an increased risk of stroke, heart failure and all-cause mortality.[2]

AF is a complex, progressive disease that results in structural and electrical remodeling in the heart.[3] Progression can be slowed or stopped by electrically isolating the pulmonary veins (PVs) from the left atrium (LA).[4] According to the 2017 HRS consensus statement, complete electrical isolation of the pulmonary veins (PVs) from the LA is recommended for all AF ablation procedures.[5] Radiofrequency (RF) catheter ablation has provided excellent results for treating paroxysmal AF (PAF), with high rates of elimination of the arrhythmia.[6-12]

While ablation with RF catheters has provided good results for treating PAF,[7-12] misplaced, overly forceful or prolonged contact with the RF tip can lead to thermal burn injury to non-PV structures.[13,14] Because the mechanism of action of RF catheters is to induce cell death by temperature increases, the risk of thrombus formation and steam pop are of concern.[15,16] It is generally accepted that RF ablation carries a major complication rate of approximately 4.5%.[17] 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.[18]

However, the first open irrigated-tip catheters introduced for clinical use required increasing volumes of saline to be delivered with increasing number of RF applications. Therefore, although irrigation of the RF catheter tip was found to reduce temperature at the ablation sites and decrease the associated thrombus formation and steam pops,[18] there is a risk of volume overload from high volumes of perfused saline.

Although acute pulmonary vein isolation (PVI) is almost always achieved with RF ablation, AF recurrence is common.[5] Several studies have correlated inadequate electrode-tissue contact with ineffective RF lesion generation.[19-23] Higher contact force can lead to serious complications such as steam pops, cardiac perforation or esophageal injury.[21,22,24]

Until recently,[25,26] there was no reliable mechanism to provide continuous measurement of the direct contact force (CF) between the tip of the RF ablation catheter and the endocardial tissue. In preliminary studies, feedback from the addition of a CF sensor to RF ablation catheters showed a high degree of between- and within-investigator variability in CF, indicating that even with careful catheter manipulation, operators do not have good control over CF.[25] Moreover, lower CFs were associated with intermittent contact with tissue and were most often applied at sites with high rates of reconduction.[25,27,28]

Technology of RF Catheter Ablation

RF energy utilizes a high frequency (350 kHz to 1 MHz) alternating current to cause resistive heating of a narrow rim of tissue that is in direct contact with the electrode tip.[21] Heating beyond this rim is based on transfer of thermal energy to the surrounding tissues, and is the primary mechanism by which RF lesions are formed.[22] Increasing temperature at the electrode-tissue interface increases the lesion size, but if the temperature exceeds 80 to 100°C, coagulum on the electrode tip can form and lead to an abrupt rise in impedance and a marked decrease in tissue heating.[23] The temperature of the electrode-tissue interface, therefore, is a limiting factor to increasing RF lesion size and depth. The Biosense Webster THERMOCOOL SMARTTOUCH® SF family of catheters features two improvements over standard irrigated RF catheters. First, the THERMOCOOL SMARTTOUCH® catheters provide real-time measurement of contact force (CF) between the catheter tip and heart wall, as well as location information, when used with CARTO® 3 Navigation System. 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 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 energy from the generator to the desired ablation site. Second, the THERMOCOOL SMARTTOUCH® SF catheters incorporate "surround flow" technology, which features a 66-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 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.

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,[25] and that CF measurement during ablation correlates with clinical outcome in AF patients.[27]

Subsequent studies with the THERMOCOOL SMARTTOUCH® catheters showed the ability to monitor CF in real time to be associated with decreased total procedure time and fluoroscopy time,[29] and increased acute and long-term procedural success in the paroxysmal AF population.[29,30] Data have shown the 12-month effectiveness success rate was 74%.[30] Additionally, sub-analysis showed success rate was consistently above 80% when investigators stay within their pre-selected contact force range > 80% of the time.[30] There is ex vivo evidence that a higher contact force may result in an increased incidence of serious adverse events.[21] Therefore, a catheter with the capability to provide real-time electrode-tissue contact force measurements may facilitate better control of RF energy application, resulting in an optimal lesion.

The THERMOCOOL SMARTTOUCH® SF catheter features a porous electrode tip (66 very small holes) in comparison to the predecessor device, the THERMOCOOL SMARTTOUCH® catheter which featured 6 larger holes at the distal electrode tip. In subjects with paroxysmal AF, the THERMOCOOL® catheter with this Surround Flow

(SF) technology was as successful as the predecessor THERMOCOOL® catheter in achieving PV isolation.

Both treatment groups received similar amounts of RF energy, but the saline volume administered was reduced in the THERMOCOOL® SF group.[31] Procedural efficiency was also enhanced; time to PV isolation and total RF duration,[32,33] as well as saline irrigation volume,[33,34] were diminished in paroxysmal AF subjects who underwent ablation with the THERMOCOOL® SF catheter compared to the THERMOCOOL® catheter without SF.

Commercialization of the THERMOCOOL® SF catheters has been associated with a higher complaint rate of cardiac adverse events. Investigation of this trend revealed that the majority of Serious Adverse Events (SAEs) were occurring at centers that were not using the catheter according to the instructions for use. Serious adverse events related to atrial esophageal fistula/tamponade/perforation have occurred at 9% of sites where the product has been distributed. One and a half percent (1.5%) of these centers have reported more than one SAE (2-5 events). Most sites experiencing SAEs were found to be targeting an electrode tip temperature above the safety cut-off for THERMOCOOL® SF.

Catheter tip temperature and electrode impedance are commonly used to monitor safe RF delivery.[35] While intramural tissue temperature during RF application cannot be accurately assessed with conventional irrigated ablation catheter, the placement to the tip thermocouples in conventional irrigated catheters has allowed observation of temperature increases in the catheter tip as the tissue heats.[35] In comparison to conventional irrigated-tip catheters with lower numbers of irrigation holes, there is no temperature rise at the catheter tip in the porous tip cooling pattern of the THERMOCOOL® SF catheters.[36] The result is an observed constant temperature throughout the RF application even with increasing power levels.[36] This has led to suggestions that RF applications of the THERMOCOOL® SF catheter with similar power settings used with the conventional THERMOCOOL® catheter are associated with a higher incidence of complications.[37]

The THERMOCOOL SMARTTOUCH® SF-5D catheter has been designed to address this concern. Temperature sensing, contact force and micro-electrodes (intended to streamline ablation workflow) are features that may potentially enhance the safety of the THERMOCOOL SMARTTOUCH® SF catheter. This study is designed to demonstrate the optimal workflow and the acute performance of the THERMOCOOL SMARTTOUCH® SF-5D catheter when the instructions for use are followed.
The addition QMODE algorithm to THERMOCOOL SMARTTOUCH® SF-5D catheter temperature regulation introduces temperature controlled ablation to irrigated catheters. Temperature controlled ablation allows RF power to be delivered safely without tip char or steam pops. When using the QMODE algorithm the irrigation rate will vary based on temperature to both cool the catheter tip adequately and retain temperature sensitivity, ensuring the safety profile.

3. INVESTIGATIONAL MEDICAL DEVICES

3.1 General Device Description

3.1.1 THERMOCOOL SMARTTOUCH® SF-5D Catheter

The Biosense Webster THERMOCOOL SMARTTOUCH® SF-5D Catheter is a steerable multi-electrode luminal catheter with a deflectable tip designed to facilitate electrophysiological mapping of the heart and to transmit radiofrequency (RF) energy to the catheter tip 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 a compatible 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.

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 energy from the RF generator to the desired ablation site. The tip electrode and ring electrodes are made from noble metals.

The catheter incorporates six thermocouple temperature sensors and ECG electrodes that are 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, two symmetric curve combinations (designated “DF” and “FJ”), provide 180° opposed, single planed curves.

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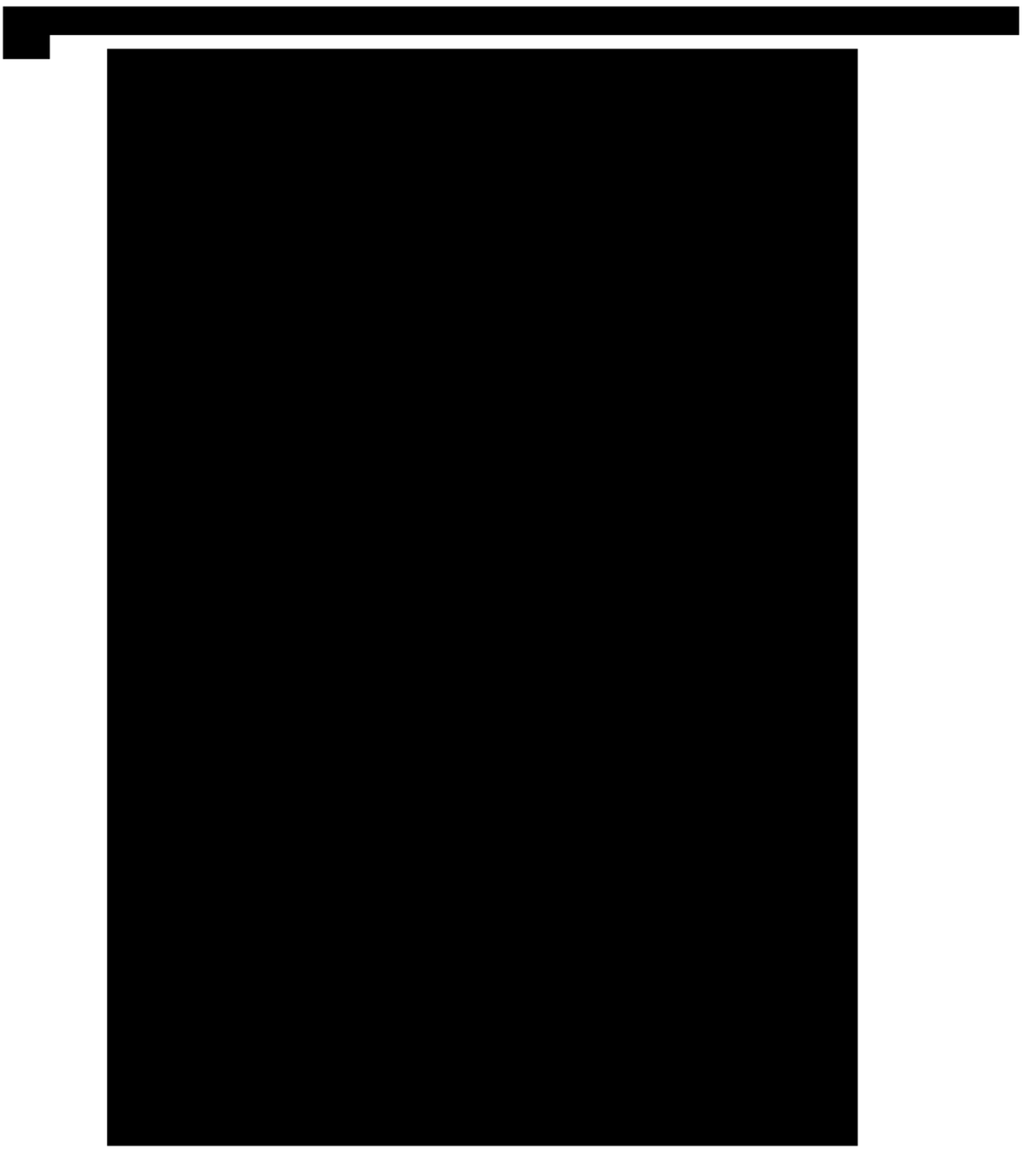

