ATrial FibrillaTion ProgrESsion Trial
(ATTEST Trial)

Sponsor:	BIOSENSE WEBSTER, INC. 3333 Diamond Canyon Road Diamond Bar, CA 91765
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1.0 Protocol Agreement Form

Study Title: Atrial Fibrillation Progression Trial (ATTEST)

I, the undersigned, have read and understand this clinical study, including the appendices. I will conduct the clinical study in strict compliance with the protocol and in accordance with appropriate in-country ethical and regulatory considerations. I will ensure that all persons assisting in this study are adequately informed about the protocol, study product(s), and their clinical study-related duties and functions.

I agree to maintain all information supplied by Biosense Webster, Inc. in confidence and when information regarding this study is presented to an institutional review board (or equivalent; e.g., ethics committee [EC] or ethics board [EB]), it will include information regarding the confidential nature of all study-related material.

Principal Investigator Name (Print)	**Signature**	**Date**

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3.0 Protocol Summary

Title:	Atrial Fibrillation Progression Trial (ATTEST)
Design:	This is a prospective, multi-center, randomized (1:1), controlled, two-arm, open-label, clinical study.
Objective:	The objective of this study is to determine whether in subjects with Paroxysmal AF (PAF), early RF ablation treatment using the THERMOCOOL® Catheter Family in conjunction with the CARTO® 3, CARTO® XP or CARTO® RMT System, delays progression of AF compared with drug therapy (either rate or rhythm control) using current AF management guidelines.[1-4]
Enrollment:	Up to 330 subjects will be enrolled in this study.
Clinical Sites:	Up to 50 sites primarily in Europe, and/or Asia and/or North America.
Subject Population:	PAF patients with recurrent AF for at least 2 years who have failed at least 1 but no more than 2 prescribed drugs (either anti-arrhythmic or rate control drug) Eligible subjects who sign the study informed consent form will be randomized into one of two study arms:
PVI (Test) Group:	RF ablation to achieve pulmonary vein isolation (PVI) using the THERMOCOOL® Catheter Family in conjunction with the CARTO ® 3, CARTO® XP or CARTO® RMT System
Drug Therapy (Control) Group:	AAD therapy (either rate or rhythm control) using current AF management guidelines[1-4]
Primary Endpoint:	Time to persistent AF/AT (excluding isthmus-dependent atrial flutter) at 3 years. Persistent AF/AT is defined as AF/AT lasting longer than 7 consecutive days or requiring termination by cardioversion after 48 hours.[a]
Secondary Endpoints:	Rate to persistent AF/AT; Number of repeat ablations and new AAD drugs; Rhythm (% subjects in SR, % subjects with recurrent AF); Pre-existing or new onset/worsening condition(s) that may be associated with AF progression; Catheter-related complications (ablation), adverse drug reactions (AAD); Health care utilization and Quality of Life.
Study Duration:	4.5 years (18 months enrollment period and 3 years follow-up per subject)

[a] Unnecessary Cardioversion < 7 days should be discouraged, but within ethical bounds. If the investigator believes the subject's AF symptoms are sufficiently severe to warrant cardioversion, he/she should proceed, regardless of timing. AF symptoms sufficiently severe to warrant cardioversion are angina, shortness of breath and/or systolic blood pressure < 90 mmHg related to AF.

Study Inclusion Criteria

1. Patients with recurrent paroxysmal AF for at least 2 years, with ≥ 2 episodes over the last 6 months;
2. HATCH Score of at least ≥1 and ≤ 4.[b]
3. Eligible for catheter ablation and for anti-arrhythmic or rate control medications, after having failed at least 1 but no more than 2 prescribed drugs (either anti-arrhythmic or rate control drug).
4. Age 60 years or older.
5. LA diameter ≤ 55mm by TTE.
6. LV ejection fraction ≥ 50% when in sinus rhythm or LV ejection fraction ≥ 35% when in AF.

NOTE: For patients entering the study in AF with an ejection fraction ≥ 35% and < 50%; the ejection fraction should be re-checked when in sinus rhythm. In case the ejection fraction is ≥ 50% the subject can continue in the study.

7. Patient signed the Informed Consent Form and is able and willing to comply with protocol requirements, including all baseline and follow- up testing.

Study Exclusion Criteria

1. Patients awaiting cardiac transplantation or other cardiac surgery.
2. Acute illness (ongoing) or active systemic infection or sepsis which in the opinion of the investigator, may adversely affect the safety and/or effectiveness of the participant of the study.
3. Reversible causes of AF, e.g. but not limited to thyroid disorders, acute alcohol intoxication, recent major surgical procedures or trauma,…
4. Recent cardiac events including MI, PCI, or valve or bypass surgery in the preceding 3 months.
5. Heart failure decompensation.
6. Previously diagnosed with persistent/permanent AF/AT
7. Previously required cardioversion >48 hours after onset of AF/AT
8. Subject having previous TIA or stroke (cerebrovascular accident) one year prior to patient enrolment and/or no sufficient recovery.
9. Pulmonary embolism or recent atrial embolism/thrombosis.
10. Hypertrophic obstructive cardiomyopathy.
11. Class IV angina or Class IV CHF (including past or planned heart transplantation).
12. Mandated anti-arrhythmic drug therapy for disease conditions other than AF.
13. Heritable arrhythmias or increased risk for torsade de pointes with class I or III Drugs.
14. Prior LA catheter ablation with the intention of treating AF; prior surgical interventions for AF such as the MAZE procedure.
15. Prior AV nodal ablation.
16. Patients presenting contra-indications for the study catheter(s), as indicated in the

[b] **H**ypertension (+1); **A**ge >75 years (+1); previous **T**IA or Stroke (+2); **C**OPD (+1); **H**eart failure - including systolic or diastolic heart failure (+2).

respective Instructions For Use.

17. Contraindication to warfarin, other anticoagulation therapy, or all anti-platelet medications.
18. Medical conditions limiting expected survival to < 3 years.
19. Concurrent participation in any other clinical study.
20. Prior history of non-adherence to prescribed drug regimens.
21. Women of child bearing potential whom are pregnant, lactating, or planning to become pregnant during the course of the trial

NOTE: Prior ablation of the cavo-tricuspid isthmus is not a reason to exclude, if the patient develops subsequent recurrent atrial fibrillation.

NOTE: For patients randomized to the PVI group (Test Group), a Transesophageal Echocardiography (TEE) should be performed (as per standard of care), within 48 hours pre-procedure, to exclude atrial thrombus or other structural contraindications for an ablation procedure.

Schedule of Examinations

Table 1. Summary of Subject Assessments:

Assessments	BL D0[8]	M3 D76-104	M6 D166-210	M9 D240-300	Y1 D330-420	M18 D480-600	Y2 D630-809	M30 D810-989	Y3 D990-1170	UNS
Clinic visit	X	X	X		X		X		X	X
Phone follow-up[1]				X		X		X		
Patient Information and Consent	X									
Medical history	X									
HATCH score	X	X	X		X		X		X	X
ECG[2]	X	X	X		X		X		X	X
TTM[3]		X	X	X	X	X	X	X	X	X
TEE[4]	X									
TTE[5]	X				X		X		X	
QoL (EQ-5D, AFEQT)[6]	X	X	X		X		X		X	
Health status[7]	X	X	X		X		X		X	X
Cardiac medication	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
Cardioversion / re-ablation documented		X	X	X	X	X	X	X	X	X

1. Phone follow-up calls include check for AEs, changes in cardiac medication and TTM.
2. To be collected if completed as standard of care.
3. Dispensation of TTM device at Month 3. Additional details/instructions regarding TTM monitoring are provided below.
4. Only for patients randomized to PVI, within 48 hours pre-procedure.
5. TTE to be performed within 30 days pre-treatment. For the Test Group, TTE must be repeated prior to discharge
6. AFEQT questionnaire is only to be completed by a subpopulation due to limited validated translations
7. LA Size, blood pressure, NYHA Functional Classification of heart disease, Diabetes, lipid profile, renal function and dementia.
8. Day 0 Test Group (PVI)= Index ablation procedure and Day 0 Control Group (AAD) = Randomization

