CLINICAL INVESTIGATION PROTOCOL

Biosense Webster
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RAPID-AF: Repetitive Activation Patterns and Focal Impulses Identification and Ablation in Persistent AF using the RHYTHMFINDER-192

Sponsor:	BIOSENSE WEBSTER, INC. 3333 Diamond Canyon Road Diamond Bar, CA 91765
Protocol number:	CF-171
Protocol Version Date:	Version 2.0 -16 September, 2016

History of Changes

Version Date	Description
Version 1.0 – 10 November 2015	Original document
Version 2.0 – 16 September, 2016	Updated protocol design

The RHYTHMFINDER™ 192 Catheter or RF-192 is for investigational device use only and is not commercially available anywhere in the world. '(RAPID-AF)' 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 RHYTHMFINDER™ 192 Catheter may be different.

[redacted]

[redacted]

Repetitive **A**ctivation **P**atterns and Focal Impulses **Id**entification and Ablation in Persistent **AF** using the RHYTHMFINDER-192

RAPID-AF ("CF-171")

Clinical Investigation Number	CF-171
Clinical Investigation Name	RAPID-AF
Revision	Version 2.0
Date	September 16, 2016
Sponsor	Biosense Webster, Inc. 3333 Diamond Canyon Road Diamond Bar, CA 91765 Tel +1 909-839-8500 Fax +1 909-839-8804
Contacts	[redacted]
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	[redacted]
	[redacted]
Whereas, the Clinical Study is sponsored by Biosense Webster Inc., Responsibilities for the conduct of this clinical study have been transferred in EMEA to Johnson and Johnson Medical NV/SA with registered offices at Leonardo Da Vincilaan 15, 1831 Diegem, Belgium. Responsibilities for the conduct of this clinical study, have been transferred in Canada to Johnson & Johnson Medical products, a devision of Johnson & Johnson Inc., 200 Whitehall Drive, Markham, Ontario, Canada L3R 0T5	
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 REB/IRB/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 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 21 CFR Part 812 and ISO: 14155-2011 Standards and any other applicable local laws and regulations.
- To permit trial-related monitoring, audits, REB/IRB/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 immediately but no later than 3 calendar days after becoming aware of the event of occurrence to Biosense Webster; 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. 3333 Diamond Canyon Road Diamond Bar, CA 91765 Tel +1 909-839-8500 Fax +1 909-839-8804
Protocol Title	**R**epetitive **A**ctivation **P**atterns and Focal Impulses **Id**entification and Ablation in Persistent **AF** using the RHYTHMFINDER-192
Abbreviated Title	**RAPID-AF**
Study Purpose	The purpose of this study is to assess safety and effectiveness of the RHYTHMFINDER™ 192 Catheter in conjunction with the CARTOFINDER™ (CF) Algorithm when used for treatment of Persistent Atrial Fibrillation (PsAF).
Study Devices	RHYTHMFINDER basket catheter (Investigational) CARTOFINDER™ workstation (CE-mark) CARTO® 3 with CARTOFINDER™ module (CE-mark)
Scope and study centers	Geographic involvement may include centers worldwide, mainly Europe and Canada. Approximately 6 to 10 centers worldwide will participate
Study Population	All subjects with persistent AF who are scheduled to undergo a clinically-indicated ablation procedure for management of their persistent AF will be the target population for screening.
Study Design	The study will enroll approximately 40-70 subjects. Subjects will undergo CARTOFINDER™ guided ablation (CFGA) followed by PVI. Subjects will have follow-up visits at 7 days, 3, 6 and 12 months post-procedure. Subjects where no CF ablation target is identified on the baseline CARTOFINDER™ map using the RHYTHMFINDER™ 192 Catheter, will exit the study after 7 day follow up.
Study Duration	Approximately 20 months (8 months recruitment, 12 months follow-up)

Study Endpoints	**Effectiveness** • Acute success defined as: Rate of conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia, after CFGA and PVI (without cardioversion) • Procedural success defined as: Conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia after CFGA and PVI, with or without the need for cardioversion • Rate of conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia, after CFGA only (before PVI and without cardioversion) • Freedom from documented symptomatic AF/AT/AFL recurrence (episodes ≥ 30 seconds on an arrhythmia monitoring device) post the 3-month blanking period through the 12-month follow up. • Incidence of PVI (entrance block) after adenosine/isoproterenol challenge • Change of intra-cycle length from pre-CFGA to post-CFGA and post-PVI **Safety** • Incidence of early-onset primary adverse events within 7 days of the ablation procedure. • Incidence of study device and procedural related SAEs during follow-up period (12M) • Incidence of all SAEs during follow-up period (12M) • Incidence of study device and procedure related adverse events

Other Study Assessments	• Number of identified CF ablation targets
	• Max #of active RF 192 electrodes during initial mapping procedure
	• AAD use post the 3-month blanking period
	• Incidence of repeat ablation procedures for AF post the 3 month blanking period
	• Procedural data:
	  o All target sites for RF lesion application
	  ▪ Location of ablation targets
	  ▪ Number of RF applications per target
	  ▪ Total RF duration per application
	  o RF ablation parameters (including but not limited to: power, contact force, impedance, flow rate, temperature)
	  o Total fluoroscopy time and dose
	  o Total procedure, mapping and ablation time

Study Inclusion Criteria	Subjects must meet the following **inclusion criteria**:
	1. Age $\geq$ 18 years.
	2. Patients who have signed the Patient Informed Consent Form (ICF)
	3. Scheduled to undergo a clinically-indicated catheter ablation procedure for treatment of
	  a. persistent atrial fibrillation (defined as continuous atrial fibrillation that is sustained beyond seven consecutive days).
	  b. drug-resistant atrial fibrillation. (failed 1 or more class I or III antiarrhythmic drugs) and demonstrating Persistent AF (requiring drugs or electrical shock to terminate AF)
	4. In AF at the time of the baseline CARTOFINDER™ Map (spontaneous)
	5. Left Atrium (LA) must demonstrate sufficient electrical activity to allow for the identification of ablation targets.
	6. Able and willing to comply with all pre-, post-, and follow-up testing and requirements (e.g. patients not confined by a court ruling)

Study Exclusion Criteria	Subject who meet any of the following **exclusion criteria** are not eligible for enrollment. 1. Paroxysmal Atrial Fibrillation 2. Continuous AF > 12 months (1-Year) (Longstanding Persistent AF) Subjects previously diagnosed as Long Standing Persistent (LSP) but have demonstrated the ability to maintain Normal Sinus Rhythm for >30 days after cardioversion and have not been in AF greater than 1 year at the time of the procedure remain eligible for inclusion. 3. Previous ablation procedure for PsAF (defined as ablations involving more than only PV isolation) 4. Patients with a left atrial size >55 mm (echocardiography, parasternal long axis view). 5. Inability to restore sinus rhythm for 30 seconds or longer in the opinion of the investigator. 6. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study. 7. Atrial arrhythmia patients with structural atrial disease such as a prior history of atriotomy from prior atrial surgery, presence of an atrial septal defect, and/or presence of an atrial septal closure patch.

	8. History of or current blood clotting or bleeding abnormalities, contraindication to systemic anticoagulation (i.e., heparin, warfarin, dabigatran, or a direct thrombin inhibitor). 9. significant pulmonary disease, cardiac surgeries, unstable angina, uncontrolled heart failure, acute illness or systemic infection, or any other disease or malfunction that would preclude treatment in the opinion of the investigator. 10. Current enrollment in a study evaluating another device or drug. 11. A complex arrhythmia secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause. 12. Any cardiac surgery within the past 60 days (2 months) (includes PCI) 13. Subjects that have ever undergone valvular cardiac surgical procedure (i.e., ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve) 14. Prior ICD or pacemaker implanted 15. Presence of intramural thrombus, tumor or other abnormality that precludes catheter introduction or manipulation. 16. Presence of a condition that precludes vascular access. 17. Subject has a contra-indication to the device under study per the IFU 18. Women of child bearing potential whom are pregnant, lactating, or planning to become pregnant during the course of the trial.
Treatment, Follow-up Schedule and Data Elements	<u>Baseline/Pre-procedure Assessments:</u> ▪ Demographics& NYHA ▪ Medical history ▪ Arrhythmia history ▪ Cardiovascular medication history including anticoagulation regimen ▪ ECG (12-lead) ▪ CHADS-VASC2 score ▪ Imaging (using standard detection techniques) for atrial size and thrombus detection ▪ INR (before procedure), when applicable ▪ Pregnancy test (pre-menopausal women only) Subjects who sign the informed consent form and who meet all inclusion and no exclusion criteria at screening/baseline will undergo a CARTOFINDER™ (CF) map using the RHYTHMFINDER™ 192 Catheter