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3.2 Rationale for Design

3.2.1 Previous Experience with the THERMOCOOL SMARTTOUCH ® catheter

The THERMOCOOL® SMARTTOUCH® Catheter approved in the European Union. By displaying precise contact force and direction information, the THERMOCOOL® SMARTTOUCH® Catheter provides an important new parameter for the mapping and ablation of complex cardiac arrhythmias, such as Atrial Fibrillation (AF).

3.2.2 Previous Experience with the THERMOCOOL SMARTTOUCH® SF catheter

The THERMOCOOL SMARTTOUCH® SF catheter, approved in the European Union, features a porous electrode tip (56 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 SMARTTOUCH® SF catheter with Surround Flow (SF) technology was as successful as the predecessor THERMOCOOL SMARTTOUCH® catheter in achieving PV isolation, with delivery of similar amounts of RF energy.

Moreover, the saline volume administered by the catheter was reduced when compared to the SMARTTOUCH® Catheter.[31] Procedural efficiency was also enhanced; time to PV isolation and total RF duration,[32,33] as well as saline irrigation volume,[33,34] were

diminished in paroxysmal AF subjects who underwent ablation with the THERMOCOOL SMARTTOUCH® SF catheter compared to the THERMOCOOL SMARTTOUCH® catheter without SF technology.

3.2.3 Previous Experience with THERMOCOOL SMARTTOUCH® SF-5D catheter

This clinical feasibility study will be the first experience using THERMOCOOL SMARTTOUCH SF-5D (D-1395-05-SI) in conjunction with the nMARQ™ Multi-Channel RF Generator (D-1341-07; Software V3.0.1).

Bench and animal testing has been performed using the THERMOCOOL SMARTTOUCH SF-5D Catheter and the nMARQ™ Multi-channel RF Generator. Please refer to the Investigator's Brochure for detailed summaries of the test protocols and corresponding reports. A synopsis of the In Vivo animal studies is presented below.

3.2.3.1 Animal studies

3.2.3.1.1 **Animal Study Thigh Prep Lesion Model**

Animal testing was performed using the catheter and complete system per study protocol P-0022114 and test report TR-0022114, Design Verification Test Report For Verification of Qdot MICRO-Electrode Catheter with Q-mode Ablation Mode – Canine Thigh Preparation Test.

Purpose

The purpose of this study was to evaluate the safety and performance of the QDOT MICRO-electrode catheter in QMODE ablation mode (Test Catheter) when compared with STSF and ST catheters in power control mode (Control catheters) using a well-established canine thigh muscle model.

Summary

The overall incidence of coagulum and steam pop observed with the QDOT MICRO catheter in QMODE ablation mode was significantly less compared to the control catheters (ST and STSF). The lesion characteristics were similar between the QDOT MICRO catheter and the control catheters. The overall performance of the QDOT MICRO catheter, in the QMODE ablation mode was similar or better compared to the control catheters (ST and STSF) in power control ablation mode.

3.2.3.1.2 **Animal Testing: Endocardial Study**

Animal testing was performed using the catheter and complete system per study protocol P-0023068 and test report TR-0023068, Evaluation of Qdot MICRO-Electrode Catheter with Q-mode Ablation Mode - Beating Heart Animal Study.

Purpose

The purpose of this acute study was to evaluate the safety and overall functional performance of the QDOT MICRO electrode catheter, in the QMODE ablation mode (nMARQ multichannel RF generator), when simulating a clinical pulmonary vein isolation (PVI) procedure. The overall safety and functional performance of the QDOT MICRO electrode catheter and QMODE ablation mode was compared to the control catheter (SmartTouch SF) being used in power control mode (SmartAblate generator).

Summary

The QMODE Beating Heart study was conducted according to the study protocol design and its requirements. No protocol deviations were noted.

No char/coagulum was observed on the test catheter (QDOT). The overall incidence of steam pop observed with QDOT (5/9 in the LV and 0 in all other locations) was lower compared to the control STSF catheter (5/12 in LA, 5/6 in LV, 1/7 in RV). Of note, there were zero incidence of steam pop occurred at both atrial ablations using the QDOT catheter under the QMODE at the experimental settings.

The QDOT MICRO ablation catheter used in conjunction with the QMODE ablation mode was able to:

- Deliver RF energy at a target site
- Demonstrate acute isolation of the pulmonary vein.
- Demonstrate clinically acceptable signal quality which was comparable to control.
- Pace from ring electrodes and microelectrodes during idle-state and during ablation.
- Provide significantly better temperature feedback during ablation than control catheter.
- Function effectively when used in conjunction with ancillary equipment like nMARQ multichannel RF generator, QDOT Dongle, CoolFlow pump and CARTO 3 mapping system.

The QDOT MICRO ablation catheter, when used with QMODE ablation mode, was able to produce effective electrogram signal attenuation and equivalent (or better) lesions as compared with that of STSF in four cardiac chambers. and demonstrate signal attenuation.

The nMARQ generator was able to successfully modify the irrigation flow rate based on QDOT catheter electrode temperature response and power settings to maintain temperature limit when used in the QMODE ablation mode.

4. RISK – BENEFIT

RF catheter ablation has been used for over 20 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:

4.1 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%).[10,11,38-42]

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%).[43,44] 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 clinical sites/centers suggests that the risk of coronary occlusion is less than 0.5%.[43,44] 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, this can also occur in the absence of an impedance rise. The thrombus could become dislodged and embolize to produce a stroke, myocardial infarction, or other ischemic injury. The risk of an embolus is reduced by quickly terminating the application of current after an impedance rise, which limits the size of the coagulum on the electrode. Probably the most important aspect 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 current. Published risks of cardiac perforation range from <1% to 2.5%.[17,30,45-48] This may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. In a recent study using the THERMOCOOL SMARTTOUCH® Catheter with contact force sensing technology, there were 4 (2.48%, 4/161) reported incidents of tamponade.[30,45] 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.

Peri-esophageal 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.[5] While these complications are rare (approximately < 1%), they can potentially compromise the clinical outcome severely, requiring surgical treatment.[49,50] 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.[5]

Injury to a cardiac valve may result from catheter manipulation or the application of RF current (risk <1%).[43,44] 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.[17,47] 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 right pulmonary veins. The reported incidence of phrenic nerve injury varies from 0% to 0.48% when RF energy is used for catheter ablation.[51,52] Prior to ablation in the region of the right superior pulmonary vein, precautionary measures are

recommended to be performed by investigators to evaluate proximity to the phrenic nerve, such as pacing maneuvers.

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%).[53-55]

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%).[56-60]

Hemorrhage could occur as a result of anticoagulation (risk <0.5%), which may require transfusion.[43,44]

The percutaneous procedure carries risk of infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%).[43,44] This risk can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.

4.1.1 THERMOCOOL SMARTTOUCH® SF-5D catheter and potential procedural risks

Invasive electrophysiological evaluation and catheter ablation may impart some degree of risk to the patient. 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 and the potential benefit of the treatment of persistent or recurrent arrhythmia should be determined by a qualified physician. Cardiac catheterization and electrophysiological procedures should be performed by qualified and appropriately trained personnel in an electrophysiology laboratory. The laboratory should contain sufficient resuscitative equipment and facilities to manage any potential complication.

Failure to observe any of the contraindications, warnings, and precautions in these instructions may result in procedural complications. Risks 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.

Additional contraindications for device use include: hemodynamic instability, bacteremia, coagulopathy, prosthetic tricuspid valve, intra-atrial or venous thrombosis, and pregnancy.

4.1.2 nMARQ Multi-Channel RF generator risks

Note that the nMARQ™ Multi-Channel RF Generator (D-1341-07) (SW version 2.3.1) was CE marked on Oct, 25, 2013. In order to allow for an interface with the THERMOCOOL SMARTTOUCH® SF-5D Catheter, the software was modified to SW version 3.0.1. As a result of the software modification, the nMARQ™ Multi-Channel RF Generator will be designated as an investigational device. Further reference can be made to the User manual and addendum, for more information. Enhanced versions of the SW v3.0.1 might be released and used during the course of this study. A protocol Amendment will be submitted for approval if any additional significant risks would be identified in newly released software versions.

For SW V3.0.1 there are no anticipated potential direct risks to the subject, the risk is mitigated by the temp cutoff setting of the generator. Further reference can be made to the pre-clinical testing reports and Investigator Brochure for more information.

4.2 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-5D catheter, is similar to conventional irrigated catheters that do not include this technology. Similarly, the Surround Flow technology found in the THERMOCOOL SMARTTOUCH® SF-5D catheter confers a decreased risk of volume overflow associated events such as CHF and pulmonary edema in patients with impaired LVEF or kidney dysfunction.[31, 34]

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.[32]

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 carefully prior to enrollment in the study to ensure compliance with the inclusion and exclusion criteria. The exclusion criteria have been developed to exclude subjects with a medical history or condition that increases their risk of adverse events (refer to Section 8.3 for the Exclusion Criteria). All subjects will have pre-procedure imaging as described in section 9.1.2.1 to screen for the presence of LA thrombus, which is intended to decrease the potential for thromboembolic complications.