4.0 List of Acronyms/Abbreviations and Study Terms/Definitions

Acronym / Abbreviation	Expanded Term
AAD	Antiarrhythmic Drug
ACC/AHA/ESC	American College of Cardiology/American Heart Association/European Society of Cardiology
ADE	Adverse Device Effect
ADR	Adverse Drug Reaction
AE	Adverse Event
AF	Atrial Fibrillation
AFEQT	Atrial Fibrillation Effect on QualiTy-of-life
ARDS	Acute Respiratory Distress Syndrome
AT	Atrial Tachycardia
BB	Beta Blocker
CCB	Calcium Channel Blocker
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
COPD	Chronic Obstructive Pulmonary Disease
CPK	Creatine Phosphokinase
CRF	Case Report Form
CVA	Cerebrovascular Accident or Stroke
EB	Ethics Board
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EMEA	Europe, Middle East and Africa
EP	Electrophysiology
FDA	Food and Drug Administration
Fr	French
GCP	Good Clinical Practices
HM	Holter Monitoring
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IFU	Instruction For Use
ILR	Implantable Loop Recorder
ISO	International Organization for Standardization
LA	Left Atrium
LV	Left Ventricle
MDR	Medical Device Reporting
MDV	Medical Device Vigilance
MI	Myocardial Infarction
PAF	Paroxysmal Atrial Fibrillation
PCI	Percutaneous Coronary Intervention
PI	Principal Investigator
PV	Pulmonary Vein
PVI	Pulmonary Vein Isolation
QoL	Quality Of Life
RA	Right Atrium
RF	Radiofrequency
RSPV	Right Superior Pulmonary Vein
RV	Right Ventricle
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SR	Sinus Rhythm
TEE	Transesophageal Echocardiography
TIA	Transient Ischemic Attack
TTE	Transthoracic Echocardiography
TTM	Transtelephonic Monitoring
UADE	Unanticipated Adverse Device Effect

Term	Study Definition
Symptomatic AF	Symptom(s) that is/are exhibited by the subject, which make him/her seek medical attention, and are concurrent with a documented episode (i.e., by ILR [implantable loop recorder], ECG [electrocardiogram], TTM [transtelephonic monitoring], Holter Monitor, or telemetry recording. Symptoms may include but are not limited to: palpitations, irregular pulse (e.g., rapid, racing, pounding, fluttering, bradycardia), dizziness, weakness, chest discomfort, and breathlessness.
Paroxysmal AF	Recurrent AF that terminates spontaneously within 7 days.
Persistent AF/AT	AF/AT which is sustained beyond seven days; or, lasting more than 48 hours and less than seven days but necessitating pharmacologic or electrical cardioversion.
Long-standing persistent AF/AT	Continuous AF of greater than one-year duration.
AF episode	An episode of AF > 30 seconds. Atrial fibrillation and atrial flutter (including atypical flutter) are considered episodes of AF. Atrial flutter alone is not considered an episode of AF.
Complete PVI	Entrance block confirmed with or without the use of a focal catheter.
Procedure time	Time from introduction of first catheter to withdrawal of last catheter (minutes).

5.0 Introduction

5.1 Background

Atrial fibrillation is the most common cardiac arrhythmia, with prevalence ranging from 0.1% in adults under 55 to 9% in adults over 80 years old.[5-7] Patients with atrial fibrillation (AF) are at increased risk of stroke, cardiac dysfunction, and death, and may also experience an impaired quality of life due to AF symptoms.[8-10] Frequency and duration of AF episodes vary, with ACC/AHA/ESC guidelines dividing the condition into paroxysmal, persistent, and permanent types.[1] Transition from one form to another occurs, with episodes generally increasing in frequency and eventually failing to respond to attempts to restore sinus rhythm. Rates of disease progression are not well established, especially in regard to updated classification schemes and in the context of current AF management.[11]

Rates of progression (from paroxysmal AF to more frequent and intractable forms) of up to 30% at 5 years have been reported, with annual risk estimates generally 3-6%.[12-15] In the first year of observation, rates of progression of 8-15% have been reported for paroxysmal AF.[14, 16, 17] Two studies with follow-up of 8 and 14 years[12,13] reported well over half of all paroxysmal AF patients eventually progressing to persistent or permanent AF. In contrast, a Mayo Clinic study of lone AF (no hypertension or structural heart disease, diagnosed before age 60) found only 31% of patients progressing over 25 years of follow-up, with mortality rates similar to age- and gender- matched population controls.[18]

Variation in reported rates of AF progression is certainly due in part to the varying definitions used and in the baseline populations studied. The most common definitions in recent published studies are consistent with recommended terminology of paroxysmal, persistent, and permanent AF from ACC/AHA/ESC guidelines.[1] Briefly, paroxysmal AF is defined as recurrent AF that terminates spontaneously within 7 days. Persistent AF is defined as AF sustained beyond 7 days, or lasting less than 7 days but necessitating pharmacologic or electrical cardioversion. Permanent AF is long-standing AF in which cardioversion has failed or is no longer attempted. More recently, the HRS/EHRA/ECAS Consensus Statement includes similar definitions for paroxysmal and persistent AF with long standing persistent

AF defined as “continuous AF of greater than 1 year duration”. Additionally, terms such as "intermittent," "constant," "long-lasting," "sustained" and "chronic" have also been used, particularly in studies conducted prior to 2000.[19-21] Progression of paroxysmal AF from baseline is often captured as development of either persistent or permanent AF. These patients are not always described as moving from paroxysmal to persistent then to permanent AF. In several studies, progression to permanent AF is reported as an endpoint for patients experiencing paroxysmal AF at baseline.[22-25] Despite use of standard AF definitions, there is some element of subjectivity related to treatment decisions impacting the assigned "type" of AF. For permanent AF in particular, a key component of most definitions is no further attempts to restore sinus rhythm, a treatment decision that is clearly subject to influence by practice patterns, individual physician and patient preferences, and even health care system factors. A community-based study in Spain illustrates this problem.[26] The authors defined patients as having "permanent AF" if their general practitioner managed them for rate control only. The mean age of the patients in this study was 75 years, and high rates of both permanent AF at baseline (59% of 798 patients), and of progression (6.6% in the first 7 months of follow-up) were observed. Likewise, in the RECORDAF registry, very high rates of progression to permanent AF were reported in patients being treated with a rate control strategy (vs. rhythm control).[27] The authors note that this distinction is "partly semantic", and related to a perception on the part of physicians that choosing a rate control strategy means accepting arrhythmia, contributing to the categorization of these patients as having "permanent" AF.

Variables such as patient age and the presence of comorbidites must also be considered when determining rates of AF progression. Age is the most well-studied and consistently significant factor associated with AF progression. Two studies quantifying the increased risk of AF progression for each decade of age found 40% and 82% increases in risk, respectively.[14, 28] Left atrial (LA) size/volume and hypertension have been frequently studied, with LA volume somewhat more likely to be significant in univariate analyses but not significant in predictive multivariate models. A study from Japan focused on LA wall thickness as a marker of structural remodeling; the authors suggested it to be a stronger predictor of AF progression than LA volume in their cohort of patients.[29] Valvular disease and heart failure were each reported as significant in 4 studies using multivariate models. Valvular disease[13,14, 16, 23, 30, 31] (univariate or multivariate analyses) and heart failure[11, 14, 16, 19, 32] have also been reported as linked to AF progression. In one study, a composite score (HATCH score), which incorporates hypertension (1 point), age >75 years (1 point), stroke/TIA (2 points), COPD (1 point), and heart failure (2 points), was found to be strongly predictive of AF progression; patients with a moderate to high HATCH score (2-7 points) faced a 25-40% annual risk of AF progression, as compared to below 10% for patients scoring 0 or 1.[16]
In another AF study, the HATCH score was not found to be predictive of AF progression among patients treated by catheter ablation.[33]

The predictive power of patient age seems sensible in the context of AF as a self-perpetuating arrhythmia with interdependent mechanisms.[34] Animal studies of atrial remodeling have proposed that "AF begets AF." Experimental induction of sustained AF in dogs and in goats support this model.[35, 36] Changes to atrial architecture (fibrotic disorganization and increased atrial size) have also been documented in these animal models.[37] With animal models supporting the concept that “AF begets AF”, similar progression, though not well-studied, is thought to occur in humans, which may warrant treatment (either with AADs or catheter ablation) to delay or prevent such progression and/or changes.

Though catheter-based PVI has been developed as a treatment for patients with AF, whether this procedure prevents or delays progression towards permanent AF has not been well-

studied in patients with PAF. Comparative data on AF progression after catheter ablation vs. no ablation are limited.

Three randomized trials of AADs versus catheter ablation, by Santinelli, *et al* Wazni, *et al* and Pappone, *et al*, reported disease progression,[38-40] however, disease progression was not a primary or secondary endpoint in these studies. In the Santinelli study, AF rates were low and disease progression did not differ significantly between assigned treatment groups. In the Wazni study, 3 patients in the AAD group developed chronic AF, and there was no mention of AF progression in the RFA group. The definition of chronic AF and the timing of these events was not clear (during or at some unspecified time after the 1-year study follow-up). Rates of AF progression were not analyzed between groups; therefore, no level of significance is reported. In the Pappone study, the primary endpoint was freedom from AF and atrial tachycardia (AT), irrespective of crossover, 4 years after randomization; however, rates of AF progression were also reported for both groups. Among AADs patients, 19 progressed to persistent AF before crossover, after a median follow-up of 32 months (min-max, 25-47). Among RFA patients, persistent AF developed just in one patient with previous myocardial infarction, hypertension, diabetes mellitus and left atrial enlargement (59 mm), which, at the time of progression, further increased to 65 mm. Evidence regarding rates of disease progression from high-quality sources (randomized, controlled trials) is limited. Available data suggests radiofrequency catheter ablation may delay or possibly prevent AF progression, compared to medical therapy; but, no definitive studies have been conducted to date.