	Procedural Flow 1. **Baseline CARTOFINDER™ (CF) Mapping** ▪ Fast Anatomical Mapping (FAM) of the Right Atria (RA) using the commercially available THERMOCOOL® SMARTTOUCH™ Catheter and/or SMARTTOUCH® SF Catheter. ▪ Baseline CF (map) recording of the RA using the RHYTHMFINDER™ 192 Catheter ▪ FAM map of the Left Atria (LA) using the THERMOCOOL® SMARTTOUCH™ Catheter and/or SMARTTOUCH® SF Catheter ▪ Baseline CF (map) recording of the LA using the RHYTHMFINDER™ 192 Catheter 2. **CF Baseline Map Analysis** ▪ Analysis of the baseline CF map ▪ Ablation Targets (FI/RAP) identification: ▪ Identify areas with ablation targets including focal impulse (FI) or repetitive activation patterns (RAPs) ▪ If an ablation target is identified, the subject will receive CFGA followed by PVI and be followed up until 12 months post procedure ▪ If no CF ablation target is identified, the subject will be treated per investigator's standard of care and followed up until 7 days post procedure
	3. **Procedure for CARTOFINDER™ Guided Ablation** ▪ Confirm identified ablation targets on the Baseline CF map ▪ Ablate areas using the THERMOCOOL® SMARTTOUCH™ or SMARTTOUCH® SF Catheter identified by the CARTOFINDER™ map o If a post CFGA map is performed on the ablated atrium(a), analysis of the post-CFGA CF map for the existence of ablation targets should be performed ▪ Complete above steps until one of the following conditions is met: o No further ablation targets are identified on the CF Map o Subject achieves normal sinus rhythm or an atrial tachycardia The final decision to not further ablate remaining RAP/FIs regardless of above criteria being met or not, remains at investigator's discretion ▪ After performing any CFGA, a CF map may be created at the investigator's discretion, but is not required ▪ If subject is in AF (or other arrhythmia) after CFGA, no cardioversion is permitted. RF192 catheter must not remain in the subject (being deployed in the atrium) for cumulative duration greater than 1.5 hours (90 mins)

	4. **PVI Ablation** ▪ PVI ablation after CFGA is required for all subjects ▪ Perform PVI* via Wide Area Circumferential Ablation (WACA) per your (institution's) standard of care (SOC). ▪ Perform entrance block confirmation ▪ In case NSR is achieved through PVI, no further ablations are permitted other than to complete the PVI. ▪ In case AT is achieved, additional ablations are permitted to ablate the Atrial Tachycardia at the investigator's discretion. ▪ In case AFL is achieved, the placement of additional RF lesions (i.e.. Linear lesions at the cavotricuspid isthmus) is at the discretion of the investigator ▪ Perform a final CF Map** within same atrium(a) in which baseline map was collected, using the RHYTHMFINDER™ 192 Catheter ▪ AT: once achieved, one "post" ablation map is required ▪ NSR: "post" ablation map is at the discretion of the investigator ▪ If subject is in AF/AFL/AT, cardioversion may be performed ONLY after completing PVI. **Prophylactic ablation of empirical sites is not allowed per protocol.** **All linear lesions require confirmation of conduction block by pacing and/or mapping maneuvers**

	Follow-up Schedule <u>Post-Procedure -Discharge:</u> ▪ Adverse Events Procedural complication collection and notification ▪ Arrhythmia assessment ▪ Electrocardiogram (12-lead ECG) ▪ Cardiovascular medication and anti-coagulation therapy <u>Follow-up visit at 7-Day Post-Procedure (Clinic Visit or Telephone visit):</u> ▪ Arrhythmia assessment ▪ Medical/hospitalization assessment ▪ Adverse Events assessment and notification ▪ Concomitant cardiovascular medication and anti-coagulation therapy changes <u>Follow-up visits at 3 months, 6 months and 12 Months (Clinic visit):</u> ▪ Medical and hospitalization assessment ▪ Concomitant cardiovascular medication and anti- coagulation therapy ▪ Arrhythmia recurrence, if observed ▪ Electrocardiogram (12-lead ECG) ▪ Arrhythmia Monitoring (Holter Monitoring) ▪ Adverse Event assessment and notification

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1 ABBREVIATIONS

AAD	AntiArrhythmic Drug
ACT	Activated Clotting Time
AE	Adverse Event
AF/Afib	Atrial Fibrillation
AT	Atrial Tachycardia
BP	Blood Pressure
bpm	Beats per minute
BMI	Body Mass Index
CE	Conformité Européen
CFAE	Complex Fractionated Atrial Electrogram
CF	CARTOFINDER™
CFGA	CartoFinder Guided Ablation
CHF	Congestive Heart Failure
CI	Confidence Interval
CL	Cycle Lenght
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CT scan	Computerized Tomography scan
EC	Ethics Committee
ECG	ElectroCardioGram
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
EEC	European Economic Community
EOS	End-Of-Study
EP	ElectroPhysiological Mapping
ER	Emergency Room
EU	European Union
FAM	Fast Anatomical Mapping
FDA	Food and Drug Administration
FI	Focal Impulses
GCP	Good Clinical Practice
GI	GastroIntestinal
HCP	Health Care Provider
HR	Hazard Ratio
ICD	Implantable Cardioverter-Defibrillator
ICE	Intra-Cardiac Echography
ICH	International Conference on Harmonisation
IFU	Instructions for Use
IRB/EC	Institutional Review Board / Ethics Committee
ISO	International Organization for Standardization
ITT	Intent-To-Treat
IV	IntraVenous
LA	Left Atrium
LAT	Local Activation Time
LV	Left Ventricle
LVEF	Left Ventricular Ejection Fraction
MedDRA®	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
N	Number
NSR	Normal Sinus Rhythm
PE	Physical Examination
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QA	Quality Assurance
RA	Right Atrium
RAP	Repetitive Activation Patterns
RF	RHYTHMFINDER
RV	Right Ventricle
RF	RadioFrequency
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analyis Plan
SAS	Statistical Applications Software
SOC	System Organ Class
SVC	Superior Vena Cava
UADE	Unanticipated Adverse Device Effect
UAE	Unanticipated Adverse Event
US	United States
VT	Ventricular Tachycardia

2 INTRODUCTION

2.1 Background

The ability to diagnose complex arrhythmias has enabled technologies such as catheter ablation to become more prevalent; however, even with these technologies, 1-year success rate for AF ablation off medications is 40% to 60% for 1 procedure [1,2,3] with a "70% ceiling" for 3 or more procedures. Multiple studies have demonstrated that success rates of PVI are lower in patients with persistent AF[4,5].

The possible explanation for the low success rates is that the current tools may not create durable lesions as evidenced by pulmonary vein reconnection [6, 7] and gaps in linear lesions [8, 9] in patients with recurrent AF after ablation. Also, the mechanisms that sustain AF are not identified [2, 10, 11]. Haissaguerre and colleagues found that linear lesions were often arrhythmogenic due to gaps in the ablation lines and that many patients were ultimately cured with ablation of a single rapidly firing ectopic focus [12].

Map-guided ablation showed to be more effective than conventional ablation alone at preventing early and late arrhythmia recurrences [13,14]

Mapping and catheter ablation of ablation targets including repetitive activation patterns (RAPs) and focal impulses (FI) appear to show advantage to reduce recurrence of atrial arrhythmias versus the conventional AF ablation approach. The further development of mapping techniques and software to analyze and as such identify locations that sustain arrhythmia and help guide the ablation procedure may increase the long- term outcome for subjects with persistent AFib.

2.2 Clinical Investigation Overview

The purpose of this trial is to assess safety and effectiveness of using the CARTOFINDER™ (CF) maps created by the RHYTHMFINDER (RF) basket catheter [redacted] and the CARTOFINDER™ System using the 4D LAT algorithm in treating persistent atrial fibrillation (PsAF). The CARTOFINDER™ 4D LAT Algorithm provides automatic analysis of multiple simultaneous ECG signals when recorded by a multi-electrode catheter by generating a CARTOFINDER™ Map that helps to facilitate the identification of ablation targets including Repetitive Activation Patterns (RAPs) or Focal Impulses (FI) or other ablation targets.