Investigators will undergo training on the use of the THERMOCOOL SMARTTOUCH® SF-5D Catheter with Contact Force Sensing Capability technology prior to subject enrollment. Investigators skilled 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 electrophysiology laboratories with the assistance of skilled nurses and technicians.

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, safety data will be evaluated periodically during enrollment and follow-up by medical safety officer or designee.

4.3 Potential benefits

In patients with PAF, elimination or amelioration of symptoms is a major driving force for therapy. The primary clinical benefit of catheter ablation of AF is an improvement in quality of life (QoL) resulting from the elimination of arrhythmia-related symptoms such as palpitations, fatigue, or effort intolerance.

The investigational device may allow cardiac ablation procedures to be done with greater efficiency, safety, and effectiveness. This THERMOCOOL SMARTTOUCH® SF-5D Catheter with Tip/Endocardial Surface Interface Temperature Sensing Capability and micro electrodes used in conjunction with CARTO 3 v6.0 QDOT-MICRO Module is the first catheter designed with this functionality.

Further reference can be made to the Risk-Benefit Analysis (RBA) for more information.

5. CLINICAL INVESTIGATION DESIGN

The Qdot-MICRO study is a prospective, multi-center, non-randomized clinical study to evaluate the workflow and acute performance of the THERMOCOOL SMARTTOUCH® SF-5D system in subjects diagnosed with Paroxysmal Atrial Fibrillation (PAF).

The study population will consist of approximately 50 evaluable subjects with PAF as an indication for radiofrequency (RF) ablation. PAF is defined as AF that terminates spontaneously or with intervention within 7 days of onset. Episodes may recur with variable frequency (ACC guidelines, 2014).[67]

The study will be conducted at approximately 5 sites in Europe. Follow-up will be conducted at 7 days and 3-month post-ablation procedure.

6. CLINICAL INVESTIGATION OBJECTIVE

The purpose of this study is to evaluate the workflow and acute performance, during standard electrophysiology mapping and RF ablation procedures, of the THERMOCOOL SMARTTOUCH® SF-5D catheter with temperature sensing capabilities and micro electrodes used in combination with the CARTO® 3 Navigation System with THERMOCOOL SMARTTOUCH® SF 5D Module.

7. CLINICAL STUDY ENDPOINTS

7.1 Primary Study Endpoints

Acute Device Performance

Acute Device Performance is defined as confirmation of entrance block in all targeted PVs after adenosine and/or isoproterenol challenge.

7.2 Secondary Study Endpoints

- **Safety**
  - Incidence of early onset (within 7 days of ablation procedure) primary Adverse Events.

    Serious Adverse Events occurring within the first week (7 days) following an ablation procedure with the THERMOCOOL SMARTTOUCH® SF-5D catheter and AE term is one of the adverse events listed, will be considered for Primary Event assessment (refer to Appendix A '' Primary Adverse Event Classification" for PAE description/criteria)

Table 3 Primary Adverse Events

• Death
• Atria-Esophageal Fistula*
• Cardiac Tamponade**/Perforation
• Myocardial Infarction
• Stroke/Cerebrovascular Accident
• Thromboembolism
• Transient Ischemic Attack
• Diaphragmatic Paralysis
• Pneumothorax
• Heart Block
• Pulmonary Vein Stenosis
• Pulmonary Edema (Respiratory Insufficiency)
• Vagal Nerve Injury
• Pericarditis
• Major Vascular Access Complication/Bleeding

* Pulmonary vein (PV) stenosis and atrio-esophagael fistula that occurs greater than one week (7days) post-procedure shall be deemed Primary AEs. ** Hemodynamic compromise or instability is defined as Systolic BP < 80 mmHg

  - Incidence of Serious Adverse Device Effects (SADEs) during follow-up period (3 month)

- **Procedural data**
    - Rate for touch-up RF application post adenosine and/ or isoproterenol challenge
    - Target sites for RF lesion application
        - Target sites
        - Number of RF applications per target
        - Total RF duration per application (sec)
    - Ablation parameters, including but not limited to:
        - Total RF ablation time
        - Temperature (generator files)
        - Contact Force (CARTO® datafiles)
        - Power (generator files)
        - Impedance
    - Total Fluoroscopy time/dose
    - Total procedure time
    - ECG data

- **Investigational device performance (rating with survey):**
    - Contact and stability of catheter
    - Signal Quality
    - Temperature visualization
    - Ease of use

8. STUDY POPULATION

8.1 Subject identification

Subjects will be identified sequentially at each site by number only. The subjects will be identified by site number and subject number.

All information and data sent to the sponsor concerning subjects or their participation in this clinical investigation will be considered confidential and transmitted anonymously. Only authorized sponsor personnel or designee, or local government authorities acting in their official capacities will have access to these confidential files. All data used in the analysis and reporting of this evaluation will be without identifiable reference to the subject.

The following inclusion and exclusion criteria were selected to ensure the appropriate study population is enrolled.

8.2 Study Inclusion Criteria

Subjects must meet ALL of the following inclusion criteria to be eligible for participation in this clinical investigation:

1. Age 18 or older

2. Patients who have signed the Patient Informed Consent Form (ICF)

3. Subjects diagnosed with symptomatic documented PAF* who are candidates for catheter ablation *(*defined as AF that terminates spontaneously or with intervention within 7 days of onset. Episodes may recur with variable frequency (HRS guidelines, 2017).*

4. Able and willing to comply with all pre-, post-, and follow-up testing and requirements (e.g. Patient not confined by a court ruling)

8.3 Study Exclusion Criteria

Subjects who meet ANY of the following exclusion criteria are not eligible for enrollment:

1. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
2. Previous ablation for atrial fibrillation.
3. Previously diagnosed with persistent AF.
4. Documented Left Atrial thrombus
5. Any carotid stenting or endarterectomy
6. LA size >50mm (parasternal long axis view)
7. LVEF <40%
8. Uncontrolled heart failure or NYHA function class III and IV
9. History of blood clotting or bleeding abnormalities or contraindication to anticoagulation (heparin, warfarin, or dabigatran)
10. History of a documented thromboembolic event (including TIA) within the past 12 months.
11. Previous PCI/MI within the past 3 months
12. Previous cardiac surgery (e.g. CABG) or valvular cardiac surgical/percutaneous procedure (e.g ventriculotomy, atriomy, valve repair or replacement, presence of a prosthetic valve) within the past 6 months.
13. Awaiting cardiac transplantation or other cardiac surgery within the next 6 months.
14. Unstable angina
15. Significant pulmonary disease (eg, 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.
16. Acute illness, active systemic infection, or sepsis.
17. Presence of intracardiac thrombus, myxoma, tumor, interatrial baffle or patch or other abnormality that precludes catheter introduction or manipulation.
18. Presence of a condition that precludes vascular access.
19. Presence of implantable cardioverter-defibrillator (ICD)
20. Significant congenital anomaly or a medical problem that in the opinion of the investigator would preclude enrollment in this trial.

21. Currently enrolled in an investigational study evaluating another device, biologics, or drug.
22. Women of child bearing potential whom are pregnant, lactating, or planning to become pregnant during the course of the clinical investigation (as evidenced by pregnancy test if of child-bearing potential).
23. Life expectancy less than 12 months.
24. Presenting contra-indication for the devices used in the study, as indicated in the respective instructions for use.

8.4 Subject Disposition

The following subject groups are defined:

- Enrolled subjects: subjects who have signed and dated the Informed Consent Form
- Excluded subjects: subjects who are enrolled but never undergo the insertion of the investigational device. Excluded subjects will not be included in the safety or functionality evaluation of the investigational device.
- Discontinued subjects: subjects who are enrolled and have the investigational device inserted but no RF energy is administered by the investigational device. Discontinued subjects will remain in the safety cohort. These subjects will be followed-up until 7 days post-procedure for safety purpose.
- Evaluable subjects: subjects who are enrolled and meet the eligibility criteria and who undergo ablation with the study catheter.
- Lost to Follow-up subjects: subjects who are enrolled and evaluable, but contact is lost after most recent follow-up visit (despite 3 documented attempts to contact the subject).
- Withdrawn / Early Termination Subjects: subjects who withdraw consent for study participation or are withdrawn by the investigator (as described in Section 8.5) or are terminated from the study prior to completion of all follow-up visits.
- Completed subjects: subjects who are enrolled and that have not expired, been excluded, discontinued, withdrawn, terminated early or lost to follow-up from the study, prior to the final study visit.

8.5 Early Subject Termination

Every subject should be encouraged to remain in the study until they have completed the protocol-required 3-month follow-up period. If the subject terminates prematurely from the study, the reason for termination must be documented by the investigator in the source documents and in the appropriate electronic CRF section.

Possible reasons for early termination may include but are not limited to the following:

- Withdrawal of consent - Subject decides to withdraw from the study. This decision must be an "independent decision" that is documented in the source documentation and in the electronic CRF.

- Lost to follow-up: All subjects should be encouraged to return for protocol required office, clinic visit 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 to the subject. If the subject does not respond to the letter, then the subject will be considered "lost to follow-up" for the current study visit. Subject contact must be attempted at each follow-up time point and if unable to contact the subject after 3 phone calls, the subject should once again be sent a certified letter.

Only after failing to contact the subject at the final follow-up visit will the subject be considered lost to follow-up and the study termination/end form will be completed in the individual case report form

- Investigator discretion - The investigator may choose to withdraw a subject from the study if there are safety concerns.

- Death

- Study Termination - The sponsor can decide to discontinue the study prematurely for various reasons.

8.6 Suspension or premature termination of the study

The sponsor may either suspend or prematurely terminate the study for significant and documented reasons.

A principal investigator, EC, or regulatory authority may suspend or prematurely terminate participation in the study at the study sites for which they are responsible.

If suspicion of an unacceptable risk to subjects arises during the study, or when so instructed by the EC or regulatory authorities, the sponsor shall suspend the study while the risk is assessed. The sponsor shall terminate the study if an unacceptable risk is confirmed.

The sponsor shall consider terminating or suspending the participation of the particular study site or investigator in the study if monitoring or auditing identifies serious or repeated deviations on the part of an investigator.

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

If, for any reason, the sponsor suspends or prematurely terminates the study, the sponsor shall inform the responsible regulatory authority as appropriate and ensure that the EC is notified, either by the principal investigator or by the sponsor.