Though observational in nature, some studies provide comparisons of AF progression in ablation-treated versus non-ablation treated subsets.[11, 16, 32] The raw percentages of patients experiencing AF progression in these studies tended to favor catheter ablation; however, the number of patients undergoing ablation was relatively small, and no multivariate analyses were reported, attempting to adjust for other variables.

The impact of catheter ablation in progression of PAF among RCT and observational studies (comparing the percent of progression for ablation versus no ablation) ranges from 0-6% per year for ablation groups to 2-53% per year for non-ablation groups.[11, 16, 32, 38, 39] In single-arm studies, rates ranging from 0-11% were reported.[22, 33, 41-46] In appraising this evidence, it is important to note that some studies limit the patient population to only those with successful ablation or available long-term follow-up and, in doing so are likely to create bias by avoiding the sicker patients. Thus, rates estimated from these studies may be lower than those seen in prospective studies which follow patients from intention to treat forward. For example, 2010 studies by Bertaglia[22] and Fichtner[41] limited analysis to patients free of recurrence at 12 months. In the Fichtner study, this subgroup comprised less than half of the patients initially undergoing ablation (150/356); AF progression was not reported for the remaining 206 patients with recurrence in the first year, as the focus of the study was on late recurrence.

To better understand the progression of AF following catheter ablation in humans, a well-controlled study should be conducted, in which AF terminology is defined according to current AF management guidelines, factors associated with AF progression are evaluated, an appropriate comparison group is included, and long-term follow-up is planned.

5.2 Rationale

Disease progression, as an outcome in AF, has been studied less commonly than other long term outcomes such as AF recurrence in general (in catheter ablation studies) and cardiovascular events / mortality (in trials of anti-thrombotic and anti-arrhythmic drug therapy). There are no published randomized trials, comparing ablation to medical treatment, that include this outcome as a primary endpoint; although, Veasey, *et al*[47] conducted a

randomized trial (long-MinVPACE study) comparing pacemaker strategies in patients with paroxysmal AF and a bradycardia pacing indication and used time to persistent AF as a co-primary endpoint. Variable definitions and small numbers of events in some studies, particularly prospective studies of catheter ablation, mean that point estimates of progression risk are likely to be imprecise. Indeed, published annual rates of progression have varied from approximately 1%[18] to more than 20%[17, 32] depending on the patients studied.

Delay of disease progression is of interest both as a clinical outcome in its own right, and as an important causal link for establishing the potential effect of AF treatments to improve longer-term cardiovascular outcomes and mortality. Currently, the THERMOCOOL® Navigation Family of catheters and the CARTO® 3, CARTO® XP and CARTO® RMT Systems are widely used for treating patients with PAF. Though drug therapy has long been considered first-line treatment for AF, well-controlled studies are needed to compare the effectiveness of catheter ablation with drug therapy to determine whether catheter ablation delays or prevents progression of AF in the PAF patient population. Differences between these treatment modalities would be better understood in a prospective, randomized, controlled clinical study.

This study is being conducted to evaluate progression to persistent AF/AT in patients with recurrent, symptomatic PAF undergoing PVI with THERMOCOOL® Family of catheters, when used with the CARTO® 3, CARTO® XP or CARTO® RMT System (Biosense Webster, Inc.), compared with those undergoing drug therapy (either rate or rhythm control) using current AF management guidelines.[1-4]

The risks posed are expected to be comparable to those anticipated during routine use of catheter ablation systems for intracardiac radiofrequency (RF) ablation procedures and use of drug therapy according to current AF management guidelines.[1-4] Appropriate measures have been outlined in this protocol to minimize the risk to subjects, while still providing the possible benefits of the two treatment options.

5.3 Device Description

All devices to be used in this study are commercially available, conform to the applicable local regulations and are to be used according to the approved indication and their Instructions for Use (IFU).

The study devices of ATTEST are the commercially available THERMOCOOL® Catheter Family. Subjects in this study who undergo PVI are to have their procedure performed and completed using the study device (a THERMOCOOL® navigational catheter) in conjunction with the CARTO® 3, CARTO® XP or CARTO® RMT System.

Each site will be required to have specific equipment for performing RF ablation procedures. Sites will be instructed to refer to the User's Manual / Instructions for Use for the set-up of each system / device / component.

The CARTO® 3, CARTO® XP and CARTO® RMT Systems are electroanatomical mapping systems for use in performing catheter-based electrophysiological RF ablation procedures.

[redacted]

[redacted]

[redacted]

5.4 Risk Analysis

The risks posed are expected to be comparable to those anticipated during routine use of catheter ablation systems for intracardiac radiofrequency (RF) ablation procedures and use of AAD therapy according to current AF management guidelines.[1-4] Appropriate measures have been outlined in this protocol to minimize the risk to subjects, while still providing the possible benefits of the treatment options to be studied.

The risks and complications of the different AAD medications are listed in their respective Package Inserts/Summaries of Product Characteristics. The use of AAD is routine treatment for many patients with Atrial Fibrillation, no additional risks are anticipated for subjects enrolled in this study compared to subjects undergoing AAD treatment outside of the study as per the current AF Management Guidelines[1-4].

RF catheter ablation has been used for nearly two decades, and the risks and complications are well understood. The use of non-irrigated and saline-irrigated ablation catheters is routine for many PAF ablation procedures. No additional risks are anticipated for subjects enrolled in this study compared to subjects undergoing ablation for symptomatic PAF outside of the study. A summary of risks associated with catheter ablation, including analysis of and plans to minimize these risks is provided in Appendix A.

6.0 Study Hypothesis

For subjects undergoing early RF ablation for recurrent, symptomatic PAF, it is hypothesized that, compared to the Drug Therapy (control) Group, the PVI (test) Group will demonstrate superior effectiveness as evidenced by a longer time needed to progress to persistent AF/AT during follow-up through 3 years.

7.0 Objective

The objective of this study is to determine whether in subjects with Paroxysmal AF (PAF), early RF ablation treatment using the THERMOCOOL® Catheter Family in conjunction with the CARTO® 3, CARTO® XP or CARTO® RMT System delays progression of AF compared with drug therapy (either rate or rhythm control) using current AF management guidelines.[1-4]

8.0 Investigational Plan

8.1 Study Design

This is a prospective, multi-center, randomized (1:1), controlled, two-arm, open-label, clinical study, which will evaluate the effectiveness of early RF ablation intervention in delaying progression of PAF to persistent AF/AT, compared with drug therapy (either rate or rhythm control). Patients with recurrent, symptomatic PAF who meet the inclusion criteria will be considered for study participation and may be enrolled if no exclusion criteria apply.

8.2 Treatment Groups

Eligible subjects who sign the study informed consent form will be randomized into one of two treatment groups:

- **PVI (Test) Group:** RF ablation to achieve PVI using the THERMOCOOL® Catheter Family in conjunction with the CARTO® 3, CARTO® XP or CARTO® RMT System.

- **Drug Therapy (Control) Group:** AAD therapy in accordance with current AF management guidelines[1-4]

The Test Group will be compared to the Control Group to determine differences with respect to various effectiveness and safety endpoints. Planned statistical analyses of endpoints and outcomes are described in Section 14 (Statistical Analysis) of this protocol.

8.3 Number of Centers

Up to 50 sites in Europe and/or the Asia Pacific, North-America region will participate in this study. Previous studies have reported cross-over rate ranges from 42% to 59% during the 1-year follow-up time; Santinelli *et al* study (2009)[37] reports 87.9% cross-over rate during the four years follow-up time. To mitigate high cross-over rates and minimize the unilateral and random efflux from the Control Group, sites with the potential to minimize potential cross-over will be selected for study participation (refer to Section 9.2, Informed Consent and Enrolment Procedures, for additional detail). Total enrolment among all sites of up to 330 subjects is expected, with an approximately equal distribution between Test and Control Groups.

8.4 Study Duration, Completion, and Termination

- **Duration:** The study duration is anticipated to be 4-5 years; 1-2 years to complete screening/enrollment, and 3 years to complete follow-up for all subjects.

- **Completion:** The planned time of study completion is after all subjects have completed the required 3-year follow-up visits with the following exceptions: (a) subjects who withdraw from the study or who terminate early per protocol or investigator decision; and, (b) premature study stoppage for futility (see Termination).

- **Termination:** The study may be terminated prematurely at the discretion of the Sponsor or on statistical grounds (i.e., effectiveness or futility is determined). The Sponsor may also terminate a site prior to study completion if the Sponsor believes the site is no longer capable of participating (e.g., cannot fulfil subject enrolment goals, site suspension by EC / EB).