2.3 Device Description

Table 2.3 below outlines the required devices for the study and their current regulatory status.

Table 2.3 Cross-Jurisdictional Regulatory Status of Study Devices

Devices	Europe	Canada
CARTOFINDER™ Workstation, with 4D LAT Algorithm installed	CE Marked	Investigational
CARTO® 3 EP Navigation System, with CARTOFINDER™ installed (CARTOFINDER™ Module)	CE Marked	Investigational
RHYTHMFINDER Basket Catheter	Investigational	Investigational

The CE marked devices are compliant with Medical Device Directive 93/42/EEC and the relevant harmonized standards as well as conform to the applicable local regulations and are to be used according to the approved indication and their instructions for Use (IFU).

2.3.1 CARTOFINDER™ Workstation with 4D LAT Algorithm

The CARTOFINDER™ Workstation is a computerized system that assists in the diagnosis of complex cardiac arrhythmias and displays the arrhythmias in a dynamic visual format.

The CARTOFINDER™ Workstation takes recorded electrical signals collected from multi-electrode catheters as inputs. It then generates output data that is displayed as static or dynamic 4D maps which can assist in the diagnosis of cardiac arrhythmias.

Specifically, the CARTOFINDER™ accesses stored data of recorded electrical heart activity obtained via conventional electrophysiological methods using multi-electrode catheters placed in the heart. Using the 4D LAT software algorithm, these recorded signals are analyzed by the CARTOFINDER and presented as 4D maps of the activation patterns of various heart rhythms that include normal sinus rhythm (NSR), atrial flutter (AFL) and atrial fibrillation (AF). The 4D maps are graphically displayed on a monitor screen for review by the investigator during an electrophysiology study.

2.3.2 CARTO® 3 EP Navigation System with CARTOFINDER™ Module

The CARTO® 3 EP Navigation System with CARTOFINDER™ Module is a catheter- based atrial and ventricular mapping system designed to acquire and analyze data points, and use this information to display 3D anatomical and electroanatomical maps of the human heart in real-time. The location information needed to create the cardiac maps and the local electrograms are acquired using specialized mapping catheters and location reference devices. The system allows real-time display of electrograms and cardiac maps in a number of different formats based on the intra- cardiac signals received from the catheters. For example, maps may be displayed as anatomical maps, cardiac

electrical activation maps, cardiac electrical propagation maps, cardiac electrical potential maps, impedance maps, cardiac chamber geometry, and ECG fragmentation maps. The acquired patient signals, including body surface ECG and intracardiac electrograms (ICECG) may also be displayed on the display screen.

The CARTO® 3 EP Navigation System with CARTOFINDER™ Module maintains the identical intended use, fundamental scientific technology, software, magnetic location mapping technology, and location sensor accuracy as that of the currently cleared CARTO® 3 EP Navigation System.

The addition of the CARTOFINDER™ Module to the currently cleared CARTO® 3 EP Navigation System, enables the CARTO® 3 EP System to interface with a newly developed cardiac mapping system called the CARTOFINDER™ Workstation. This interface displays the CF maps computed by the CARTOFINDER™ Module.

2.3.3 RHYTHMFINDER™ 192 Catheter ([redacted])

The Biosense Webster RHYTHMFINDER™ 192 Catheter is a multi-electrode mapping catheter. This basket-style catheter is designed to provide a global view of the cardiac surface with electrical activation information and is meant for atrial mapping only. [redacted]

The RF-192 mapping catheter [redacted] is intended to be deployed in the atria through a commercially available sheath utilizing the CARTO® 3 EP Navigation System. This catheter is not compatible with CARTO® 3 EP Navigation Systems prior to Version 5. The catheter is "basket-like" in design and can be used for recording of intracardiac signals during the EP procedure. The design is intended to maximize contact and coverage within the chambers of the right and left atrium.

[redacted]

2.3.4 Ablation catheters

The THERMOCOOL® SMARTTOUCH™ and THERMOCOOL® SMARTTOUCH® SF Diagnostic /Ablation Deflectable Tip Catheters with Contact Force Sensing Capability, are the only study catheters to be used in this study within their country specific commercial availability and indications for use. It's recommended that for this study the investigator uses the same catheter type, THERMOCOOL® SMARTTOUCH™ or THERMOCOOL® SMARTTOUCH® SF, throughout the study conduct for all his/her patients.
A copy of the IFU for the Study Catheters and interface cable is included in each product package.

3 CLINICAL INVESTIGATION OBJECTIVES

The primary purpose of this trial is to assess safety and effectiveness of using the CARTOFINDER™ (CF) maps created by the RHYTHMFINDER (RF) basket catheter [redacted] and the CARTOFINDER™ System using the 4D LAT algorithm in treating persistent atrial fibrillation (PsAF).. The CARTOFINDER™ 4D LAT Algorithm provides automatic analysis of multiple simultaneous ECG signals when recorded by a multi-electrode catheter by generating a CARTOFINDER™ Map that helps to facilitate the identification of ablation targets including Repetitive Activation Patterns (RAPs) or Focal Impulses (FI) or other ablation targets enables one to evaluate the effects of treatment. In addition, the study will also assess, procedural data, mapping data and mapping catheter functionality.

4 CLINICAL INVESTIGATION OUTCOME MEASURES

4.1 Study Endpoints

Effectiveness

- Acute success defined as: Rate of conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia, after CFGA and PVI (without cardioversion)
- Procedural success defined as: Conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia after overall ablation procedure, with or without the need for cardioversion
- Rate of conversion of Atrial Fibrillation to Normal Sinus Rhythm or Atrial Tachycardia, after CFGA only (before PVI and without cardioversion)
- Freedom from documented symptomatic AF/AT/AFL recurrence (episodes ≥ 30 seconds on an arrhythmia monitoring device) post the 3-month blanking period through the 12-month follow up.
- Incidence of PVI (confirmed entrance block) after adenosine/isoproterenol challenge
- Change of intra-cycle length from pre-CFGA to post-CFGA and post-PVI

Safety

- Incidence of early-onset Primary Adverse Events (refer to section 14 for a list of events).
- Incidence of study device and procedural related SAEs during follow-up period (12M)
- Incidence of all SAEs during follow-up period (12M)
- Incidence of study device and procedure related adverse events

4.2 Other Study assessments

- Number of identified CF ablation targets
- Max #of active RF 192 electrodes during initial mapping procedure
- AAD use post the 3-month blanking period
- Incidence of repeat ablation procedures for AF post the 3-month blanking period

- Procedural data:
  - All target sites for RF lesion application
    - Location of ablation targets
    - Number of RF applications per target
    - Total RF duration per application
  - RF ablation parameters (including but not limited to: power, contact force, impedance, flow rate, temperature)
  - Total fluoroscopy time time anddose
  - Total procedure, mapping and ablation time

5 CLINICAL INVESTIGATION DESIGN

The study is a prospective, single arm, non randomized, open label, multicenter study.

Subjects fulfilling the inclusion / exclusion criteria and who sign the informed consent form (ICF) will be enrolled in the RAPID-AF study. The clinical investigation is targeting approximately 6-10 centers located worldwide. The study will enroll approximately 40 to 70subjects.

This study will serve to generate a clearer perspective of the CARTOFINDER™ System's ability to generate maps for guiding ablation and the investigator's ability to maneuver, acquire signals etc. using the RF-192 catheter.

Subjects displaying an ablation target on the CARTOFINDER™ (CF) map will undergo CARTOFINDER™ Guided Ablation (CFGA) followed by PVI (WACA) ablation. Subjects not displaying an ablation target on CARTOFINDER™ will be will be treated per investigator's standard of care and followed up until 7 days post-procedure.

6 STUDY PROCEDURE GUIDELINES

The devices itemized below are required for this protocol, and investigational devices will be provided by the sponsor. Refer to the Table 2.3 for the status of the devices in your region.