If suspension or premature termination occurs,

a. the sponsor shall remain responsible for providing resources to fulfill the obligation from the Protocol and existing agreements for following up the subjects enrolled in the study, and
b. the principal investigator or authorized designee shall promptly inform the enrolled subjects at his/her study site, if appropriate, and
   Note: the method and the timing of this communication will depend on the circumstances and the perceived risks
c. Arrangements will be made for the return of all unused investigational medical devices and other material in accordance with the sponsor procedures for the study.
d. The manufacturer or his authorized representative shall notify the competent authorities of the Member States concerned of the end of the clinical investigation, with a justification in case of early termination. In the case of early termination of the clinical investigation on safety grounds this notification shall be communicated to all Member States and the Commission.

When the sponsor concludes an analysis of the reason(s) for the suspension, implements the necessary corrective actions, and decides to lift the temporary suspension, the sponsor shall inform the principal investigator, the EC, and, where appropriate, the regulatory authority of the rationale and provide them with the relevant data supporting this decision.

Concurrence shall be obtained from the EC and, where appropriate, regulatory authorities before the study resumes.

If subjects have been informed of the suspension, the principal investigator or authorized designee shall inform them of the reasons for resumption.

8.7 Stopping Rules

The clinical investigation team will review and monitor the clinical safety data on a regular basis for any safety or catheter design issues. Should the team identify any

safety issues, the impacted clinical sites, EC's and CA's will be immediately notified to ensure the safety of their patients and the study may be stopped.

8.8 Clinical Investigation Timelines/Duration

Clinical investigation duration is expected to be 9 months (including enrollment phase). The enrollment phase is expected to take 6 months following enrollment of the first subject.

9. STUDY PROCEDURES

9.1 Screening/Baseline

9.1.1 Informed Consent

Prior to screening or performing any study related procedures that are solely for the purpose of determining eligibility for this study, any potential benefits and risks of the study must be explained to the subject directly. Subjects will be informed about all aspects of the study that are relevant to the subject's decision to participate throughout the study and requested to grant their approval to review their medical records, to collect and analyze personal medical information, while maintaining confidentiality of the records at all times.

The informed consent needs to be made up in a native non-technical language that is understandable to the subject and needs to be approved by Ethics Committee (EC). The subject will be provided ample time to read and understand the informed consent form and to consider participation in the study. The informed consent will be requested prior to screening and must be personally signed and dated by the subject directly prior to performance of any study related activity or procedure. If a subject is unable to read or write, informed consent shall be obtained through a supervised oral process.

An independent witness (as applicable) shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject and, whenever possible, subject shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent form attesting that the information was accurately explained and that informed consent was freely given. The point of enrollment corresponds with the time that subjects signs the informed consent.

The investigator and/or designee must also clearly document the process of obtaining informed consent in the subject's source documents. The voluntary process of obtaining informed consent confirms the subject's willingness to participate in the study. It's the investigator's responsibility to ensure that the informed consent process is performed in accordance with ICH-GCP and where applicable local and federal regulations. Failure to provide written informed consent renders the subject ineligible for the study. If new information becomes available that can significantly affect a subject's future health and medical care, this information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked

to confirm their continuing informed consent in writing by dating and signing the amended informed consent form.

9.1.2 Screening/Baseline Visit

A screening log that is maintained at the clinical site will be used to document all patients that were reviewed for potential inclusion into the clinical investigation

All patients considered for a radiofrequency ablation procedure for paroxysmal Atrial Fibrillation should be screened for study eligibility. The investigator or designated member of the research team will evaluate each patient for eligibility for enrollment.

9.1.2.1 Pre-procedure Assessments

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

- **Transthoracic Echocardiogram (TTE)** – Imaging to determine the atrial size within 30 days prior to the AF procedure. If the subject has undergone an imaging procedure within the 6-months prior to signing an informed consent that assessed and documented the left atrial size, the pre-procedure TTE is not required.
- **Imaging for detection of LA thrombus** – to be performed the day before the procedure or the day of the ablation procedure. Subjects meeting either of the following 2 criteria must have a pre-procedure TEE to screen for the presence of LA thrombus:
    - Subjects with known risk factors such as structural heart disease, presence of risk factors for stroke (i.e., CHADS2 score >1), and atrial enlargement.
    - Subjects who have been in AF for 48 hours or longer or for an unknown duration unless systemic anticoagulation at a therapeutic level has been maintained for at least three weeks.

  All other subjects who do not meet the criteria above must either undergo TEE or one of the following methods to screen for LA thrombus on the day before or the day of the ablation procedure. The imaging method used is at the discretion of the investigator based on the patient's medical history and the investigator's medical judgment:
    - Computed Tomography (CT)
    - Intracardiac Echocardiography (ICE)
    - Magnetic Resonance Imaging (MRI)
- **Pregnancy Test** – Woman of child-bearing potential only, performed within 1 week prior to the procedure.

- Baseline **Medical History**
- **Arrhythmias History** (including findings from TTM, ECG, Holter monitor, etc.)
- **Baseline** Concomitant Cardiac **Medications** (including anticoagulation regimen)
- **Electrocardiogram** (12-Lead ECG)
- **Adverse events**, if any

9.2 Study Ablation Procedure

9.2.1 General Medication Guidelines

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

- Medication **Prior** to AF Ablation Procedure
  - Uninterrupted systemic anticoagulation therapy is required 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.
  - ACT levels should be checked prior to administering RF energy and rechecked approximately every 15-30 minutes during the ablation procedure to ensure ACT ≥325 seconds. All recordings should be documented in the medical records as source documentation.
  - Adenosine: A bolus (I.e. 24mg) to sufficiently confirm PV isolation; rule out dormant conduction

    AND/OR
  - Isoproterenol to achieve a ≥ 20 beats per minute increase in heart rate to induce AF upon completion of the ablation procedure is recommended if pacing maneuvers are not performed (recommended dose range is 2-20 mcg/min).
- Medication **Following** AF Ablation Procedure
  - Anticoagulation therapy is strongly recommended for 2 months following ablation. Thereafter, subjects should receive anticoagulation therapy in accordance with the 2017 HRS.[46] Anticoagulation therapy will be recorded on the appropriate case report form.
  - Systemic oral anticoagulation is achieved using INR- dose adjusted warfarin (INR must be maintained at 2.0-3.0), direct thrombin inhibitor or factor Xa inhibitor.
  - Decisions regarding continuation of systemic anticoagulation more than 2 months post ablation should be based on the patient's stroke risk

profile and not on the perceived success or failure of the ablation procedure.

9.2.2 Instructions for Use (please refer to separate document)

9.2.3 Study Ablation Procedure Guidelines

[redacted]

Refer to Table 2 for an overview of equipment and devices required for the AF ablation procedure during this study

9.2.3.1.1 Recommendation for CoolFlow® Irrigation Pump Setting and RF Power-delivery

The QDOT catheter with Q-mode algorithm is designed to maximize RF lesion efficiency by using temperature feedback from the tip to adjust power and irrigation flow. For all power levels, the generator changes the pump irrigation flow rate from low (4 mL/min) to high flow (15 mL/min) or from high to low flow to reach and maintain the set maximum power without exceeding the set target temperature. The Q-mode algorithm minimizes the irrigation rate thus increasing temperature sensitivity at the catheter tip.

The CoolFlow® Irrigation Pump will deliver a continuous infusion of 4 ml/min (Qmode) of room temperature heparinized saline (1 u heparin/1 ml saline) when not delivering RF energy. Increase the irrigation to high flow rate starting up to 2 seconds before the onset of RF energy delivery and maintaining this higher flow rate until 5 seconds after termination of the energy application.

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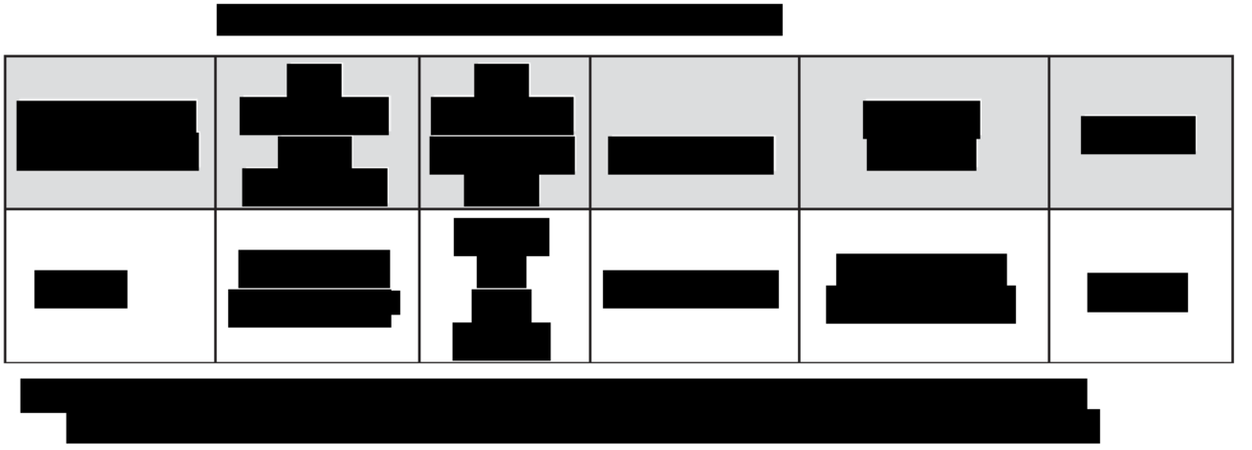

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9.2.3.1.1 General AF Ablation Guidelines

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

- Diagnostic catheter placement (discretion of investigator)
- 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 the ablation procedure.
  - An anatomical map is not required of triggers outside of the left atrium (e.g., SVC/CS etc.)
- Introduction of the study catheter and study ablation procedure (see section 9.2.3.1.2)
- Post ablation pacing procedure(s) and/or infusion of cardiac medications to induce AF (eg, Isoproterenol 2-20 mcg/min)

9.2.3.1.2 General Introduction of the Study Catheter

- Detailed Power setting for RF application at LA anatomical locations are provided in Section 9.2.3.1.3
- To minimize the risk of PV stenosis, it is recommended that RF energy applications are at least 1 to 2 cm outside the PV ostium to isolate the left and right-sided PVs.
- When ablating near adjacent anatomical structures, take precautions to minimize collateral damage to the adjacent structures.
  - When ablating near the esophagus (along the posterior wall of the left atrium), take precautions to avoid injuring the esophagus, including appropriately reducing RF power and contact force duration (see Section 9.2.3.1.6 for required esophageal monitoring instructions)
  - Prior to ablation in the region of the right superior PV, precautionary measures are recommended to evaluate proximity to the phrenic nerve, such as pacing maneuvers.