9.0 Subject Selection and Disposition

9.1 Recruitment and Screening Procedures

Patients who have failed at least 1 but no more than 2 prescribed drugs for AF (either anti-arrhythmic or rate control drug) will be screened for this study if eligible for both (i) RF ablation for treatment of recurrent, symptomatic PAF and (ii) medication management with either anti-arrhythmic or rate control drug. A screening log, maintained at each study site, will be used to document the subjects reviewed for potential enrolment into the study. The screening log should be completed for any patient considered for study inclusion, regardless of whether the patient is selected or not, as this will allow better management of the study enrolment rate.

9.2 Informed Consent and Enrolment Procedures

For this study, it is important to minimize the number of Control Group subjects who undergo RF ablation for AF, after cross-over, and thus confound the treatment group analyses. Because high cross-over rates from the drug treatment group to the ablation treatment group have been reported in studies similar to this one, the following measures will be implemented at each study site to minimize subject cross-over (refer to Appendix B for additional detail):

- Avoid recruiting/enrolling patients who are initially referred specifically for RF ablation.
- Select sites with:
  - Significant experience with RF ablation; and that also with a large AF patient population on medication management alone.
  - Commitment to enrolling subjects who do not show an obvious bias toward one treatment arm over another and who will agree to accept the treatment to which they are randomized.

The informed consent process will include a thorough discussion of the importance of minimizing cross-over in the Control Group (refer to Appendix B). Patients who exhibit a clear understanding of this and who are deemed eligible for and willing to participate in the study must sign (or have their legal representative sign on their behalf) the study's informed consent form (ICF), prior to enrolment and collection of any study-related data. The ICF and any revisions must have prior approval of the study site's ethics committee (EC) / ethics board (EB). The signed ICF will be kept in the subject's files.

9.3 Study Inclusion Criteria

1. Patients with recurrent paroxysmal AF for at least 2 years, with ≥ 2 episodes over the last 6 months;
2. HATCH Score of at least ≥1 and ≤ 4.[c]
3. Eligible for catheter ablation and for anti-arrhythmic or rate control medications, after having failed at least 1 but no more than 2 prescribed drugs (either anti-arrhythmic or rate control drug).
4. Age 60 years or older.

[c] **H**ypertension (+1); **A**ge >75 years (+1); previous **T**IA or Stroke (+2); **C**OPD (+1); **H**eart failure - including systolic or diastolic heart failure (+2).

5. LA diameter ≤ 55mm by TTE.
6. LV ejection fraction ≥ 50% when in sinus rhythm or LV ejection fraction ≥ 35% when in AF.

NOTE: For patients entering the study in AF with an ejection fraction ≥ 35% and < 50%; the ejection fraction should be re-checked when in sinus rhythm. In case the ejection fraction is ≥ 50% the subject can continue in the study.

7. Patient signed the Informed Consent Form and is able and willing to comply with protocol requirements, including all baseline and follow- up testing.

9.4 Study Exclusion Criteria

1. Patients awaiting cardiac transplantation or other cardiac surgery.
2. Acute illness (ongoing) or active systemic infection or sepsis which in the opinion of the investigator, may adversely affect the safety and/or effectiveness of the participant of the study.
3. Reversible causes of AF, e.g. but not limited to thyroid disorders, acute alcohol intoxication, recent major surgical procedures or trauma,…
4. Recent cardiac events including MI, PCI, or valve or bypass surgery in the preceding 3 months.
5. Heart failure decompensation.
6. Previously diagnosed with persistent/permanent AF/AT
7. Previously required cardioversion >48 hours after onset of AF/AT
8. Subject having previous TIA or stroke (cerebrovascular accident) one year prior to patient enrolment and/or no sufficient recovery.
9. Pulmonary embolism or recent atrial embolism/thrombosis.
10. Hypertrophic obstructive cardiomyopathy.
11. Class IV angina or Class IV CHF (including past or planned heart transplantation).
12. Mandated anti-arrhythmic drug therapy for disease conditions other than AF.
13. Heritable arrhythmias or increased risk for torsade de pointes with class I or III Drugs.
14. Prior LA catheter ablation with the intention of treating AF; prior surgical interventions for AF such as the MAZE procedure.
15. Prior AV nodal ablation.
16. Patients presenting contra-indications for the study catheter(s), as indicated in the respective Instructions For Use.
17. Contraindication to warfarin, other anticoagulation therapy, or all anti-platelet medications.
18. Medical conditions limiting expected survival to < 3 years.
19. Concurrent participation in any other clinical study.
20. Prior history of non-adherence to prescribed drug regimens.
21. Women of child bearing potential whom are pregnant, lactating, or planning to become pregnant during the course of the trial

NOTE: Prior ablation of the cavo-tricuspid isthmus is not a reason to exclude, if the patient develops subsequent recurrent atrial fibrillation.

NOTE: For patients randomized to the PVI group (Test Group), a Transesophageal Echocardiography (TEE) should be performed (as per standard of care), within 48 hours pre-procedure, to exclude atrial thrombus or other structural contraindications for an ablation procedure.

9.5 Subject Disposition

- **Enrolled Subjects:** subjects who sign the study informed consent form and are randomized.

- **Excluded Subjects:**
  - **Test Group:** subjects who are enrolled and randomized to ablation therapy but never undergo insertion of the THERMOCOOL ablation catheter.
  - **Control Group:** subjects who are enrolled and randomized to medication management (AAD) but never begin taking investigator-prescribed AAD and are ineligible for ablation therapy.

- **Discontinued Subjects:**
  - **Test Group:** subjects who are enrolled and randomized to ablation therapy, undergo insertion of the THERMOCOOL ablation catheter, but do not undergo further ablation therapy (i.e., no RF energy is delivered). These subjects will be categorized as 'discontinued' if therapy is not possible due to equipment failure or if their arrhythmia is determined, at the time of electrophysiologic study, to be a non-study arrhythmia, e.g. atrial flutter, instead of PAF under investigation.
  - **Control Group:** subjects who are enrolled and randomized to medication management and have started an investigator-prescribed AAD, but do not complete the dose-loading period (~ 2 weeks), for reasons other than a safety failure or if their arrhythmia is determined to be a non-study arrhythmia, e.g. atrial flutter.

- **Lost to Follow-up Subjects:** 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, the subject will be considered lost to follow-up and the study termination/end form will be completed in the individual case report form.

- **Withdrawn / Early Termination Subjects:** investigator termination of a subject for reasons stated below in Section 9.6; or, subjects who withdraw consent for study participation and are terminated from the study prior to completion of all follow-up visits.

- **Completed Subjects:** enrolled subjects who have not been discontinued, withdrawn or lost-to-follow-up from the study, prior to the final 3-year study visit.

9.6 Subject Withdrawal

The investigator may remove a subject from the study for any of the following reasons: no longer meets eligibility criteria, withdrawal is in the subject's best interest, subject preference, concurrent illness, noncompliance, or any other situation the investigator deems a compromise to the integrity of the study. Subjects will be informed prior to study entry that they are free to withdraw from the study at any time and for any reason, without prejudice to his or her future medical care by the physician or the institution. The Sponsor also has the right to withdraw a subject from the study at any time and for any reason.

If a subject is removed from the study, the date and reason for withdrawal will be recorded on the appropriate electronic case report form (eCRF). If the subject is withdrawn due to an adverse event (AE) or serious adverse event (SAE), the Investigator must comply with all reporting requirements and must follow the subject until the AE/SAE has resolved or stabilized.

10.0 Study Endpoints

10.1 Primary Endpoint

Time to persistent AF/AT (excluding isthmus-dependent atrial flutter) at 3 years. Persistent AF/AT is defined as AF/AT lasting longer than 7 consecutive days or requiring termination by cardioversion after 48 hours.

10.2 Secondary Endpoints

The secondary endpoints supporting the study objective are:

Effectiveness:

- Rate and time to persistent AF/AT at 1 year and 2 years, rate of persistent AF/AT by number of ablations at 3 years.
- Number of repeat ablations and new AAD drugs per subject throughout 3 years follow-up.
- Rhythm (% subjects in SR, % subjects with recurrent AF) throughout 3 years follow-up.
- Subject's pre-existing or new onset/worsened condition(s), that may be associated with AF progression, will be collected at baseline and at each follow up visit throughout the 3-year study period; parameters include subject's age and gender and the following assessments of non-AF health status: LA size; HATCH Score; blood pressure; NYHA Functional Classification of heart disease; diabetes; lipid profile; renal function and, dementia.[d]

Safety:

- Catheter-related complications (ablation); adverse drug reactions (AAD).

Health Economics (HE) Outcomes:

- Health care utilization (number and length of hospitalizations and unscheduled cardiovascular-related visits).
- Quality of Life (QoL) at 3 months, 6 months, 1 year, 2 years and 3 years by EQ-5D and AFEQT Questionnaire and change from baseline.

  Note: AFEQT Questionnaire will only be used in validated languages and therefore, only distributed to a subgroup of the study population. The AFEQT questionnaire is validated in following languages:

  French, German, Italian, Spanish (Spain), Spanish (US), Polish, Czech, Simplified Chinese (China), Traditional Chinese (Taiwan), Dutch, Korean, Norwegian, Swedish.