- CARTO® 3 EP Navigation System, with CARTOFINDER™ Module
- CARTOFINDER™ Workstation
- RHYTHMFINDER Basket Catheter (Mapping Catheter)

Ablation catheters used for this study protocol are THERMOCOOL® SMARTTOUCH™ or SMARTTOUCH® SF Catheter (Ablation Catheter) (commercially available and used within indication for use as applicable for your country).
Biosense Webster representatives will provide training to the study site personnel in the use of the investigational devices.
Refer to the Instructions for Use for the set-up of the devices and respective connections.

6.1 Screening and Informed Consent

Subjects presenting to the institution with Persistent Atrial Fibrillation and considered for an ablation procedure should be screened by the investigator or designated member of the research team for study eligibility per the protocol inclusion and exclusion criteria.

The study investigator or designated member of the research team will obtain written informed consent from the subject. The background of the proposed study and the potential benefits and risks of the study should be explained to the subject. The subject or legal representative must sign the consent form prior to any study-specific exams or tests are provided to them that fall outside of the standard of care. The consent form used must have prior approval from the study site's Research Ethics Board/ Institutional Review Board / Ethics Committee. Failure to obtain informed consent renders the subject will be deemed ineligible for participation in the study.

Each subject screened for enrollment in the clinical investigation who signs the patient informed consent form will be enrolled into the study.

6.2 Baseline /Pre-Procedure Assessments

Pre-procedure assessments and data collection must be performed within 30 days prior to the ablation procedure unless otherwise noted.

- Demographics
- Medical history
- Arrhythmia history
- Cardiovascular medication including anticoagulation regimen
- Electrocardiogram (12-Lead ECG)
- INR (prior to ablation procedure), when applicable
- CHADS-VASC2 Score
- NYHA assessment
- Imaging (i.e. TTE) to determine the atrial size (if the subject has undergone an imaging procedure within the last 6-months where the atrial size was assessed, the pre-procedure imaging assessment is not required)
    - If left atrial size exceeds 47 mm on TTE, left atrial <u>volume</u> should be measured.
- Imaging for detection of LA thrombus is mandatory within 24 hours prior to ablation procedure. The imaging method used is at the discretion of the investigator and institution standard practices:
    - Transesophageal Echocardiogram (TEE)
    - Intracardiac Echocardiography (ICE)
    - Computed Tomography (CT)
    - Magnetic Resonance Imaging (MRI)
- Pregnancy test must be done on pre-menopausal women only, within <u>1-week</u> <u>of the procedure</u> and documented in the subject's medical chart.

Subjects who signed the informed consent form and who meet all inclusion and no exclusion criteria

at screening/baseline will undergo a CARTOFINDER™ (CF) baseline map using the RHYTHMFINDER™ 192 Catheter

6.3 Baseline/Pre-procedure CARTOFINDER™ (CF) mapping:

Subjects will arrive to the electrophysiology laboratory for their clinically indicated ablation procedure and will undergo preparation for the ablation procedure according to the hospital's standard protocol (discretion of investigator), CARTO3 navigational and electro-anatomical mapping system. CARTOFINDER™ System is connected to CARTO®3 workstation with Ethernet cable for file sharing as per Instruction For Use (IFU).

6.3.1 Baseline Mapping Sequence

All eligible subjects will undergo the CARTOFINDER™ Mapping Procedure, using the RF-192 catheter. The subject must be in AF prior to the insertion of the RF-192 Mapping catheter. If the subject is not in AF at the time of the procedure the patient will be regarded as discontinued per inclusion criteria, followed for 7-days post-procedure and exited from the study.

- Standard Fast Anatomic Mapping (FAM) procedure of the Right Atria (RA) using the THERMOCOOL SMARTTOUCH™ or SMARTTOUCH® SF Catheter.
- Baseline CARTOFINDER™ map, recording of the RA using the RF-192 catheter
  - On deployment of the RF-192 catheter, the basket catheter will be placed in optimal position to maximize contact with the RA wall
  - Once the catheter's position is confirmed and contact is optimal, the investigator will obtain intra-cardiac signals
  - One 30 second recording will be obtained

DO NOT perform any RA ablations at this point

- Transseptal Puncture
- Standard FAM of the Left Atria (LA) using the THERMOCOOL® SMARTTOUCH™ or SMARTTOUCH® SF Catheter.
- Baseline CARTOFINDER™ map, recording of the LA using the RF-192 catheter
  - On deployment of the RF-192 catheter, the basket catheter will be placed in optimal position to maximize contact with the LA wall
  - Once the catheter's position is confirmed and contact is optimal, the investigatorinvestigator will obtain intra-cardiac signals
  - One 30 second recording will be obtained

  RF192 catheter must not remain in the subject (being deployed in the atrium) for cumulative duration greater than 1.5 hours (90 mins)

6.4 Analysis of the CARTOFINDER™ Baseline Map

After completion of the CARTOFINDER™ baseline mapping procedure, the CARTOFINDER™ maps will be

processed and analyzed for the presences of ablation targets including FI/RAPs by the treating/ablating investigatorwho has been trained by Biosense Webster personnel knowledgeable in analyzing CF maps and the operation of the CARTOFINDER™ system.

Ablation Targets (FI/RAP) identification:

- Identify areas with ablation targets including focal impulse (FI) or repetitive activation patterns (RAPs)
  - If an ablation target is identified, the subject will receive CFGA followed by PVI
  - If no CF ablation target is identified, the subject will be treated per standard of care and exits the study after 7 day follow up.

No RF ablation should occur prior to analysis of the CARTOFINDER™ Maps.

6.4.1 CARTOFINDER™ Guided Ablation

All subjects will undergo CARTOFINDER™ Guided Ablation procedure followed by PVI.

- Confirm identified ablation targets on the Baseline CF map
- Ablate areas using the THERMOCOOL® SMARTTOUCH™ or SMARTTOUCH® SF Catheter identified by the CARTOFINDER™ map
  - If a post CFGA map is performed on the ablated atrium(a), analysis of the post-CFGA CF map for the existence of ablation targets should be performed
- Complete above steps until one of the following conditions is met:
  - No further ablation targets are identified on the CF Map
  - Subject achieves normal sinus rhythm or an atrial tachycardia

    The final decision to not further ablate remaining RAP/FIs regardless of above criteria being met or not, remains at investigator's discretion.
- After performing any CFGA, a CF map may be created at the investigator's discretion, but is not required.
- If subject is in AF (or other arrhythmia) after CFGA, no cardioversion is permitted.

RF192 catheter must not remain in the subject (being deployed in the atrium) for cumulative duration greater than 1.5 hours (90 mins)

6.4.2 PVI Ablation:

All subjects enrolled in the study will undergo the following PVI procedure as outlined below.

1. Pulmonary Vein Isolation will be performed using Wide Area Circumferential Ablation (WACA)

technique per the institution's standard practice.

2. Confirmation of complete entrance block must be performed after the WACA

   ⇨ *If NSR is achieved through PVI, no further ablations are permitted other than to complete the PVI.*

   ⇨ *If AT is achieved, additional ablations are permitted to ablate the Atrial Tachycardia at the investigator's discretion.*

   ⇨ *If AFL is achieved, the placement of additional RF lesions (i.e. Linear lesions at the cavotricuspid isthmus) is at the discretion of the investigator*

   Prophylactic ablation of empirical sites is not allowed per protocol.

   All linear lesions, if any, require confirmation of conduction block by pacing and/or mapping maneuvers

3. Perform a final CF Map* within the same atrium (a) in which the baseline map was collected.

   **AT: once achieved, one "post" ablation CF map is required*

   **NSR: a "post" ablation CF map is at the discretion of the investigator*

4. If subject in AF/AFL/AT after completing ablations, cardioversion may be performed at the discretion of the investigator ONLY after completing all ablations.

7 DATA COLLECTION AND FOLLOW-UP SCHEDULE

7.1 Procedural Data Collection

The following procedural data will be collected:

- Mapping sequence
- Procedural flow
- Procedural time including RF ablation and mapping times
- Fluoroscopy usage
- Ablation targets and parameters
  - Areas/location of ablation targets including RAPs/Focal impulses identified by CARTOFINDER™
  - # RF applications per target
  - RF duration per application
- Cycle length
- Max #of active RF 192 electrodes
- Fluid inputs/outputs
- Subject's heart rhythm (pre-and post-ablations)
- Rate controlling medications provided inter-operatively
- Intra-Procedural complications.

- All CARTOFINDER™ maps with associated catheter locations
- Investigator feedback on quality of signal collection and mapping at the end of the procedure. The survey will contain questions to rate on a scale of 1 to 5 and will be entered into the eCRF for analysis.