9.2.3.1.3 [redacted]

9.2.3.1.6 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
    - Esophageal displacement during RF application

9.2.3.1.7 Ablation Procedures

The circumferential anatomical approach will be used to isolate all PVs. To minimize the risk of PV stenosis, it is recommended that RF energy applications are at least 1 to 2 cm outside the PV ostium to isolate the left and right-sided PVs.

Note: confirmation of entrance block in all PVs is required.

In the event of spontaneous or induced AF and/or atrial flutter, the placement of additional RF lesions outside of the PV ostia is at the discretion of the investigator and includes the following:

- Linear lesions between both superior PVs (roof line), the mitral annulus and the left inferior PV (mitral isthmus line) or between the LA roof and mitral annulus (anterior line)
- Ablation for any non-PV foci in the LA and/or RA, including isolation of the superior vena cava (SVC)
- Linear lesions in the cavotricuspid isthmus, if the subject has a medical history of AFL or AFL is induced spontaneously during the procedure

If linear lesions are placed, it is recommended that complete conduction block across the ablation line be demonstrated by mapping and/or pacing maneuvers.

9.2.3.1.8 Post-Ablation

- Verification of entrance block is required for all PVs.
    - **A 20-minute waiting period is REQUIRED from the last RF application at a PV before verification may be confirmed.** The time of the last RF application in a PV and the time of entrance block verification MUST be documented in the medical record as source documentation. If reconduction is noted, additional RF applications should be applied. A second and/or third waiting period will be upon investigator's discretion.
    - **Mapping the Ablation lines with the Study catheter's micro electrodes is REQUIRED during the 20-minute waiting period**. If

breaks in the RF lines are found additional RF applications should be applied.

- To verify entrance block, analyze electrograms in sinus and/or atrial paced rhythm to confirm that no PV potentials are present.
    - After a **REQUIRED** 20-minute waiting period, administer:
        - Adenosine (24mg bolus) to rule out dormant conduction and/or
        - Isoproterenol: to achieve a ≥ 20 beats per minute increase in heart rate to induce AF upon completion of the ablation procedure (recommended dose range is 2-20 mcg/min).
- Demonstration of entrance block MUST be confirmed and documented by the Lasso® or Pentaray® Circular Mapping Catheter.
- The ablation procedure is considered complete when confirmation of entrance block in the pulmonary veins is confirmed and documented.
- Bidirectional block should be confirmed if linear lines are placed (Posterior Wall, Roof, Isthmus)

9.2.4 Post Procedure Assessments

Before hospital discharge:

- **Occurrence of AF or other arrhythmias**, if any
- **Concomitant medications** (only cardiac related AADs, anticoagulation regimen, etc.)
- **Electrocardiogram** (12-Lead ECG)
- Post-procedure **Pericarditis Evaluation**

  Prior to discharge, all subjects are required to undergo a transthoracic echocardiogram (TTE) to assess the pericardium. In the event significant pericardial effusion is identified, subjects should be followed until the condition resolves.

- **PV Stenosis Imaging Assessment**

  Subjects who exhibit symptoms suggestive of PV stenosis should undergo imaging (CT/MRI) to confirm and assess severity, if identified. In the event severe PV stenosis is diagnosed, subjects should be followed until the condition resolves or stabilizes.

- **Adverse events**, if any

9.3 Follow-up Requirements post-discharge

9.3.3 7 days follow-up (telephone or clinic visit)

- **Occurrence of AF** or other arrhythmias, if any
- **Concomitant medications** only cardiac related (AADs, anticoagulation regimen, etc.)
- **PV Stenosis Imaging Assessment**: Subjects who have symptoms suggestive of PV stenosis should undergo imaging (CT/MRI)
- **Adverse events**, if any

9.3.4 3 Month follow-up (clinic visit)

- **Medical / Hospitalization History**
- **Electrocardiogram** (12-Lead ECG)
- **Occurrence of AF** or other arrhythmias, if any
- **Concomitant medications** only cardiac related (AADs, anticoagulation regimen, etc.)
- **Adverse events**, if any
- **PV Stenosis Imaging Assessment**: Subjects who have symptoms suggestive of PV stenosis should undergo imaging (CT/MRI)
- **End of Study Follow up** (3-Month)

9.4 Management of Arrhythmia Recurrences and Repeat Ablation Procedures during follow-up

Repeat ablation(s) and management of arrhythmia recurrences during follow-up may be managed per investigator discretion. It's recommended to perform repeat ablations with the THERMOCOOL SMARTTOUCH® SF-5D Catheter utilizing its microelectrodes and the Qdot MICRO system. **The investigator must verify the lesion for gaps and if any, document locations.** The follow-up schedule will remain based on the initial ablation procedure.

9.5 Required schedule for subject treatments and evaluations

Refer to Table 1 for summary of required schedule for subject treatments and evaluations.

10. ADVERSE EVENT AND DEVICE DEFICIENCY REPORTING

10.1 Adverse Events (AE)

An Adverse Event is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

NOTE 1: This definition includes events related to the investigational device or the comparator.

NOTE 2: This definition includes events related to the procedures involved.

NOTE 3: For users or other persons, this definition is restricted to events related to investigational medical devices.

As from point of enrollment, at each evaluation and whenever the investigator becomes aware of an event, the investigator determines for each enrolled subject whether any adverse events (AE) have occurred, and determines their relationship to the investigational medical device and procedure as well as the seriousness of the event.

All adverse events must be recorded in the electronic CRF(s) in a timely manner throughout the clinical investigation and shall be reported to the sponsor together with an assessment without unjustified delay.

The date of the adverse event, treatment, resolution, assessment of both seriousness and relationship to the investigational device should be provided if available.

Subjects should be encouraged to report AEs immediately or in response to general, non-directed questioning (e.g., "How has your health been since the last visit?"). Any time during the clinical investigation, the subject may volunteer information that resembles an AE. If it is determined that an AE has occurred, the investigator should obtain all the information required to complete the AE Form of the electronic CRF.

All AEs must be followed until resolution or until a stable clinical endpoint is reached. The safety officer or designee of this clinical investigation will decide if more follow up information is needed in case the event is not resolved or stable at study completion. All required treatments and outcomes of the adverse event must be recorded in the electronic CRF(s).

The Sponsor is responsible for the classification of adverse events and ongoing safety evaluation of the clinical investigation and shall review the investigator's assessment of all adverse events. The Sponsor will determine and document in writing their seriousness and relationship to the investigational device. In case of disagreement between the Sponsor and the principal investigator(s), the sponsor shall communicate both opinions to the concerned parties.

10.1.3 Intensity and Severity

The following categories of adverse event severity are to be used:

Table 5 Adverse Event Intensity or Severity Definitions

Classification	Definition of classification
Mild	Any event resulting in minimal transient impairment of a body function or damage to a body structure, and/or does not require intervention other than monitoring.
Moderate	Any event resulting in moderate transient impairment of a body function or damage to a body structure, or which requires intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure
Severe	Any life-threatening event, resulting in permanent impairment of a body function or damage to a body structure, or requiring significant intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

10.1.4 Outcome

Outcomes should be assessed as follows:

Table 6 Adverse Event Outcome Classifications

Classification		Definition
Resolved	Without sequelae	Subject fully recovered with no observable residual.
	With sequelae	Subject recovered with observable residual effects.
Ongoing	Improved	Subject's condition improved, but residual effects remain.
	Unchanged	AE is ongoing without changes to the overall condition.
	Worsened	Subject's overall condition worsened.
Death		Subject died as a result of the AE (whether or not the AE is related to the device or procedure).

10.1.5 Cause/Relationship

The causal relationship to the investigational medical devices and procedure should be rated as follows, please refer to MEDDEV 2.7/3 Rev3 for detailed definitions:

Table 7 Adverse Event Causality Classifications:

Caused by	Relation	Definition of Relation

Device	**Definitely**	The event is associated with the investigational device beyond reasonable doubt as described per MEDDEV 2.7/3 Rev3.
	Probable	The relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained as described per MEDDEV 2.7/3 Rev3.
	Possibly	The relationship with the use of the investigational device is weak but cannot be ruled out completely as described per MEDDEV 2.7/3 Rev3.
	Unlikely	The relationship with the use of the investigational device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained as described per MEDDEV 2.7/3 Rev3.
	Not related	Relationship to the investigational device can be excluded as described per MEDDEV 2.7/3 Rev3.
Study Procedure	**Definitely**	The event is associated with the study procedure beyond reasonable doubt as described per MEDDEV 2.7/3 Rev3.
	Probable	The relationship with the study procedure seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained as described per MEDDEV 2.7/3 Rev3.
	Possibly	The relationship with the study procedure is weak but cannot be ruled out completely as described per MEDDEV 2.7/3 Rev3.
	Unlikely	The relationship to the study procedure seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained as described per MEDDEV 2.7/3 Rev3.
	Not related	Relationship to the procedure can be excluded as described per MEDDEV 2.7/3 Rev3.

10.2 Reportable Serious Adverse Events (MEDDEV 2.7/3 Rev 3)

The following events are considered reportable events in accordance with MEDDEV 2.7/3 Rev 3).

1. Any Serious Adverse Event that:

   a) led to a death,

   b) led to a serious deterioration in health of the subject, that either resulted in:

   - a life-threatening illness or injury, or
   - a permanent impairment of a body structure or a body function, or
   - in-patient hospitalization or prolongation of existing hospitalization, or
   - in medical or surgical intervention to prevent life threatening illness or
   - injury or permanent impairment to a body structure or a body function.

   c) led to foetal distress, foetal death or a congenital abnormality or birth defect.

NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

2. Any Device Deficiency that might have led to a SAE if:

   a) suitable action had not been taken or
   b) intervention had not been made or
   c) if circumstances had been less fortunate

3. New findings/updates in relation to already reported events.

The following clinical events are not considered adverse events for this clinical study:

- Study Arrhythmia recurrence (Paroxysmal Atrial Fibrillation), independently of action taken, by itself is considered a recurrence of disease (pre-existing condition), and, therefore, does not meet the definition of an AE.
- New onset AF/AFL/AT requiring pharmacological or synchronized electrical cardioversion during the hospitalization for the index ablation procedure
- Re-ablation for pre-existing condition itself is not an Adverse Event but any procedural complication is considered an Adverse Event and shall be reported within the applicable timelines

The investigator must submit to the sponsor (or designee) any SAEs and device deficiencies that could have led to a SADE occurring during the clinical investigation within 72 hours after being notified of the event and provides additional information, if required by the sponsor. The investigator will ensure an appropriate follow-up with the enrolled subjects in order to become aware of any serious adverse events in an acceptable timely condition.

All SAEs need to be followed until the event is resolved (with or without sequelae). The safety officer or designee of this clinical investigation will decide if more follow up information is needed in case the event is not resolved or stable at study completion. All required treatments and outcomes of the SAE must be recorded in the electronic CRF(s).

The investigator notifies his/her EC of SAEs and device deficiencies that could have led to a SADE, occurred at his/her site (and any additional information) as required by Ethics Committee or local regulations.

The sponsor will submit on regular basis (unless otherwise indicated by the Ethics Committee or recommended by the Sponsor's safety officer) to all participating clinical investigators an update of all SAEs and all device deficiencies that could have led to a SADE occurred at the participating site.

Event reporting to relevant competent authorities will occur by the sponsor and/or by the investigator, depending upon the local requirements and will be done per MEDDEV 2.7/3 rev3 guidelines.

10.3 Primary Adverse Events

The investigator is responsible for reporting, through the electronic data capture system (EDC system), all PAEs to the sponsor and/or designee within 72 hours of learning of the event.

Serious Adverse Events occurring within the first week (7 days) following an ablation procedure with THERMOCOOL SMARTTOUCH® SF-5D Catheter and AE term is one of the adverse events listed, will be considered for Primary Event assessment (Appendix A).

• Death
• Atria-Esophageal Fistula*
• Cardiac Tamponade**/Perforation
• Myocardial Infarction
• Stroke/Cerebrovascular Accident
• Thromboembolism
• Transient Ischemic Attack
• Diaphragmatic Paralysis
• Pneumothorax
• Heart Block
• Pulmonary Vein Stenosis
• Pulmonary Edema (Respiratory Insufficiency)
• Vagal Nerve Injury
• Pericarditis
• Major Vascular Access Complication/Bleeding

* Pulmonary vein (PV) stenosis and atrio-esophagael fistula that occurs greater than one week (7days) post-procedure shall be deemed Primary AEs. ** Hemodynamic compromise or instability is defined as Systolic BP < 80 mmHg

10.4 Anticipated Adverse Events

An anticipated Adverse Event is an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Anticipated adverse events are described in risks analysis (Refer to Investigators Brochure and Instruction for Use). Refer to Appendix B for a comprehensive list of foreseeable and anticipated adverse events reported in previous studies of RF ablation.

10.5 Adverse Device Effect and Serious Adverse Device Effects

Adverse Device Effects (ADE's) are adverse events related to the use of an investigational medical device.

> NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the investigational medical device.

NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of the investigational medical device.

Serious Adverse Device Effects (SADE's): adverse device effects that has resulted in any of the consequences characteristic of a serious adverse event.

10.6 Unanticipated Serious Adverse Device Effects (USADE)

Unanticipated serious adverse device effect (USADE) is a 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 (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

Anticipated adverse device effects are described in risks analysis (Refer to Investigators Brochure and Instruction for Use). Refer to Appendix B for a comprehensive list of foreseeable and anticipated adverse events reported in previous studies of RF ablation.

10.7 Device Deficiency and Complaints

Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

If a device deficiency occurs that could have led to a SADE, the investigator must report the event within 72 hours after being notified of the event and provides additional information.

The sponsor will review all reported device deficiencies and will determine and document whether they could have led to a serious adverse device effect (SADE) and report accordingly to the regulatory authorities, and ECs.

Incident reporting of concomitant CE marked devices:

If a device deficiency of a CE marked device manufactured or distributed by Biosense Webster has occurred, the event has to be notified immediately to the sponsor via Biosense Webster regular complaints handling process and procedures.

If this event is considered as an incident according to the definition given in the MEDDEV 2.12/1 guidelines, the sponsor will notify the incidents to the competent authorities, according to the regulatory requirements and company procedures applicable for CE marked medical devices.

A device deficiency related to a medical device not manufactured by Biosense Webster should be reported by the investigator to their respective manufacturer as per relevant regulation.

Complaints related to products manufactured and/or distributed by Biosense Webster, used during the procedure related to other devices (other than the study device under investigation), are to be reported according to current Biosense Webster procedures and other policies as necessary (i.e., institutional policies, EC policies, and local regulations), investigators are instructed to return devices in accordance with current company procedures and other relevant regulations.

Complaints related to non-Biosense Webster, Inc. products must be handled according to institutional policies, EC policies, and local regulations.

10.8 Documentation/Follow-up reporting

All AE/SAE must be monitored until they are adequately resolved or explained, including submission of follow-up reports to the sponsor or designee as soon as the information becomes available. Additional documentation may be requested by the Sponsor or designee, including but not limited to, a written subject narrative detailing the clinical course of the AE/incident, a copy of any correspondence with the local EC, hospital records, death certificate, and an autopsy report, if available.

10.8.3 Reporting requirements to sponsor and regulatory/competent Authorities

All Primary AEs, Serious AEs (SAE/SADE, whether or not they are related to the device or procedure), Unanticipated Serious Adverse Device Effects (USADE) and study device deficiencies must be reported to the Sponsor (Biosense Webster Clinical Operations) or designee and entered into the eCRF within 72-hours of awareness by the clinical investigation site personnel.

The sponsor will submit in a timely fashion (unless otherwise indicated by the Ethics Committee or regulatory authority) to all participating clinical investigators a safety update. Event reporting to relevant competent authorities will occur by the sponsor and/or by the investigator, depending upon the local requirements and will be done per MEDDEV 2.7/3 rev3 guidelines.

11. STATISTICAL ANALYSIS METHODS

11.1 Sample Size

This is a clinical feasibility study for evaluation of workflow and acute performance of THERMOCOOL SMARTTOUCH® SF-5D system. This clinical investigation is intended to provide preliminary estimates of workflow and acute outcomes.

Because this study is a feasibility study, there is no statistical power calculation and no hypothesis to be generated. 50 evaluable subjects are deemed sufficient to characterize the workflow and acute outcomes.

Enrollment in the clinical investigation will be approximately 50 evaluable subjects with approximately 10 subjects per investigational site, distributed over approximately 5 centers in Europe.

11.2 Analysis Population

The following analysis populations will be used to complete the analyses of data:

Safety Population: The Safety population will include all enrolled subjects who have the investigational device inserted, regardless if RF energy is delivered.

Evaluable Population: The evaluable population will include all enrolled subjects who meet the eligibility criteria and who undergo ablation with the study catheter.

Effectiveness Population: The effectiveness population will include all enrolled subjects who have had the investigational device inserted and underwent ablation with the study catheter under guidance of the THERMOCOOL SMARTTOUCH® SF-5D Module.

11.3 Statistical Methods

All data will be summarized by descriptive analyses. No formal statistical inference will be made.

11.3.1 Acute Device Performance

Acute success is defined as achieving confirmation of entrance block in all targeted PVs after adenosine and/ or isoproterenol challenge. The number and percentage of subjects who have reached acute success will be summarized.

11.3.2 Acute Safety

Acute safety outcome will be reported as the number of primary adverse events and the number of subjects experiencing primary adverse events (within 7 days of catheter ablation, with exception for PV stenosis and AE fistula (Appendix A)). The percentage of subjects experiencing primary adverse events will also be reported.

11.3.3 Safety

The number and percentage of subjects with early onset (within 7 days of ablation procedure with exception for PV stenosis and AE fistula) pre-defined primary Adverse Events will be summarized overall and by AE type, seriousness, severity, causality, anticipated or not and outcome etc. The subjects with primary adverse events will also be listed.

The number and percentage of subjects with Serious Adverse Device Effects (SADEs) during follow-up period (3 months) will be summarized overall and by

AE type, timing (< 7 days, 7-30 days, > 30 days), seriousness, severity, causality, anticipated or not and outcome etc. Listing of SADEs will also be provided.

11.3.4 Procedural Data

Procedural data will be summarized and listed. For continuous variables, number of subjects with non-missing data, mean, standard deviation, median, 25% percentile, 75% percentile, minimum, and maximum will be reported. For categorical variables, the frequency and percentage will be presented for each category.

11.3.5 Investigational device performance

Investigational device performance (THERMOCOOL SMARTTOUCH® SF-5D Catheter (D-1395-05-SI) and nMARQ™ Multi-Channel RF Generator (D-1341-07) with Software V. 3.0.1, will be reported by means of survey questions. The scores of survey questions will be summarized by presenting the number of subjects with non-missing data, mean, standard deviation, median, minimum, and maximum for each sub-scale measurement. Listings of survey answers/scoring will also be provided. Workflow questions and interactions with system setup (Dongle (EM-5050-055F), Interface Cable (D-1357-03-SI), and CARTO 3 v6) might also be subjected to investigator feedback.

12 DATA MANAGEMENT

The Sponsor or designee will perform all data management activities for this clinical investigation. These activities include development and validation of a clinical database, into which all clinical investigation data will be entered. The Sponsor or designee will be responsible for ensuring overall integrity of the data and database.

12.1 Data Collection

Electronic Case Report Forms (eCRF) will be used to collect all subject data during this clinical investigation. The eCRF will be developed to capture the information outlined in this protocol. Data collected on the eCRFs will be analyzed as defined in the clinical investigation protocol. Modification of the eCRF will only be made if deemed necessary by the sponsor. All CARTO® 3 v6.0 and Generator data files created during the procedure will be downloaded/ extracted and an anonymized copy provided to the sponsor for further evaluation.

12.2 Data Reporting

The investigator, or a designated individual, is responsible for ensuring that clinical investigation data are properly recorded on each subject's eCRF and related documents. The investigator is required to electronically sign the eCRF on the appropriate pages to verify that he/she has reviewed and attests to the correctness of the recorded data.