[d] Baseline presence of dementia would preclude subject enrolment in this study; however, new onset dementia could occur during the course of the study. If the dementia became sufficiently serious to preclude continued adherence to protocol requirements (Section 9.6), an Investigator may decide to terminate this subject from the study.

10.3 Definition of Effectiveness Success

Subjects will be considered an **effectiveness success** if they do not progress to persistent AF through the 3-year follow-up period.

11.0 Treatment Description

11.1 Ablation Procedure and Medication Management Guidelines

For Test Group Subjects, physicians are to perform procedures (i.e., EP study, ablation, verification of ablation, and post-ablation assessments) per institutional Standards of Care ("SOC", which is defined as the clinical work flow that the physicians follow in their practice, without any mandated protocol requirements) and processes required by their institution. For Control Group Subjects, physicians are to manage medication in accordance with published, current AF Management Guidelines[1-4], the recommended approaches found in Appendix B, and with the SOC and procedures required by their institution.

11.2 Schedule of Examinations

11.2.1 Study Visits and Phone Follow-up

Table 1 displays the required schedule for subject treatments and evaluations for Test and Control Groups. Sites participating in this study have been selected upon their capabilities to successfully carry out those assessments. Subjects will need to return to the hospital for a follow-up clinical visit at 3 months, 6 months, 1 year, 2 years and 3 years. Follow-up by phone will be conducted for all subjects at 9 months, 18 months and 30 months. Arrhythmia monitoring assessments, as described in Table 1, will be discontinued once subjects have progressed to persistent AF/AT.

All subjects will be followed through 3-years. Subjects who reach the primary endpoint (progress to persistent AF/AT) will only have to return for the final visit at 3 years; however, they will be followed for safety through the 3-years study period by their hospital and all adverse events are to be reported by the investigator as per protocol requirements. Subjects in the Test Group who undergo a repeat ablation procedure will continue follow-up according to the schedule of their index (first) ablation procedure. Thus, subject visits will be counted from the time of the index ablation procedure and not from the date of the repeat ablation procedure. Subjects in the Control Group who undergo an ablation procedure (cross-over), will continue follow-up according to their initial schedule.

Table 1. Summary of Subject Assessments:

Assessments	BL D0[8]	M3 D76-104	M6 D166-210	M9 D240-300	Y1 D330-420	M18 D480-600	Y2 D630-809	M30 D810-989	Y3 D990-1170	UNS
Clinic visit	X	X	X		X		X		X	X
Phone follow-up[1]				X		X		X		
Patient Information and Consent	X									
Medical history	X									
HATCH score	X	X	X		X		X		X	X
ECG[2]	X	X	X		X		X		X	X
TTM[3]		X	X	X	X	X	X	X	X	X
TEE[4]	X									
TTE[5]	X				X		X		X	
QoL (EQ-5D, AFEQT)[6]	X	X	X		X		X		X	
Health status[7]	X	X	X		X		X		X	X
Cardiac medication	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
Cardioversion / re-ablation documented		X	X	X	X	X	X	X	X	X

1. Phone follow-up calls include check for AEs, changes in cardiac medication and TTM.
2. To be collected if completed as standard of care.
3. Dispensation of TTM device at Month 3. Additional details/instructions regarding TTM monitoring are provided below.
4. Only for patients randomized to PVI, within 48 hours pre-procedure.
5. TTE to be performed within 30 days pre-treatment. For the Test Group, TTE must be repeated prior to discharge
6. AFEQT questionnaire is only to be completed by a subpopulation due to limited validated translations
7. LA Size, blood pressure, NYHA Functional Classification of heart disease, Diabetes, lipid profile, renal function and dementia.
8. Day 0 Test Group (PVI = Index ablation procedure and Day 0 Control Group (AAD) = Randomization

Transtelephonic monitoring (TTM)

All subjects (test and control) will be provided with a TTM device to enable transmission of scheduled and symptom-triggered ECG recordings per the schedule described in Table 1. Both symptomatic and asymptomatic recordings will be analyzed by a Core Lab. Subjects will be trained by the study site personnel on the use of the TTM device and transmission of the recordings. A study specific Core Lab instruction manual, including procedures to be followed, will be made available.

TTM monitoring (both groups) will be conducted as follows:

- Start TTM monitoring at Day 104
- Daily TTM monitoring if symptoms present (to capture symptomatic episodes).
- Weekly TTM monitoring as from Day 104 until Day 300 (to capture some asymptomatic episodes)
- Monthly TTM monitoring as from Day 300 until last study visit (3 Year) (to capture some asymptomatic episodes).

→ If AF is present, the subject will be contacted to begin daily monitoring for 7 consecutive days.

→ Discontinue TTM monitoring when AF is present for 7 consecutive days or requires termination by cardioversion after 48 hours (primary endpoint reached).

Copies of TTM reports are to be filed in the subject's medical chart.

12-lead Electrocardiogram (ECG) – standard of care
Data from 12-lead ECG recordings will be collected as described in Table 1. Data from unscheduled ECG's between two consecutive follow-up visits will be collected and reported on the appropriate eCRF. Copies of ECG reports should be filed in the subject's medical chart with the participating investigator.

Transthoracic Echocardiography (TTE) – standard of care
Transthoracic echocardiograms must be performed according to requirements in Table 1. TTE is to be performed within 30 days pre-treatment start. For the Test Group, TTE must be repeated before discharge to evaluate volume parameters, valve abnormalities, and exclude presence of pericardial effusion. Copies of TTE reports should be filed in the subject's medical chart with the participating investigator.

Transesophageal Echocardiography (TEE) – standard of care
Transesophageal echocardiography must be performed for the Test Group within a 48-hour period immediately prior to the ablation procedure, to exclude atrial thrombus or other structural contraindications to an ablation procedure. Presence of a thrombus will require postponement of the ablation procedure or may even lead to exclusion of the subject from further study involvement. Copies of TEE reports should be filed in the subject's medical chart with the participating investigator.

Quality of Life questionnaires
The EQ-5D and AFEQT instruments must be completed at specified follow-up visits according to Table 1.

Note: AFEQT Questionnaire will only be used in validated languages and therefore, only distributed to a subgroup of the study population. The AFEQT questionnaire is validated in following languages: French, German, Italian, Spanish (Spain), Spanish (US), Polish, Czech, Simplified Chinese (China), Traditional Chinese (Taiwan), Dutch, Korean, Norwegian, Swedish.

Factors Associated with AF Progression
Subject's pre-existing or new onset/worsened condition(s), that may be associated with disease progression, will be collected at baseline and at specified follow-up visits, according to Table 1. At each follow up visit, subjects will be assessed for recent onset or worsening of a comorbidity. Follow up visit assessments will focus upon increased LA size (per TTE), hypertension, diabetes, hyperlipidemia/dyslipidemia, renal insufficiency or dementia. No additional diagnostic tests will be required per protocol.

Adverse Events (AEs)
Any untoward medical occurrence in a subject whether or not there is a relationship between the AE and the device under investigation and/or the drug therapy administered will be documented and reported to the Sponsor as outlined in Section 12 (Adverse Events) of this protocol.

Cardiac Medication
All cardiac medications will be documented in subject charts and reported on the appropriate eCRF(s). In case an AE is related to intake of medications, details must be provided on the appropriate eCRF(s).

11.2.2 Unscheduled Visits

If a subject returns for a cardiovascular related visit outside of the protocol-defined visit schedule provided in Table 1, the visit will be considered "unscheduled" (UNS). If the

unscheduled visit is for a repeat ablation procedure, the protocol follow-up schedule will be based on the index procedure. For all cardiovascular related unscheduled visits, an unscheduled visit eCRF must be completed and the subject must also return for his/her next scheduled study visit.

11.3 Medication Management

During this study, current AF management guidelines[1-4] and the investigator's Institution Standards of Care (SOC) are to be followed as closely as possible. These include the use of anticoagulants and AADs. AADs are defined as class I or class III, or AV nodal blocking agents such as beta blockers (BB) and calcium channel blockers (CCB). Previously ineffective AADs may be used and new AADs may be started during the study. The choice of rate control versus rhythm control therapy and the specific drugs used will be left to the investigator's discretion.

At the time of study enrolment, if subjects who are randomized to the AAD Group have already been switched from a failed medication to a new AAD, they will continue with the latter drug after enrolment; otherwise, subjects will begin the study with a newly prescribed AAD medication.

A subject in the AAD Group may complain to his/her Investigator about the prescribed medication and request a cross-over to receive ablation. In evaluating this request, the Investigator may uncover evidence that the subject did not take his/her medications as prescribed and/or took concurrent incompatible medications for other chronic diseases. In such a circumstance, a subject should undergo Medication Management[e] and then return to the hospital 3 weeks later for re-evaluation.