7.2 Post-Procedure/Discharge

Once the investigator has achieved the desired results for the subject's arrhythmia, the subject will be monitored as per the institution standard of care (post procedure practice) and subject will be discharged from the hospital in accordance with the hospitals standard procedures.

The following data will be collected at Discharge:

- Arrhythmia assessment
- Adverse Events Procedural complication collection and notification
- Electrocardiogram (12-Lead ECG andcycle length in diagnosed rhythm)
- Cardiovascular medication and anti-coagulation therapy.

7.3 7-Day Follow-Up (Clinic Visit or telephone visit)

All subjects will be contacted 7-days post procedure via telephone or by attending a clinic visit.

The following data will be collected for all subjects at 7 days post- procedure:

- Arrhythmia assessment
- Medical/hospitalization assessment
- Concomitant cardio-vascular medication and anti-coagulation therapy
- Adverse event assessment and notification

7.4 3, 6 and -12 Months Follow-Up (Clinic Visit)

The following data will be collected for all subjects:

- Medical / Hospitalization assessment
- Arrhythmia assessment
- Electrocardiogram (12-Lead ECG and cycle length in diagnosed rhythm)
- Arrhythmia Monitoring:
  - 24-hour Holter at 3 month visits
  - ≥72 hours Holter at 6 and 12 months
- Concomitant cardiovascular medication and anti-coagulation therapy: subjects are recommended to stop their AAD medication after 3- months at the discretion of the investigator
- Adverse event assessment and notification

Repeat ablations may be performed at the discretion of the investigator. Investigators are recommended to treat the subject using the same commercial available ablation catheter (THERMOCOOL® SMARTTOUCH™ Catheter and/or SMARTTOUCH® SF Catheter) as the initial procedure. The follow-up schedule will remain based on the initial procedure.

Table 7.4 Time and Follow-up Schedule

	Screening / Baseline	Ablation Procedure[1]	Discharge	7 Days +/- 2 day	3 Month +/- 1 wks.	6 Month +/- 2 wks.	12 Month +/- 4 wks.
Informed consent[1]	X						
Inclusion & exclusion criteria	X						
Demographics	X						
Medical assessment	X [history]			X	X	X	X
Arrhythmias	X [history]		X	X	X	X	X
ECG (12 lead andCL measurement)	X		X		X	X	X
NYHA/CHADS-VASC2 score	X						
Pregnancy Test[2]	X						
Assessment LA Thrombus[3]		X					
TTE[4]	X						
Ablation assessments		X					
Arrhythmia Monitoring (Holter)[8]					X	X	X
Device Deficiency		X					
Concomitant Medications[5]	X	X	X	X	X	X	X
Adverse events[6]	X	X	X	X	X	X	X

1 Informed Consent to be obtained and collected prior to any study specific assessments

2 Pregnancy test must be done on pre-menopausal women only within 1 week prior to procedure.

3 Imaging method as per standard hospital practice (TEE, ICE,...); within 24 hours prior to procedure

4 Imaging TTE to determine the atrial size (if the subject has undergone an imaging procedure within the last 6-months where the atrial size was assessed, the pre-procedure imaging assessment is not required). If LA diameter is ≥47mm, LA volume to be measured.

5 Concomitant medications: only cardiac related (AAD drugs, anticoagulation regimen, etc.).

6 AEs will be collected once consent has been signed

7 End of study (CRF) page to be completed for ALL enrolled subjects

8 Holter: Dispensation of Holter device at Month 3 visit. 24-hour Holter monitoring at 3 month and ≥72-hour Holter monitoring at 6 and 12 months follow-up.

8 CONCOMITANT THERAPY

The following medications may be administered (as indicated and per standard of care and per the IFU) for subjects undergoing catheter ablation.

Before Ablation:

- Anticoagulation: therapy is recommended for 30 days before the ablation procedure.
- Anti-Arrhythmic Drug (AAD): subjects AAD therapy should be managed per the institutions/investigator's standard of care.

An intravenous bolus of Heparin should be administrated before introducing RF-192.

Mapping Procedure: While the RF-192 catheter is in the subject's right atrium, the ACT must be maintained at ≥ 300; while placed in the left atrium, the ACT must be maintained at ≥ 350. When the RF-192 catheter is not in the subject's atrium e.g. in between mapping procedures, the ACTs may be reduced, but must remain at ≥ 300 while the catheter is inside the subject.

Ablation Procedure: Maintain an ACT greater than 300 seconds for right- sided procedures and above 350 seconds for left-sided procedures as in accordance with the current ACC/AHA/ESE guidelines. Post ablation pacing procedure(s) and/or infusion of cardiac medications to induce AF are at the discretion of the investigator (e.g., Isoproterenol 2 to 20 mcg/min).

Following Ablation:

- Anticoagulation therapy is strongly recommended for 3 months following ablation. Thereafter, subjects are recommended to receive anti-coagulation therapy in accordance with the ACC/AHA/HRS 2014 Guidelines for the Management of Patients in Atrial Fibrillation [2, 15]
- At the discretion of the investigator, a previously ineffective drug, at the same dose or lower, may be continued during the 3-month blanking period. Subsequent use of anti-arrhythmic drugs is discouraged
- Additional medications needed to treat clinical indications are at the discretion of the clinical investigation investigator

9 HOLTER MONITOR

All subjects will be provided with a Holter monitor device at pre-specified scheduled visits (refer to Table 7.4) to capture recordings of their heart rhythm status and will be asked to report on any symptoms they experience. The recordings from the Holter monitor will be transmitted to a Core Lab for analysis. Subjects will be trained by the study site personnel on the use of the Holter monitor device and transmission of the recordings. A study specific Core Lab instruction manual and patient

instruction sheet, including procedures to be followed, will be made available.
Holter monitoring will be conducted as follows:

- 3-Month Visit: 24-hour Holter Monitor
- 6 and 12 Month Visits: ≥72 hours Holter Monitor

10 STUDY POPULATION

10.1 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.

10.2 Inclusion Criteria

1. Age ≥ 18 years.
2. Patients who have signed the Patient Informed Consent Form (ICF)
3. Scheduled to undergo a clinically-indicated catheter ablation procedure for treatment of
    a. persistent atrial fibrillation (defined as continuous atrial fibrillation that is sustained beyond seven consecutive days).
    b. drug-resistant atrial fibrillation. (failed 1 or more class I or III antiarrhythmic drugs) and demonstrating Persistent AF (requiring drugs or electrical shock to terminate
4. In AF at the time of the baseline CARTOFINDER™ Map (spontaneous)
5. Left Atrium (LA) must demonstrate sufficient electrical activity to allow for the identification of ablation targets.
6. Able and willing to comply with all pre-, post-, and follow-up testing and requirements (e.g. patients not confined by a court ruling)

10.3 Exclusion Criteria

1. Paroxysmal Atrial Fibrillation
2. Continuous AF > 12 months (1-Year) (Longstanding Persistent AF)
    Subjects previously diagnosed as Long Standing Persistent (LSP) but have demonstrated the

ability to maintain Normal Sinus Rhythm for >30 days after cardioversion and have not been in AF greater than 1 year at the time of the procedure remain eligible for inclusion.

3. Previous ablation procedure for PsAF (defined as ablations involving more than only PV isolation)
4. Patients with a left atrial size >55 mm (echocardiography, parasternal long axis view).
5. Inability to restore sinus rhythm for 30 seconds or longer in the opinion of the investigator.
6. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study.
7. Atrial arrhythmia patients with structural atrial disease such as a prior history of atriotomy from prior atrial surgery, presence of an atrial septal defect, and/or presence of an atrial septal closure patch.
8. History of or current blood clotting or bleeding abnormalities, contraindication to systemic anticoagulation (i.e., heparin, warfarin, dabigatran, or a direct thrombin inhibitor).
9. Significant pulmonary disease, cardiac surgeries, unstable angina, uncontrolled heart failure, acute illness or systemic infection, or any other disease or malfunction that would preclude treatment in the opinion of the investigator.
10. Current enrollment in a study evaluating another device or drug.
11. A complex arrhythmia secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
12. Any cardiac surgery within the past 60 days (2 months) (includes PCI)
13. Subjects that have ever undergone valvular cardiac surgical procedure (i.e., ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve)
14. Prior ICD or pacemaker implanted
15. Presence of intramural thrombus, tumor or other abnormality that precludes catheter introduction or manipulation.
16. Presence of a condition that precludes vascular access.
17. Subject has a contra-indication to the device under study per the IFU
18. Women of child bearing potential that are pregnant, lactating, or planning to become pregnant during the course of the trial.