Completed eCRF will be monitored by the sponsor personnel, or an appropriately qualified and trained designee, at regular intervals throughout the clinical investigation.

The investigator and institution must permit the inspection of any clinical investigation related documentation and eCRF by clinical investigation representatives, responsible government agencies, or both.

All eCRF data should be entered by the designated site personnel in a timely manner after the subject visit. For AE reporting, refer to the Adverse Event Reporting Requirements and timelines within this clinical investigation protocol.

12.3 Missing Data Handling

Missing questions will be queried for reasons and handled on an individual basis.

12.4 Source Documentation

Source documents will serve as the basis for monitoring the eCRF. Source documents may include subject's medical records, hospital charts, clinical charts, the investigator's subject clinical investigation files, admissions and discharge summaries, as well as the results of diagnostic tests such as X-rays, laboratory tests, and electrocardiograms.

If no standard hospital or office document exists to capture information that may be unique to this clinical investigation, a worksheet may be developed to record this information, which may be signed by the site and serve as the source document for unique clinical investigation data.

Electronic subject records will be considered source documents on the condition that the hospital's database is a validated system. If this is not the case, electronic records will have to be printed and added to the subject's paper file. A print-out of an eCRF cannot be used as source documentation.

Regulations require that investigators maintain information in the subject's medical records, which corroborate data collected on the eCRF. In order to comply with these regulatory requirements, at minimum, the following is a list of information that should be maintained on source documentation:

- Medical history/physical condition of the clinical investigation subject before involvement in the clinical investigation sufficient to verify protocol selection criteria (if not already present).
- Dated and signed notes on the day of entry into the clinical investigation including the name of the clinical investigation sponsor (Biosense Webster), protocol number, clinical site identifier, subject number assigned and a statement that consent was obtained.

- Dated and signed notes from each clinical investigation visit with reference to the eCRF for further information, if appropriate (for specific results of procedures and examinations).
- AEs reported and their resolution, including supporting documents such as discharge summaries, EP lab reports, ECGs, laboratory results, etc.
- Notes regarding protocol-required medication and prescription medications taken during the clinical investigation (including start and stop dates).
- Clinical investigation subject's condition upon completion of or withdrawal from the clinical investigation.

12.5 Data Verification and Review

All eCRF will be subjected to automated and manual validation checking for omitted data, gross data inconsistencies, and overall data integrity. The sponsor or designees will employ a clinical investigation database on a server, available to site and sponsor personnel over an Internet connection. Periodic analysis of data (across cases) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data entry errors. For first cases at each site, the investigators and/ or sponsor may wait for the result of the case analysis before enrolling the next patient in this study site.

12.6 Final Data Analysis

All exported datasets for analyses will undergo a final data review before final database lock. Once all critical data are monitored and locked, the final analyses of clinical investigation data will be performed.

12.7 Confidentiality and Protection of Clinical Investigation Data

During this clinical investigation, all representatives of the Sponsor will comply with all in-country privacy laws and regulations regarding contact with subjects, their medical record information, copying of information, and protection of the subject identities.

All information and data sent to Biosense Webster concerning subjects or their participation in this clinical investigation will be considered confidential. Only authorized Biosense Webster personnel or representatives (including contracted service providers, i.e. Core Lab, Clinical Research Associate, CRO, etc.), representatives of the FDA or Competent Authorities acting in their official capacities will have access to these confidential files upon request (including, but not limited to, laboratory test result reports, ECG reports, admissions/discharge summaries for hospital admission occurring during a patient's study participation and autopsy reports for deaths occurring during the clinical investigation). Some of the countries to which the study subjects and investigators personal data may be transferred may not offer as comprehensive a level of protection of personal data as within the European Union but Sponsor will take all reasonable steps to

ensure a sufficient level of data protection. All data used in the analysis and reporting of this evaluation will exclude identifiable reference to the subject.

13 QUALITY CONTROL AND QUALITY ASSURANCE

13.1 Monitoring of the study

The site will undergo periodic monitoring of the clinical investigation, as described in a separate monitoring plan and which involves a visit from a Sponsor representative, deemed qualified to perform such visit. Monitoring visits may include, but are not limited to, the following:

- Verification of accuracy of all study logs such as the Subject Log, etc.
- Verification of proper informed consent for all subjects participating in the clinical investigation.
- Verification of completeness of the Investigator Site File/Regulatory Binder
- Source verification with the eCRFs
- Identification and action to resolve any issues or problems with the clinical investigation.

13.2 Protocol Modifications and Adherence

13.2.1 Protocol Amendment

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

13.2.2 Prospective Protocol Deviation

The investigator may prospectively request in writing from the sponsor, or designee, to deviate from a specific requirement or requirements stated in the study protocol. Each request must be reviewed and approved by the sponsor prior to allowing the specific protocol deviation.

Such requests will be held to a minimum in order to preserve the integrity of the data being collected in the study.

13.2.3 Protocol Deviations/Other Non-compliance issue

The study monitors shall verify that the conduct of the study is in compliance with the currently approved protocol and applicable regulations, and shall identify any issues of non-compliance with regulations or guidelines.

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

A protocol deviation is defined as an instance of failure to follow, intentionally or unintentionally, the requirements of the protocol (e.g. missed test or procedure, visit out of window, non-adherence to inclusion/exclusion criteria) (even if a prospective protocol deviation is granted). Investigators are not allowed to deviate from the protocol.

Protocol deviations will be monitored closely by the sponsor or designee(s) and shall be reported immediately to the EC if the deviation affects subject's rights, safety and well-being, or the scientific integrity of the study or according to EC specific requirements. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of a subject may proceed without prior approval of the sponsor and EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.

13.3 Audits and Inspections

The sponsor and/or designee and/or Regulatory Authorities may contact the participating institution to inform the investigator of an upcoming audit/inspection. The investigator should immediately notify the sponsor of any Regulatory Authority audits/inspection at the study site. The audit/inspection can include the review of documents, facilities, records and any other resources deemed by the authorities to be related to study.

13.4 Responsibilities and Record

13.4.1 Role of the Sponsor

As the Sponsor of this clinical investigation, Biosense Webster has the overall responsibility for the conduct of the clinical investigation, including assurance that the clinical investigation meets the international regulatory requirements and any national regulations, as appropriate. The Sponsor will also maintain compliance with EU Directive 93/42/EEC, Good Clinical Practice, the International standard ISO 14155:2011 (Clinical Investigation of Medical Devices for Human Subjects – Good clinical practice) and the Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, Brazil, 2013).

13.4.2 General Duties

The sponsor is responsible for providing quality data that satisfy federal regulations and informing proper authorities of reportable events and deviations from the protocol.

13.4.3 Sponsor Responsibilities

- Selection of the study investigators
- Selection of appropriately qualified and trained individuals, including monitors, to conduct the study
- Development and, if applicable, modifications of protocol and eCRFs
- Obtain study contracts with investigators/hospitals, CROs and other involved 3rd parties
- Development and/or approval of an adequate informed consent form
- Ensure that appropriate training/information is provided to the study investigators and staff
- Data and site monitoring
- Database input, management and maintenance
- Inform investigator of his/her responsibilities
- Ensure that all AEs are reported by the study investigators and where appropriate, are reported to the other investigators and relevant regulatory authorities
- Implement insurance coverage prior enrolment of patients
- Obtain applicable regulatory approval prior to enrollment of subjects
- Report deviations from the protocol as appropriate.
- Prepare written required reports and a final clinical study report and provide to ECs and regulatory authorities as applicable

13.4.4 Investigator Responsibilities

- Obtain EC approval, if applicable
- Supply the Sponsor with a current curriculum vitae and medical licenses (if applicable) for any colleague(s) involved in the study
- Obtain informed consent form and enroll patients
- Perform medical procedures
- Order all tests required by the study protocol
- Adhere to the study protocol
- Follow subjects until the end of the study protocol
- Complete eCRFs on time, completely and accurately
- Allow the Sponsor direct access to source documents to perform monitoring duties, and to perform audits
- Maintain records and provide reports according to the local legislation/regulations

- Share all relevant study-related information with colleagues involved in this study
- Inform the appropriate entities (e.g., Sponsor, EC in a timely manner regarding the occurrence of any AEs and/or device deficiencies.

13.4.4.1 Investigator Record

The investigator is responsible for the preparation, review, signature, and maintenance of the records cited below.

- EC approval letter, including approved ICF document, with associated correspondence
- EC membership list
- Signed Clinical Study Agreement
- Clinical investigation protocol/Investigational Plan and all amendments, and CRF Signed original copy of the Investigator Agreement and CV
- Correspondence relating to the clinical investigation
- CV for all Sub-Investigator(s)
- Investigational site training records
- All logs including patient ID log, screening log, enrollment log, as applicable
- Site personnel delegation of authority/responsibility
- Clinical Monitor/Site Visit sign-in log
- Reports (e.g., annual reports, final reports from investigator and Sponsor)

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

- Subject's case history records including, but not limited to medical history, procedure dates, and dates of follow-ups
- Electronic data, if applicable
- Source documents (Imaging, ECGs, Pregnancy test, …)
- Signed informed consents
- All completed CRFs
- Supporting documentation of any AE or death

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

13.4.5 Document Retention

Records and reports will remain on file for a minimum of five (5) years (unless otherwise instructed by local requirements) after the completion or termination of this post-approval study records and reports may be discarded upon notification by Biosense Webster to the clinical investigation site. The principal investigator must contact Biosense Webster prior

to destruction of any study-related records or reports to ensure adherence to appropriate record retention process.

All electronic CRFs and all source documents (e.g., informed consent forms, laboratory reports, progress notes, medical histories, physical and diagnostic findings, diagnoses, procedure dates, and investigational medical device disposition records) that support the electronic CRFs must be retained in the files of the responsible investigator for a minimum of 5 years or per country specific record retention requirements following notification by the sponsor that all investigations have been terminated or completed.

This documentation must be accessible upon request by the regulatory authorities, the sponsor or designee.

The sponsor must approve archiving or transfer of the documentation for relocation purposes off premise, in writing, prior to the actual file transfer. The investigator must notify the sponsor, in writing, of transfer location, duration, and the procedure for accessing the study documentation.