11.4 Management of Arrhythmia Recurrence During Follow-up

11.4.1 Arrhythmia Recurrence: Test Group

Each investigator's routine clinical practice is to be followed as closely as possible regarding management of arrhythmia recurrence. If a subject undergoes re-ablation(s) for arrhythmia recurrence, the decision should be made in accordance with current AF management guidelines.[1-4] All re-ablation procedure(s) must be fully documented. If a determination is made that progression to persistent AF/AT has occurred, no further arrhythmia monitoring (TTM, ECG, etc) will be required. After reaching the study endpoint, test subjects do not need to return for interim follow-up visits. These subjects will only have to return for the final visit at 3 year. However, they will be followed through the 3 years for safety by their hospital and all adverse events are to be reported by the investigator as per protocol requirements.

11.4.2 Arrhythmia Recurrence: Control Group

The investigator's routine clinical practice is to be followed as closely as possible regarding management of arrhythmia recurrence. Changes in AAD treatment are allowed if needed; however, changes should be made in accordance with current AF management guidelines.[1-4] If an investigator determines that progression to persistent AF/AT has taken place regardless of AAD regimen no further arrhythmia monitoring (TTM, ECG, etc) will be required. After

[e] *Medication management includes reviewing all medications taken and an attempt to identify drugs with possible incompatibility with AAD medication(s); review and manage drug taking routine: timing - warning about taking drugs too close together or too far apart; warning about drug holidays and dangers; discuss taking with or without food, as prescribed; coach to use robust routines (taking pills same time each day); pill organizers; and/or recruitment of family to assist subject.*

reaching the study endpoint, control subjects do not need to return for interim follow-up visits. These subjects will still be followed for safety until the 3-year follow-up visit has taken place.

If Control Group subjects are to undergo RF ablation (crossover) while not having reached the primary endpoint, they will continue follow-up through 3 years (refer to Appendix B for details regarding crossover management). If crossover subjects experience AF recurrence, the investigator will assess whether a change in AAD(s) treatment is required, if repeat ablation is appropriate, or if progression to persistent AF/AT has occurred. If a determination is made that progression to persistent AF/AT has occurred, no further arrhythmia monitoring (TTM, ECG, etc) will be required. After reaching the study endpoint, crossover subjects do not need to return for interim follow-up visits. These subjects will still be followed for safety until the 3-year follow-up visit has taken place.

11.4.3 Cardioversion for Arrhythmia Recurrence

Unnecessary Cardioversion < 7 days should be discouraged, but within ethical bounds. If the investigator believes the subject's AF symptoms are sufficiently severe to warrant cardioversion, he/she should proceed, regardless of timing. AF symptoms sufficiently severe to warrant cardioversion are angina, shortness of breath and/or systolic blood pressure < 90 mmHg related to AF.

Subjects who undergo a cardioversion within 48 hours of arrhythmia recurrence are not considered as being progressed to persistent AF/AT, and, therefore, will not have reached the primary endpoint. These subjects will continue follow-up according to the protocol visit schedule through 3 years.

Subjects who undergo a cardioversion after 48 hours of arrhythmia recurrence are considered as being progressed to persistent AF/AT and, therefore, will have reached the primary endpoint. These subjects will continue to be followed continuously for safety and will be asked to return for a final assessment at the 3-year follow-up visit but not to participate in interim follow-up visits. All adverse events are to be reported by the investigator as per protocol requirements.

11.4.4 Cardioversion as part of a (re-)ablation procedure

Subjects who undergo a cardioversion solely as part of a (re-)ablation procedure are not considered as being progressed to persistent AF/AT, and, therefore, will not have reached the primary endpoint. These subjects will continue follow-up according to the protocol visit schedule through 3 years.

11.5 Core Laboratory for Evaluation Tests

A core lab shall be used for the objective evaluation of both symptomatic and asymptomatic arrhythmia recordings. The core lab will be instructed to prioritize analysis of asymptomatic recordings in the event that progression to persistent AF/AT has occurred without the subject's awareness. Initial evaluation of TTM recordings will be performed by technical personnel trained in the evaluation of these recordings and will be reviewed by a cardiologist or an experienced EP technician. If asymptomatic AF is present, the subject will be contacted immediately to start daily TTM recordings for 7 consecutive days. AF/AT episodes will be evaluated per the definitions provided in this protocol (refer to Study Definitions).

12.0 Adverse Events

12.1 Definitions / Classifications

12.1.1 Medical Devices

Adverse Event (AE) (ISO 14155)
Any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the medical device.
This includes events related to the device used in the study and events related to procedures involved (any procedure in the clinical investigation plan).
For users or other persons this is restricted to events related to the investigational medical device.

NOTE: Physical findings (including vital signs) observed at follow-up, or pre-existing physical findings that worsen compared to baseline, are adverse events if the investigator determines they are clinically significant.
NOTE: AF recurrence by itself is considered a recurrence of disease (pre-existing condition) and therefore does not meet the definition of an AE, unless it is a worsening compared to the pre-existing condition.

Primary Adverse Event (AE):
A primary AE includes any of the following outcomes that occur within 7 days of an AF ablation procedure :

- Death
- Myocardial infarction (MI)
- Pulmonary vein (PV) stenosis*
- Diaphragmatic paralysis
- Atrio-esophageal fistula*
- Transient Ischemic Attack (TIA)
- Stroke / Cerebrovascular accident (CVA)
- Thromboembolism
- Bleeding (including haematoma) requiring blood transfusion
- Pericarditis
- Cardiac Tamponade
- Pericardial effusion
- Pneumothorax
- Astudy perforation
- Vascular Access Complications
- Pulmonary edema
- Hospitalization (initial and prolonged)†
- Heart block

* Pulmonary vein stenosis and atrio-esophageal fistula that occurs greater than one week (7 days) post-procedure shall be deemed a primary AE.
† Excludes hospitalization solely due to pre-existing arrhythmia recurrence.

Serious Adverse Event (SAE) (ISO 14155)
An adverse event that:
a) led to a death,
b) led to a serious deterioration in health that either:
1) resulted in a life-threatening illness or injury, or
2) resulted in a permanent impairment of a body structure or a body function, or
3) required in-patient hospitalization or prolongation of existing hospitalization, or
4) resulted 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 fetal distress, fetal death or a congenital abnormality or birth defect.

Under this definition, a planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse device and/or procedure effect.

NOTE: An AE would meet the criterion of "hospitalization", if the event necessitates an admission to a health care facility (e.g., overnight stay). Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes.

Adverse Device Effect (ISO 14155)

An adverse device effect (ADE) is an adverse event related to the use of a medical device, including any event resulting from insufficiencies or inadequacies in the Instructions for Use or the deployment, implantation, the installation, the operation, or any malfunction of the medical device. This includes any event that is a result of a use error or intentional misuse.

Serious Adverse Device Effect (ISO 14155)

A serious adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a SAE.

Unanticipated Serious Adverse Device Effect (ISO 14155)

An unanticipated serious adverse device effect (USADE) is any serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of risk analysis report .

Device Deficiency (ISO 14155)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. These include malfunction, misuse or use errors, and inadequate labelling.

12.1.2 Medicines

Adverse Event (AE) (Directive 2001/20/EC and CT-3)

Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom or disease temporarily associated with the use of a medicinal product whether or not considered related to the medicinal product.

Serious Adverse Event (SAE) (Directive 2001/20/EC and CT-3)

Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Adverse (Drug) Reaction (ICH-E2A)

Adverse (drug) reaction (A(D)R) is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

NOTE: All drugs taken per protocol requirements (AAD's), drugs taken according to AF management guidelines (i.e. anticoagulants) are considered for AE recording by the Investigator to Biosense Webster.

12.2 Event categorization:

<table>
<tr><td>Adverse Events (AE)</td><td>Non-related</td><td colspan="2">Device/Procedure related</td><td colspan="2">Drug related</td></tr>
<tr><td>Non-serious</td><td>Adverse Event (AE)</td><td colspan="2">Adverse device Effect (ADE)</td><td colspan="2">Adverse drug reaction (ADR)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)</td><td colspan="2">Serious Adverse Device effect (SADE)</td><td colspan="2">Serious Adverse drug reaction</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td><td>Expected</td><td>Unexpected</td></tr>
<tr><td>Anticipated Serious Adv-erse Device Effect (ASADE)</td><td>Unanticipated Serious Adverse Device Effect (USADE)</td><td>Expected Serious Adverse Drug Reaction</td><td>Suspected Unexpected Serious Adverse Drug Reaction (SUSAR)</td></tr>
</table>

12.3 Causality

Regarding the causality of each device-, procedure-, or drug-related AE, the investigator will assess and evaluate the causal relationship according to the following classifications:

Table 2. Adverse Event Causality Classifications

Caused By	Relation	Definition of Relation
Study Device	Definitely	The device directly caused or contributed to the AE
	Probably	The device likely caused or contributed to the AE
	Possibly	The device may have caused or contributed to the AE
	Not Related	The AE is not associated with the device studied in this protocol
Ablation Procedure	Definitely	The AE is directly associated by timing and/or pathophysiology with the standard electrophysiology or ablation procedure described in this protocol that would not have happened if the procedure had not been performed.
	Probably	The procedure likely caused or contributed to the AE
	Possibly	The AE may be associated by timing and/or pathophysiologic with the standard electrophysiology/ablation procedure described in this protocol
	Not Related	The AE is not associated with the EP/ablation procedure described in this protocol
Drug	Definitely	The drug directly caused or contributed to the AE
	Probably	The drug likely caused or contributed to the AE
	Possibly	The drug may have caused or contributed to the AE
	Not Related	The AE is not associated with the drug(s) used during the study

12.4 Intensity / Severity

Regarding the intensity/severity of each AE, the investigator will assess and evaluate the relationship according to the following definitions:

Table 3. Adverse Event Intensity / Severity Definitions

Mild	Awareness of signs, symptoms, or events that are otherwise easily tolerated that may result in minimal transient impairment of a body function or damage to a body structure, but do not require intervention other than monitoring.
Moderate	Any event that results in moderate transient impairment of a body function or damage to a body structure that causes interference with usual activities, or that warrants possible intervention, such as the administration of medication, to prevent permanent impairment of a body function or damage to a body structure.
Severe	Any event that is incapacitating (an inability to do usual activities) or is life-threatening and results in permanent impairment of a body function or damage to a body structure, or requires intervention, such as major surgery, to prevent permanent impairment of a body function or damage to a body structure.

12.5 Outcome

Regarding the outcome of each AE, the investigator will assess and evaluate the outcome according to the following classifications:

Table 4. Adverse Event Outcome Classifications

Classification	Definition
Resolved without sequelae	Subject fully recovered with no observable residual effects
Resolved with sequelae	Subject recovered with observable residual effects
Improved	Subject's condition improved, but residual effects remain
Unchanged	AE is ongoing
Worsened	Subject's overall condition worsened
Death	Subject died as a result of the AE

12.6 Adverse Event Reporting and Documentation Requirements

12.6.1 Adverse Event Reporting Requirements

Investigator responsibilities:

Reporting by the Investigator to Biosense Webster:

AE information will be collected throughout the study and will be recorded on the eCRFs by the study investigator and/or study coordinator. Each AE must be reported regardless of classification, seriousness, intensity, outcome or causality. All AEs will be monitored until they are adequately resolved or explained. Timing for reporting various AEs is described in Table 5.

Table 5. AE Reporting Requirements and device return

Type of Adverse Event*	Reporting Requirements for new and follow up information
Non-serious non related AE or non serious ADR	Report to Biosense Webster as soon as possible
Non-serious ADE***	Report to Biosense Webster as soon as possible
SAE	Report to Biosense Webster immediately but not later than **24 hours** of awareness
USADE & SADE***	Report to Biosense Webster immediately but not later than **24 hours** of awareness
Subject Death	Report to Biosense Webster immediately but not later than **24 hours** of awareness
Study Device Deficiencies (failure/malfunction) **associated with an AE***	Report **both** study device failure and AE to Biosense Webster immediately but not later than **24 hours** of awareness
Study Device Deficiencies that might have led to a SAE**/***	Report study device failure to Biosense Webster immediately but not later than **24 hours** of awareness
Study Device Deficiencies **not** associated with an AE***	Report study device failure to Biosense Webster immediately but not later than **24 hours** of awareness
Other (concomitant) Device Deficiencies associated or not associated with an AE	Report to Biosense Webster as soon as possible **per regular complaint process**

* Must be reported by eCRF (telephone, e-mail or fax transmission) to Biosense Webster by the study site personnel, whether or not it is deemed related to the study device, procedure, or drug.

** Device deficiencies that could have led to serious adverse device effect if
a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

*** Devices need to be returned per Biosense Webster return procedure.

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

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

Reporting by Investigator to EC/national CA
The Investigator will report events to the EC / EB (or equivalent) as well as to the appropriate authorities (e.g., competent authorities) according to the prevailing regulations per country and/or site.

Biosense Webster responsibilities:

The sponsor shall keep detailed records of all adverse events relating to the study which are reported to him by the investigators.

Expedited reporting
General
Biosense Webster shall report all reportable events occurred throughout the study to relevant participating CA's. ECs / EBs will receive events only occurred in subjects, recruited in their own country, unless more stringent national regulations are applicable.

Device/procedure related events and device deficiencies
In accordance with 21 CFR 812 (Subpart C), 803, ISO 14155, MDD 93/93/42/EC, Meddev 2.12/1,any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might have led to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health, will be considered for reporting by Biosense Webster to the appropriate authorities (e.g., competent authorities) as well as to the ECs / EB (or equivalent) according to the prevailing regulations per country. For countries outside Europe, Biosense Webster adheres to Medical device vigilance requirements per national regulations.

Annual reporting
Biosense Webster shall perform annual safety reporting to the appropriate authorities (e.g., competent authorities), ECs / EBs (or equivalent) as well to Investigators according to the prevailing regulations per country.

12.6.2 Adverse Event Documentation

The investigator is responsible for ensuring that all AEs observed by the investigator or reported by the subject that occur from the time that the subject has signed the informed consent through the end of the study are properly assessed, recorded, and reported as defined and described in the Adverse Events section of this protocol. All AEs must be assessed by the study investigator and properly documented by completing the subject's medical records (source documents) and appropriate eCRF. Additional documentation may be requested by Biosense Webster, including but not limited to, a written subject narrative detailing the clinical course of the AE, a copy of any correspondence with the local EC, and extracts from medical records.

12.6.3 Serious Adverse Event Documentation

Subjects experiencing a SAE must be examined by a physician or qualified health care professional as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. All SAEs will be followed until resolution or until the event stabilizes according to the medical judgment of the investigator.

All efforts shall be put in place, by the investigator, to collect SAE-related documentation (e.g., eCRFs, subject's discharge summary) as soon as possible after initial notification of the event to Biosense Webster. Additional information shall be reported immediately but no later than 24 hours to Biosense Webster. Follow-up reports relative to the subject's subsequent course must be submitted to Biosense Webster or designee until the event has resolved or, in case of permanent impairment, until the condition stabilizes.
Documentation related to the SAE (e.g., additional laboratory tests, consultation reports, post-mortem reports, new information relating to a previously reported SAE, etc) will be provided

by the investigator to Biosense Webster or designee in a timely manner, when requested. If the subject is withdrawn from the study because of the SAE, the information must be included on the appropriate eCRFs.

13.0 Statistical Analysis

13.1 Clinical Study Objective

The objective of this study is to determine whether early RF ablation treatment, using the CARTO® 3, CARTO® XP or CARTO® RMT System and THERMOCOOL® Catheter Family in subjects with PAF, delays progression of AF compared with drug therapy (either rate or rhythm control) using current AF management guidelines.[1-4]

13.2 Primary Endpoint

Time to persistent AF/AT (excluding isthmus-dependent atrial flutter) at 3 years will be used to measure the primary endpoint. Persistent AF/AT is defined as AF lasting longer than 7 consecutive days or requiring termination by cardioversion after 48 hours.

13.3 Overview of Statistical Methodology

Adaptive group sequential survival design is used in this study to examine the primary endpoint. The primary endpoint will be analyzed using the Kaplan-Meier (KM) method and account for censored observations following the intent-to-treat principle. Group sequential method, multiple interim examinations of the primary endpoint using alpha spending functions and conditional power, will be performed at regular time intervals during the course of the trial to determine whether the study will be stopped early for effectiveness or futility. In addition, sample size re-estimation will be used to provide a chance to increase the sample size close to the end of the enrollment if the study is still promising but underpowered due to uncertainties regarding the effect size and cross-over rate.

13.4 Sample Size and Power Calculation

A total sample size of 322 (161:161) subjects will be required to ensure 85% power to detect the effect size measured by negative log of the hazard ratio equal to 1.154[f] (treatment group over control group). This calculation assumes a 50% cross-over rate from the AAD group to the ablation group, a 10% drop-out rate in each group over the 3 year follow-up period, and 1.5 years accrual time. This calculation is based upon one-sided superiority testing with alpha equal to 0.025. Using meta-analysis, the rates of disease progression at the end of follow-up are estimated to be 25% and 5% in the AAD and ablation group, respectively (see the point estimate justification document for details, Appendix C). The sample size calculation is based upon the method developed by Rubinstein, Gail and Santner[66] (RGS,1981) and also incorporates group sequential design with multiple interim looks.