11 SUBJECT DISPOSITION

The following subject groups are defined:

- Enrolled Subjects: Subjects who have signed and dated the Informed Consent Form.
- Excluded Subjects: Enrolled subjects who have signed an ICF but are found not meeting eligibility criteria prior to insertion of the RHYTHMFINDER™ 192 Catheter.
- Mapping Failure: Enrolled subjects who have the RHYTHMFINDER™ 192 Catheter inserted and where inability to record baseline CF mapping signals is observed, will be followed up for 7-days.

If an SAE is reported for a mapping failure subject, they will be followed until event resolution or stabilized. The investigator will document mapping failures in the electronic CRF, including reasons for failure.

- Discontinued Subjects: Enrolled subjects who have the RHYTHMFINDER™ 192 Catheter inserted but do not undergo CF guided ablation. If subject's arrhythmia is determined at the time of EP study to be a non-study arrhythmia (required for subject enrollment per study inclusion criteria), the subject will be categorized as discontinued subject. Discontinued subjects will remain in follow-up for 7-days. If an SAE is reported for a discontinued subject, they will be followed until event resolution or stabilized.
- Lost to Follow-up Subjects: Subjects who are enrolled and have the RHYTHMFINDER™ 192 Catheter inserted, but contact is lost after most recent follow-up visit (despite 3 documented attempts to contact the subject).
- Withdrawn / Early Termination Subjects: Subjects who have RHYTHMFINDER™ 192 Catheter inserted but withdraw consent for study participation or are withdrawn by the investigator or are terminated from the study prior to completion of all follow-up visits
- Completed Subjects: enrolled subjects who complete the last scheduled follow-up visit per study protocol.

12 SUBJECT WITHDRAWAL/EARLY TERMINATION CRITERIA

Every subject should be encouraged to remain in the study until they have completed the protocol-required 1 year follow-up period. If the subject terminates prematurely from the study, the reason for early 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 may withdraw from the clinical investigation at any time. The decision must be an 'independent decision' that is documented in the source documentation and in the electronic CRF.
- 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.
- 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.

13 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 benefit and risk 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.

Subjects will also be asked to agree to comply with the follow up visits during the 1-year follow up period. The informed consent needs to be written in a native non-technical language that is understandable to the subject and needs to be approved by Research Ethics Board / Institutional Review Board / Ethics Committee. 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 Informed consent should be obtained by the investigator who is a licensed doctor when necessary as per the local regulation.

14 ADVERSE EVENTS AND DEVICE DEFICIENCY REPORTING

14.1 Introduction

Below sections are mainly applicable for EU requirements and definitions, AE classifications, reporting and compliance sections might differ per local regulations for other regions.
Event reporting to relevant competent authorities in accordance with the jurisdictional

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

14.2 Adverse Events

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. This definition includes events related to the investigational medical device and to the procedures involved.

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 spontaneously 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,

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

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.

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:

Definitely Device-related	The event is associated with the investigational device beyond reasonable doubt as described per MEDDEV 2.7/3 Rev3.
Probable Device- related	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.
Possibly Device-related	The relationship with the use of the investigational device is weak but cannot be ruled out completely.

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

Outcomes should be assessed as follows:

Resolved	Without sequelae - Subject fully recovered with no observable residual effects. 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).

14.3 Reportable Serious Adverse Events (SAE) (MEDDEV 2.7/3 Rev3)

1. 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
   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, 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.
- AF/AFL/AT occurrence 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 immediately but no later than 3 calendar days 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 at study completion.

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 guidelines (in this case is applicable only for the RF-192 device) and for CE marked-devices per MEDDEV 2.12/1 guidelines.

14.4 Primary Adverse events

The Primary Adverse Events of interest include the following:

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

Table 14.4: Primary Adverse Events are defined as following:

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Death	Subject death directly related to the device or procedure and occurs at any time during or after the procedure.

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
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 than1 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

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
Thromboembolism	Formation of a clot (thrombus) inside a blood vessel causing obstruction to blood flow. The thrombus can migrate (embolus) and obstruct distal vascular sites. Diagnostic tests to help detect thromboembolisms may include but are not limited to angiography (pulmonary or distal), ventilation- perfusion (V/Q) scans, venography, Doppler ultrasonography, spiral CT, and echocardiography.
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.
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 major 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
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.

PRIMARY ADVERSE EVENT	DESCRIPTION / CRITERIA
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 a hematoma, an AV fistula or a pseudoaneurysm which requires intervention such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.

* 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.

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

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

14.5 Anticipated Adverse Events

An anticipated Adverse Event is an effect which by nature, incidence, severity or outcome has been identified as possible complications associated with the investigational medical device and/or intervention procedure.

Potential adverse events that are reasonably anticipated to occur during the cardiac electrophysiology procedure include all of the events noted in any clinical study for these types of Radiofrequency RF devices to date are listed in Table 14.5.

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

Anticipated Adverse Events	
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
42.	Heart Failure
43.	Hematoma (local) /ecchymosis
44.	Hemorrhage
45.	Hemothorax
46.	High / increased creatinine phosphokinase (CPK)
47.	Hypotension

Anticipated Adverse Events	
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

Anticipated Adverse Events	
86.	Seizure
87.	Sepsis
88.	Skin burns (due to cardioversion, tape, etc.)
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

Adverse Device Effect (ADE's) are adverse events related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use errors or from intentional misuse of the investigational medical device.

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

Unanticipated Serious Adverse Device Effect (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 Investigators Brochure or Instruction For Use.

Device Deficiency: Inadequacy of an investigational medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction (failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol), misuse or user error and inadequate labeling.

If a **device deficiency** occurs, especially that could have led to a SAE, the investigator must report the event as per MEDDEV and to the sponsor by completing the event within 24hours after awareness into the eCRF.

If a device deficiency is detected or suspected, it should be documented on the appropriate eCRF and the device must be returned according to the Sponsor's instructions.

If the device deficiency is associated with any SAE (SADE/ USADE) or if a device deficiency occurs that could have led to a SADE if suitable action had not been taken or, intervention had not been made or, if circumstances had been less fortunate or a new findings/updates in relation to already reported events, the investigator must report the event and device deficiency within 24 hours of awareness to the Sponsor.

The sponsor will review all reported device deficiencies and will determine and document in writing whether they could have led to a SADE and report accordingly to the competent and regulatory authorities, and REB/IRB/EC requirements. In case of disagreement between the sponsor and the principal investigator(s), the sponsor shall communicate both opinions to the concerned parties.

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

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

In Europe, 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 or local regulatory authorities, according to the regulatory requirements and company procedures applicable for CE marked medical devices.

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 REB/IRB/EC, hospital records, death certificate, and an autopsy report, if available.

Reporting Requirements to Sponsor and Regulatory/ Competent Authorities

All serious AE (SAE/SADE), whether or not they are related to the device or procedure, and Unanticipated Serious Adverse Device Effect (USADE) must be reported to the Sponsor or designee and entered into the eCRF within 24-hours of awareness by the clinical investigation site personnel.

15 STATISTICAL CONSIDERATIONS

15.1 Sample Size

This is a feasibility study of safety and effectiveness in which the sample size of the clinical investigation is intended to provide preliminary estimates of these 2 aspects. Enrollment in the clinical investigation will be approximately 40-70 evaluable subjects.

15.2 Analysis Populations

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

Safety Subject Population: The safety subject population will include all enrolled subjects who have the RHYTHMFINDER™ 192 Catheter inserted, regardless if cartofinder guided ablation was performed

Evaluable Subject Population: The evaluable subject population will include all enrolled subjects who have the RHYTHMFINDER™ 192 Catheter inserted and where cartofinder guided ablation was performed

15.3 Statistical Methods

Descriptive statistics and two-sided 95% confidence intervals will be presented for the effectiveness and safety endpoints. No formal statistical hypothesis and inferential statistics will be formulated and performed. Analyses of all endpoints will be performed in the proposed analysis populations excluding the subjects with missing outcomes.