If the investigator retires, relocates, or for other reasons withdraws from assuming primary responsibility for keeping the study records, custody per written notice (transfer of obligation) must be submitted to the sponsor indicating the name and address, of the person accepting primary responsibility. The EC must be notified in writing of the name and address of the new custodian. Record retention dates must be provided to all parties by the sponsor's corporation.

13.5 Subject Confidentiality

Subject confidentiality will be maintained throughout the study in a way that ensures the information can always be traced back to the source data. For this purpose, a unique subject identification code (ID number and subject name code) will be used that allows identification of all data reported for each subject. Data relating to the study might be made available to third parties (for example in case of an audit performed by regulatory authorities) provided the data are treated confidentially and that the subject's privacy is guaranteed. The privacy of each subject and confidentiality of his/her information shall be preserved in reports and when publishing any data.

13.6 Ethics Committee

This protocol, informed consent and other applicable study-related documents must be reviewed and approved by the appropriate Ethics Committee (EC) and the Competent Authorities where the clinical investigation is to be conducted before enrollment of subjects. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

The sponsor and the EC must approve in writing any changes to the protocol that affect the rights, safety, or welfare of the subjects, or may adversely affect the validity of the clinical investigation.

A signed copy of the EC Approval Form and a signed copy of the EC approval letter addressed to the investigator must be submitted to the sponsor certifying clinical investigation approval before commencement of subject enrollment. Investigators are responsible for submitting and obtaining initial and continuing review (per local regulations) of the clinical investigation by their EC.

13.7 Study Data Reporting and Processing: training

All Investigators will be required to undergo protocol training prior to starting subject enrollment. Investigator experience with AF ablation therapy will be documented. Each electrophysiologist must be skilled in intracardiac mapping and ablation of atrial fibrillation with the use of the radiofrequency ablation catheters.

The training of appropriate site personnel will be the responsibility of the sponsor or designee. The investigator is responsible for ensuring that his/her staff conduct the study according to the protocol and instructions for use accompanying the medical devices. To ensure proper device usage, uniform data collection, and protocol compliance, the sponsor or designee will present a formal training session to investigators and site personnel. Should an investigator miss the formal training session he/she may be trained to the protocol and study procedures by the site principal investigator. A sponsor representative may be present to support the procedure for the first few cases at each site to ensure that the device is being utilized appropriately.

14 INVESTIGATION AND MEDICAL DEVICE ACCOUNTABILITY

14.1 Materials

The Sponsor will keep records of all investigational devices shipped to the site.

For the THERMOCOOL SMARTTOUCH® SF-5D Catheter, complete manufacturing records of every lot of catheter manufactured for human use during this study are maintained at Biosense Webster, Inc. Each lot of catheters is released for human use under a Confirmation of Conformity from Regulatory Affairs in accordance with MDD 93/42/EEC that will certify that the investigational devices conforms to the essential requirements apart from the aspects covered by the investigations and that, with regard to these aspects, every precaution has been taken to protect the health and safety of the subject.

After obtaining appropriate approvals (CA/EC), the Sponsor initiate shipments and will keep records of all investigational devices shipped to the site. Investigators are responsible for appropriate logging of the devices received, verification of packing slip information (i.e., lot numbers and quantity shipped), date and identity that each device was used in the

study, disposition information regarding return to the Sponsor. The Sponsor will label all devices as "exclusively for clinical investigations';" in a prominent location.

14.2 Device Accountability

The Device Accountability Log shall record the following information for all investigational devices:

- Date of receipt
- Person in receipt of the devices
- Quantity received
- Catalog number
- Serial/lot numbers
- Expiry date
- Date device was used
- Subject ID on whom device was used
- Date of return
- Type of return (i.e., return to Sponsor for adverse event, complaint, etc.)
- Airway bill number of return shipment

14.3 Device Returns

All Investigational devices will be labeled as "Exclusively for clinical investigations" and are only to be used for subjects enrolled in this clinical investigation.

All shipped THERMOCOOL SMARTTOUCH® SF-5D catheters (used and unused) will be returned to the Sponsor's attention at the below address. Any suspected malfunctioning device or device associated with an adverse event (device related or possibly device related) will undergo a thorough complaint analysis and must be properly documented on the case report form (CRF).

All returned devices must be properly decontaminated per hospital policy, product labeling and properly labeled with the subject identification number, date of event, identified as a defective return, non-defective return, or adverse event.

Please retain tracking information in the event the package has been lost and requires tracking. All investigational devices should be returned to:

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

14.4 Labeling

Sample labels are included in the package approved by the Competent Authorities. All labeling clearly identifies the product as investigational.

15 SAFETY COMMITTEE

15.1 Data Safety Designee/Committee

The medical safety officer or designee will review, on regular or urgent basis, all applicable adverse events and deaths. This medical safety officer shall advise about the appropriateness of continuing or terminating the clinical investigation, based upon findings during his review of adverse events and deaths. The overall safety profile of the investigational device will be evaluated by the Sponsor at the end of the trial.

16 PUBLICATION POLICY

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

All information concerning the study and investigational medical device, sponsor operations, patient application, manufacturing processes, and basic scientific data supplied by the sponsor to the investigator and not previously published, are considered confidential and remains the sole property of the sponsor. The investigator understands that the information developed in this feasibility study may be disclosed as required to other investigators or government regulatory agencies.

Any publication or other public presentation of the investigational medical device or results from this study require prior review and written approval of the sponsor. Draft abstracts, manuscripts, and materials for presentation at scientific meetings should be provided to the sponsor at least ninety (90) working days prior to abstract or other relevant submission deadlines, unless otherwise agreed.

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18 ATTACHMENTS

Appendix A: Primary Adverse Event Classification

Primary Adverse Event (AE)

A Primary AE is a serious adverse event, which occurs within the first week (7 days),* following an AF ablation procedure with the Study Catheter and meets one of the following definitions:

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 / 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	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 h), always within 24h Neuroimaging without tissue 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 intra pleural 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. A severe PV stenosis 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.

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

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

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

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

Appendix B: Foreseeable and anticipated adverse events related to RF ablation

Anticipated Adverse Events	
1.	Acute Respiratory Distress Syndrome (ARDS)
2.	Air embolism
3.	Allergic reaction / anaphylactic shock
4.	Anemia
5.	Anesthesia reaction (e.g., hair loss)
6.	Apnea - sedation induced
7.	Arrhythmias: bradycardia, tachycardia, pro-arrhythmias, ventricular tachyarrhythmia / pro-arrhythmia
8.	Aspiration pneumonia
9.	Asthmatic attack
10.	Atelectasis
11.	Atrial fibrillation or other arrhythmia: exacerbation of pre-existing arrhythmia
12.	Atrio-Esophageal fistula
13.	Atypical left atrial flutter
14.	AV fistula
15.	Bleeding complications
16.	Bleeding requiring transfusion
17.	Cardiac arrest
18.	Cardiac perforation / Tamponade
19.	Cardiac thrombo-embolism
20.	Cerebro-vascular accident (CVA) / stroke
21.	Chest pain/discomfort
22.	Complete heart block, temporary or permanent
23.	Conduction block: ongoing / resolved
24.	Congestive Heart Failure
25.	Coronary artery dissection
26.	Coronary artery occlusion
27.	Coronary artery spasm
28.	Coronary artery Thrombosis
29.	Death
30.	Deep venous thrombosis
31.	Dislodgement of ICD (Implantable Cardioverter Defibrillator) or permanent pacing leads
32.	Disseminated Intravascular Coagulation
33.	Dyspnea
34.	Endocarditis
35.	Epistaxis
36.	Esophageal injury
37.	Expressive aphasia
38.	Fainting
39.	Fatigue
40.	Gastro-intestinal disorders like gastric reflux, nausea
41.	Gastrointestinal diverticulosis

Anticipated Adverse Events	
42.	Heart Failure
43.	Hematoma (local) /ecchymosis
44.	Hemorrhage
45.	Hemothorax
46.	High / increased creatinine phosphokinase (CPK)
47.	Hypotension
48.	Hypoxia
49.	Implantable cardioverter-defibrillator (ICD) lead malfunction
50.	Increased phosphokinase level
51.	Infection, localized or systemic
52.	Laceration
53.	Leakage of air or blood into the lungs or other organs due to perforation
54.	Liver toxicity
55.	Mobile strands in Inferior Vena Cava
56.	Myocardial Infarction
57.	Neurological disorders (tremor, poor coordination, headache, ...)
58.	Obstruction / perforation / damage to the vascular system
59.	Parkinson's disease
60.	Pericardial effusion resulting in tamponade
61.	Pericardial effusion without tamponade
62.	Pericarditis
63.	Peripheral embolus
64.	Peripheral nerve injury
65.	Peripheral thromboembolism
66.	Phlebitis
67.	Phrenic nerve damage / diaphragmatic paralysis
68.	Pleural effusion
69.	Pneumonia
70.	Pneumothorax
71.	Pseudoaneurysm
72.	Pulmonary edema
73.	Pulmonary edema / Heart failure
74.	Pulmonary embolism
75.	Pulmonary hypertension
76.	Pulmonary toxicity, like acute pulmonary syndrome
77.	Pulmonary vein dissection
78.	Pulmonary vein Stenosis
79.	Pulmonary vein thrombus
80.	Pump failure
81.	Renal failure
82.	Respiratory depression/failure
83.	Retroperitoneal hematoma
84.	Rhabdomyolysis, including produced by body position or propofol
85.	Sedation induced CO2 retention with lethargy and cholecystitis
86.	Seizure
87.	Sepsis
88.	Skin burns (due to cardioversion, tape, etc.)

Anticipated Adverse Events	
89.	Skin discoloration
90.	Skin injury / muscle or connective tissue injury due to body position, electrical cardioversion
91.	Skin rash
92.	Thrombocytopenia
93.	Thromboembolism
94.	Thrombosis
95.	Thyroid disorders
96.	Transient extremity numbness
97.	Transient ischemic attack (TIA)
98.	Unintended complete or incomplete AV, Sinus node, or other heart block or damage
99.	Urinary retention
100.	Urinary tract infection
101.	Urinary tract injury or infection related to the urinary catheter
102.	Valvular damage/insufficiency
103.	Vasovagal reactions
104.	Vision change
105.	Volume overload
106.	Worsening obstructive, restrictive, or other form of pulmonary disease
107.	X-ray radiation injury of skin, muscle and/or organ