15.3.1 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 procedure, with exception for PV stenosis and AE fistula (Table 14.4).

Incidence of (S)AEs during follow-up will be reported as the number of (S)AEs and the number of sibjects experiencing (S)AEs. The number and percentage of subjects with (S)AEs will be summarized overall and by AE type, seriousness, severity, causality, anticipated or not and outcome. Listing of (S)AEs will also be provided.

The safety population (SP) will be used as the analysis population.

15.3.2 Effectiveness

Effectiveness outcomes includes freedom from documented AF/AT/AFL recurrence post the 3-month blanking period through the 12-month follow up, conversion of atrial fibrillation to normal sinus rhythm or atrial tachycardia post CFGA or post overall ablation procedure with or without cardioversion, and entrance block confirmation post PVI. The number and percentages of subjects with effectiveness endpoints and the corresponding two-sided 95% binomial confidence intervals will be presented. Listing of effectiveness outcomes will be provided.

The evaluable population (EP) will be used as the analysis population for all effectiveness endpoints.

15.3.3 Investigational Device Performance

Investigational device performance will be reported as the number of ablation targets identified and the maximum % of active electrodes. Investigational device performance will also be reported by means of survey questions. Listings of survey answers/scoring will also be provided. These analyses will be conducted in the evaluable population (EP).

15.3.4 Procedural Data

Procedural data such as procedure duration, mapping duration, fluoroscopy time/dose, power, contact force,will be summarized with descriptive statistics and listed. These analyses will be conducted in the evaluable population (EP).

15.4 Missing Data Handling

Missing data will be queried for reasons and will not be imputed.

16 ADMINISTRATIVE PROCEDURES AND RESPONSIBILITIES

The clinical investigation will be conducted in compliance with this protocol, and according to ISO 14155: 2011, MEDDEV 2.7/3, the medical device directive 93/42/EC and amendments, the Declaration of Helsinki, the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline of Good Clinical Practice (E6) and in compliance with national regulations.

16.1 Research Ethics Board/Institutional Review Board/Ethics Committee

This protocol and the informed consent must be reviewed and approved by the appropriate REB/IRB/EC and the Competent Authorities/Health Authorities where the clinical investigation is to be conducted before enrollment of subjects. Any additional requirements imposed by the REB/IRB/EC or regulatory authority shall be followed, if appropriate. The sponsor and the REB/IRB/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 REB/IRB/EC Approval Form and a signed copy of the REB/IRB/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 REB/IRB/EC.

16.2 Monitoring of the Study

Monitoring will be conducted throughout the course of this study according to the Monitoring Plan and sponsor standard operating procedures.

Monitoring visits will be conducted to oversee the progress of the study and verification of the following:

- the rights and wellbeing of the subjects are protected;
- the study is conducted according to Good Clinical Practices (GCP) and local regulations;
- the protocol and applicable amendments are followed;
- the recorded data are accurately represented.

The sponsor and/or designee will perform on-site monitoring visits as defined in the study Monitoring Plan. Each visit will encompass activities such as verification that all subjects have signed the study's ICF, confirmation that procedures are being followed, completion of appropriate source document verification, anonymized CARTO files downloads, and identification of and action taken to resolve any issues or problems with the study.

The sponsor may request further documentation such as investigator and/or EP lab procedure notes when needed or when complications or device deficiencies are observed. To this end, the investigator and institution must permit inspection of the study files and subjects' eCRFs by Sponsor personnel.

16.3 Management of Protocol Amendments

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 effect subjects benefits/risks ratio) may be inserted with abbreviated approval. All amendments will be distributed to all original protocol recipients.

16.4 Adherence to the Protocol

The investigator is responsible for ensuring the clinical investigation is conducted in accordance with the procedures and evaluations described in this protocol (see Investigator Signature Page at the beginning of this protocol).

Deviations from the protocol shall not be made except in a medical emergency, when the intent is to reduce immediate risk to the subject. In such cases, the sponsor, REB/IRB/EC, regulatory authorities, and insurance company, as appropriate, should be notified in accordance with local requirements. Changes to the protocol may be made only when a written protocol amendment provided by the sponsor has been signed by the investigator and approved by the REB/IRB/EC and applicable regulatory agencies in accordance with local requirements and ISO 14155.

The sponsor is responsible for submitting progress reports, including safety summary and deviations, when requested, to all reviewing ECs and the regulatory authorities.

16.5 Records and Responsibilities

16.5.1 Study Early Termination, Suspension of the Study

The sponsor may suspend or prematurely terminate either the study in an individual study site or the entire study for significant and documented reasons including any significant and documented reasons as deemed appropriate by the sponsor.

A principal investigator, REB/IRB/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 REB/IRB/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 a 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 REB/IRB/EC or the regulatory authority.

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

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 devices supplied and other material in accordance with the sponsor procedures for the study

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 investigators, the REB/IRB/ECs, 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 REB/IRB /ECs 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.

In case of early termination of the clinical investigations, the sponsor or his authorized representative as applicable will notify the relevant regulatory agencies , competent authorities and EC 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 concerned regulatory agencies competent authorities and REB/IRB /EC's as applicable and directed by the Medical Device Directive 93/42/EC and amendments

16.5.2 Investigator Records

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

- REB/IRB/EC approval letter, including approved ICF document, with associated correspondence
- REB/IRB/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.

16.5.3 Investigator Responsibilities

- Obtain REB/IRB/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, REB/IRB/EC in a timely manner regarding the occurrence of any AEs and/or device deficiencies.

16.5.4 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.

16.5.5 Document Retention

Records and reports will remain on file for a minimum of five (5) years (unless otherwise instructed by local regulatory and/or institutional requirements) after completion of the clinical investigation. The investigator must notify the Sponsor before destroying any clinical investigation records.

16.6 Regulatory and Ethical Obligations

Biosense Webster will determine the appropriate local, national, and regional regulatory approval(s) that need to be obtained to conduct this clinical investigation according to appropriate legislation and guidance documents.

17 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.

17.1 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 CARTOFINDER™ maps created during the procedure will be downloaded/ extracted and an anonymized copy provided to the sponsor for further evaluation.

17.2 Device Accountability

The sponsor will keep records of all devices / materials supplied to the site. Investigators are responsible for appropriate logging of the devices received, verification of packing slip information (i.e., lot numbers and quantity shipped), date that each device was used in the study and disposition information regarding disposal or return to the sponsor.

The Device Accountability Log shall record the following information:

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

17.3 Device Returns

All investigational study devices will be returned to the sponsor. Any suspected malfunctioning device or device associated with an adverse event (device related or possibly device related) from the sponsor will undergo a thorough complaint analysis and must be properly documented on the case report form (eCRF). All returned devices must be properly decontaminated per hospital policy and properly labeled with the following:

- Subject identification number
- Date of use/event

- Return type (defective, non-defective, or adverse event)

All tracking information must be retained in the event the package has been lost and requires tracking.

17.4 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 within approximately 14 days of the subject visit. For AE reporting, refer to the Adverse Event Reporting Requirements and timelines within this clinical investigation protocol.

17.5 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.

17.6 Data Verification and Review

All eCRF will be subjected to automated and manual validation checking for omitted data, gross data inconsistencies, and timeliness of reporting. 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.

17.7 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.

17.8 Confidentiality and Protection of Clinical Investigation Data

To ensure confidentiality, protection, and attribution of the clinical investigation data, only trained and authorized sponsor and site personnel will be assigned unique user accounts and passwords to access the clinical investigation database. Each user account is designed to allow appropriate user rights and access level with the clinical investigation database system.

17.9 Publication Policy

Publication of clinical investigation results will be coordinated between the sponsor or designee. Authorship will be determined by the sponsor before development of any manuscript and in agreement with the participating Principal Investigators.

18 RISK/BENEFIT ANALYSIS

18.1 Potential Risks

A degree of risk exists with the LAT Algorithm not providing accurate information on target ablation sites. This is directly related to lack of information when recordings are collected potentially due to insufficient catheter contact. Investigators (EPs) may be asked to take multiple maps for comparison but as well as have other modalities such as the EP recording system to observe real time catheter signals and fluoroscopy to determine identified target areas for clinical relevance and risk. 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%) [16, 17, 18, 19, 20, 21, 22, 23].

Do not reprocess, resterilize, or reuse. This device is packaged and sterilized for single use only. Reprocessing, resterilizing, or reusing may compromise the structural integrity of the device and/or lead to device failure that in turn may result in patient injury, illness, or death. Also, reprocessing or resterilization of single use devices may create a risk of contamination and/or cause patient infection or cross-infection, including, but not limited to, the transmission of infectious disease(s) from one patient to another. Contamination of the device may lead to injury, illness, or death of the patient.

Other potential complications, which may result from catheter insertion and manipulation as part of the prerequisite electrophysiology trial and mapping procedure, include: Allergic reaction to the local anesthetic, sedatives, X-ray dye, heparin, protamine, or other agents administered during the procedure (risk < 1%) [21, 24-27]

Arterial or venous injury, including arterial dissection, thrombosis, occlusion or hemorrhage at the catheter insertion sites or at other sites along the vessels (risk < 1%) [16, 17]. These types of injuries may cause hemorrhage, hematoma, or ischemic injury to an extremity or major organ. Hemorrhage as a result of anticoagulation (risk < 0.5%), which may require transfusion [16, 17].

Potential risk of entanglement/and or entrapment. When the RF-192 basket catheter is within the proximity of the tricuspid valve or mitral valve, cautions need to be applied to avoid entanglement with chordae tendineae.

Infection at the catheter insertion site or systemic infection, including endocarditis and septic emboli (risk < 0.5%) [16, 17], can be minimized by using standard aseptic technique and, when indicated, by the use of antibiotic agents.

Additional contraindications for device use may include: hemodynamic instability, bacteremia, coagulopathy, prosthetic tricuspid valve, intra-atrial or venous thrombosis, and pregnancy (refer to the IFU for a complete list of contraindication for the device).

A full list of potential adverse events that are reasonably anticipated to occur as a result of the use of the clinical investigation device during the cardiac electrophysiology procedure include all of the events noted in any clinical study for these types of devices to date (refer to section 14)

18.2 Methods to Minimize Risk

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 the mapping 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.

Only investigators skilled in intra-cardiac mapping with the use of a multi-electrode (basket) catheter will be selected for participation in this study. The mapping procedures required for this study will be performed in electrophysiology laboratories with the assistance of skilled nurses and technicians. Additionally, safety data will be collected and evaluated regularly during enrollment by an unbiased investigator safety review committee, and all adverse events and device deficits will be reported to the study sponsor.

18.3 Potential Benefits

In patients with complex arrhythmias, elimination or amelioration of symptoms is a major driving force for therapy. The CARTOFINDER™ System and LAT Algorithm is designed to analyze the collected signals (electrical signals of the heart captured by the basket catheter) and show in a graphical display the specific locations in the heart which could sustain the arrhythmia. The RF192 Catheter is intended to simultaneously collect multiple [redacted] intracardiac signals and facilitate faster mapping of the atrial chambers of the heart using CARTO•3 EP Navigation System.

The CARTOFINDER™ Device provides voltage analysis of multiple, simultaneous ECG signals. A period of ECG recordings can be selected for analysis with a CARTOFINDER™ Device algorithm. The algorithm generates a 4D map display of IC voltage signal measurements over time to assist the investigators with the better understand the voltage activation patterns for analysis and therapy planning.

Through the simultaneous and sequential collection of these intra-cardiac signals and the mapping procedure, the RF192 Catheter might aid in the diagnosis of these complex atrial arrhythmias. The degree of risk of the electrophysiological procedure and the potential benefit of the treatment of complex arrhythmias should be determined by a qualified investigator. The information gathered during the conduct of this study may be of benefit in the future for the treatment of patients with complex arrhythmias and in particular persistent AF.

19 REFERENCES

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20 ATTACHMENTS

20.1 Attachment A: Definitions

Term	Definition
Adverse Event (AE)	Any unfavorable and unintended sign, medical occurrence, disease or injury (including abnormal laboratory findings) in subjects, users or other persons temporally associated with the use of a medicinal product or device (investigational) whether or not related to the investigational product. This definition includes events related to the investigational medical device and/or the comparator, and events related to the procedure in which the investigational device was used.
Adverse Device Effects (ADE's)	Adverse events related to the use of an investigational medical device. This definition includes adverse events resulting from insufficient or inadequate instructions for use deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. This definition includes any event resulting from use errors or from intentional misuse of the investigation medical device.
AF Episode	An atrial fibrillation episode is defined as AF which is documented by ECG monitoring and has a duration of at least 30 seconds, or if less than 30 seconds, is present continuously throughout the ECG monitoring tracing. The presence of subsequent episodes of AF requires that sinus rhythm be documented by ECG monitoring between AF episodes
Anticipated AE	An effect which by its nature, incidence, severity or outcome has been identified as possible complications associated with the investigational medical device and/ or intervention procedure.
Atypical Flutter	Macroreentrant circuits within the atria where activation rotates around large obstacles that does not meet the criteria for Typical Flutter.
Baseline Rate	Is the recorded rate from the subject demonstrating the ventricular response of the subjects arrhythmia.

Term	Definition
Cycle Length Measurement	Cycle Length will be measured by placing a multielectrode catheter (connected to the recording system) in the CS calculating the average CL over 10 repetitive cycles.
Device Deficiency	Inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction (failure of a medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or protocol), misuse or use error and inadequate labeling.
High-burden paroxysmal AF	AF episodes lasting less than 30 days. Episodes may terminate spontaneously or may be terminated via cardioversion.
Longstanding persistent AF	Continuous AF of > 12 months duration
Organized AF	When observing the surface leads, an organized activation is considered present if discrete atrial complexes, separated by an isoelectric baseline, were seen during three or more cycles over at least 30 msec and have variability in beat-to-beat cycle length, electrograms mainly in surface P-wave morphology. This includes other atrial rates recorded/observed in other portions of the atrium.
Paroxysmal AF	Paroxysmal AF is defined as recurrent AF (≥ 2 episodes) that terminates spontaneously within 7 days. Episodes of AF of ≤ 48 hours duration that are terminated with electrical or pharmacologic cardioversion should also be classified as paroxysmal AF episodes.
Permanent AF	Not appropriate in the context of patients undergoing catheter ablation of AF; refers to a group of patients where a decision has been made not to pursue restoration of sinus rhythm by any means, including catheter or surgical ablation.

Persistent AF	Persistent AF is defined as continuous AF that is sustained beyond 7 days. Episodes of AF in which a decision is made to electrically or pharmacologically cardiovert the patient after ≥ 48 hours of AF, but prior to 7 days, should also be classified as persistent AF episodes.
Rate of Slowing	Rate of slowing for the overall mean atrial fibrillation rate is defined by a decrease in cycle length of the ventricular/atrial rate when compared to baseline ventricular/atrial rate for each subject.

Term	Definition
Serious adverse event (SAE)	Any adverse event that: Led to a death Led to a serious deterioration in health that either: o Resulted in a life-threatening illness or injury, or o Resulted in a permanent impairment of a body structure or a body function, or o Required in-patient hospitalization or prolongation of existing hospitalization, or o Resulted in medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function Led to fetal distress, fetal death or a congenital abnormality or birth defect A planned hospitalization for pre-existing condition, or a procedure required by the protocol, without a serious deterioration in health, is not considered to be a serious adverse event. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life- threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above.
Serious Adverse Device Effects (SADE's)	Adverse device effects that has resulted in any of the consequences characteristic of a serious adverse event.
Typical Flutter	Atrial flutter is caused by a reentrant rhythm in either the right or left atrium. Typically initiated by a premature electrical impulse arising in the atria, atrial flutter is propagated due to differences in refractory periods of atrial tissue. This creates electrical activity that moves in a localized self-perpetuating loop. For each cycle around the loop, there results an electric impulse that propagates through the atria.

Term	Definition
Unanticipated Serious Adverse Device Effect (USADE)	Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report. NOTE: Anticipated SADE: an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report
Ventricular Tachycardia (VT)	Ventricular tachycardia: a tachycardia (rate _100/min) with three or more consecutive beats that originates from the ventricles independent of atrial or AV nodal conduction. Continuous VT for _30 s or that requires an intervention for termination (such as cardioversion).

20.2 Attachment B: NYHA Functional Classification

NYHA Functional Classification, per ACC/AHA guidelines	
Class I	Cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
Class II	Cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.
Class III	Cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary physical activity results in fatigue, palpitations, dyspnea or anginal pain.
Class IV	Cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.