Adaptive Sample Size Re-estimation:
Due to the uncertainties associated with the cross-over rate and the effect size, the sample size will be reestimated 1.5 years after the start of enrollment or at the end of the enrollment

[f] $-log_e\left(\frac{\hat{\lambda}_t}{\hat{\lambda}_c}\right) = -log_e((-\frac{log_e(0.95)}{3})/(-\frac{log_e(0.85)}{3})) = 1.154$

whichever occurs earlier. Conditional power (CP) will be calculated at that time to determine how promising the interim results are. CP is defined as the conditional probability that the final result will exceed a critical value given the data observed thus far, and an assumption about the trend to be observed in the remainder of the study.[67] If the CP is less than 0.3, then the study is considered not promising and the sample size will not be increased. If the CP is greater than 0.9, then the study is deemed fully powered and the sample size will not be increased. If the CP falls in the promising zone (0.3-0.9), the sample size will be reestimated based upon the observed effect size and the CHW (Cui, Hung and Wang). Adaptive Method will be used for statistical testing.[68]

13.5 Randomization

Subject randomization will be 1:1 between catheter ablation and AAD therapy. The randomized block design, stratified by gender and site, will be used to ensure a gender balance by treatment group at each site. Adaptive randomization will also be executed to further ensure the allocation balance of treatment groups by gender at each site. Subjects will be randomized in the order of their enrollment. If a randomization assignment is inadvertently disclosed prior to use, the assignment will never be used.

13.6 Analysis Populations

The study contains two treatment arms with subjects receiving either catheter ablation, with or without AAD therapy; or, AAD therapy alone. The following analysis populations will be used to complete the analyses of data:

Intent to treat subject population (ITT): The ITT subject population will include all subjects randomized, where subjects will be classified by the group to which they are randomized, regardless of the treatment received. For the ITT population, cross-over subjects will be included in the Control Group per randomization. Lost-to-follow-up and withdrawn / early termination subjects will also be included in the ITT population.

Per protocol subject population (PP): The PP subject population will include randomized subjects who satisfy the following criteria, according to the treatment actually received:

- **Test Group:** subjects who
  - have undergone RF ablation,
  - are treated with the study catheter (THERMOCOOL® Catheter Family)
  - are in compliance (no major protocol deviations) with the study protocol, and
  - have been treated for the study-related arrhythmia.
- **Control Group:** subjects who
  - have started an investigator-prescribed AAD and completed the dose-loading period (2 weeks),
  - have not undergone RF ablation,
  - are in compliance (no major protocol deviations) with the study protocol, and
  - have been treated for the study-related arrhythmia.

The analyses conducted in the PP population will be as treated analyses. Subjects who have undergone RF ablation will be included in the Test Group regardless of the original treatment assigned (original randomization). Thus, cross-over subjects will be included in the Test Group for PP analyses.

Safety Population (SP): The SP will include all subjects who have undergone insertion of an ablation catheter, either as Test Group or cross-over subjects; and, subjects who started an

investigator-prescribed AAD in the Control Group and did not initiate ablation therapy. Analysis of catheter-related complications will be limited to include only subjects who initiated ablation treatment (catheter insertion) - Test Group and cross-over subjects. Adverse drug reactions will be analysed overall for all the subjects who have taken investigator-prescribed AAD and analyzed separately for cross-over subjects, those in the Test and Control Groups (excluding cross-over patients).

The primary effectiveness analysis will be conducted in the ITT population. Secondary effectiveness analyses will be performed in the PP population. All safety data analyses will be performed in the SP.

13.7 Subject Disposition and Protocol Deviations

The number of subjects included in each of the study populations (ITT, PP, SP) will be summarized overall, by treatment group as randomized, and by study site. A listing sorted by treatment group and subject will be provided that will include the reasons for exclusion from any of the study populations. The number of subjects enrolled, excluded, discontinued, prematurely withdrawing from the study, lost to follow-up, evaluable, completed and the reasons for classification will be summarized and listed by treatment group for all subjects in the ITT population. Protocol deviations will also be summarized by treatment group and listed.

13.8 Demographic and Baseline Characteristics

Subjects' demographic and baseline characteristics include but are not limited to (1) age; (2) gender; (3) race; (4) ethnicity; (5) medical history conditions; and (6) AF history and will be summarized overall and by treatment group. The descriptive statistics including number of subjects, mean, median, 25th and 75th percentiles, minimum, maximum and standard deviation will be presented for continuous variables. Frequency and percentage will be presented for ordinal and categorical variables. Fisher's exact tests will be used to examine the categorical, demographic, and baseline characteristics between two groups, and Kruskal-Wallis tests will be used for the continuous variables as appropriate.

13.9 Primary Statistical Analyses

13.9.1 Primary Effectiveness Analysis

The primary effectiveness analysis will be a Kaplan-Meier (KM) analysis for all subjects in the ITT population and account for censored observations. The primary effectiveness analysis will be performed in the ITT population where the subjects will be attributed to the treatment group as randomized, regardless of treatment cross-over or post-randomization medical care. A log-rank test will be used to compare the hazard functions between the two groups at any observed event time. The median time to persistent AF/AT as well as the 95% confidence intervals will be reported by treatment group. The survival probability and rate of persistent AF/AT at 3 years follow-up as well as the 95% confidence intervals for both groups will be presented.

The effect size is defined as the negative log of the hazard ratio (hazard rate of the Test Group over hazard rate of the Control Group): $\delta = -log_e(\lambda_t/\lambda_c)$

This study is to test the following hypothesis using a one-sided test at alpha equal to 0.025:

H0: $\delta \leq 0$

H1: $\delta > 0$

Null hypothesis: the hazard rate in the Test Group is greater than or equal to the hazard rate in the Control Group at observed event times during the follow-up period

Alternative hypothesis: the hazard rate in the Test Group is less than the hazard rate in the Control group at observed event times during the follow-up period

At any interim monitoring calendar time l_j, we compute the Z statistic at information fraction t_j using the standardized logrank score statistic:

$$Z(t_j) = \frac{S(l_j)}{\sqrt{V(l_j)}}$$

where $S(l_j)$ is the observed logrank score statistic at calendar time l_j, and $V(l_j)$ is the variance of $S(l_j)$.

The Z test statistic will be compared with the stopping boundaries to determine whether this study will be stopped for effectiveness in each of the interim analyses. If the Z statistic crosses the stopping boundary, that is, Z is greater than the critical value at the interim look, then the study will be stopped for effectiveness. If the sample size exceeds the pre-planned sample size, then the CHW (Down-Weight) adaptive method will be used for statistical testing.[68]

Conditional power will be calculated after the 1st interim look to assist the determination of whether the study will be stopped for futility.

13.9.2 Interim Analyses

An interim examination of the primary endpoint data will be performed at regular time intervals during the course of the trial to determine whether the study will be stopped for effectiveness or futility. The primary objective of this study is to determine whether early RF ablation treatment using the CARTO® 3, CARTO® XP or CARTO® RMT System and THERMOCOOL® Catheter Family in the PAF population delays progression of AF compared with AAD therapy (either rate or rhythm control) using current AF management guidelines.[1-4] In addition, interim reporting will also involve a review of subject recruitment, compliance with the study protocol, status of data collection, safety endpoints and other factors that may affect the overall progress and integrity of the study. The results of the interim analyses and status reports will be reviewed by the Data Safety Monitoring Committee (DSMC).

The DSMC will review the accumulated data at 1 year following the study start[g] and then approximately every 6 months thereafter. Prior to each review, Biosense Webster will conduct statistical analyses and prepare an interim summary report. The progress of subject enrollment, the rates of compliance with therapy, the frequency of protocol violations and rates of safety endpoints will be reviewed. The number (status) of eCRFs completed, the number of outstanding data queries, the number of data queries completed, and the number of eCRFs reviewed through on-site monitoring will also be reviewed. Extracted data files and analysis programs for each interim report will be archived in the study files.

[g] Time-interval related statistical deliverables are subject to change depending on the evolution of the study (e.g. delay in start-up, enrolment delay, …).

Interim effectiveness reports introduce well-recognized statistical problems related to the multiplicity of statistical tests performed on an accumulating set of data. To properly account for the repeated interim testing in this study, a group sequential method similar to that proposed by O'Brien and Fleming as a guide in interpreting interim analyses will be used.[69] This procedure requires large critical values early in the study, but relaxes (i.e., decreases) the critical value as the trial progresses. Because of the conservatism early in the trial, the critical value at the final analysis is near the "nominal" critical value. Hence the sample size requirements with this group sequential procedure remain essentially the same as the conventional fixed sample size estimate. The actual method for the interim reporting that will be employed in this study is the "alpha-spending function" approach to group sequential testing developed by Lan and DeMets.[70] The Lan-DeMets approach is flexible to accommodate unequal sized groups with the number of interim looks unspecified in advance. It only requires specification of the rate at which the Type I error (which in this trial will be α=0.025 for the primary endpoint) will be "spent". This procedure allows "spending" a portion of α at each interim analysis in such a way that at the end of the study, the total Type I error does not exceed 0.025. This spending function generates boundaries that are nearly identical to the O'Brien-Fleming boundaries.

In survival trials, information time is calculated based upon number of events rather than number of subjects accrued. In practice, interim analyses are often scheduled based upon specified calendar time rather than number of events. To address the logistical inconvenience, Lan and DeMets extended their general group sequential approach for the maximum duration trial.[71] That is, the conduct of a trial is expected to occur within some period of time [0, Tc], where Tc is the maximum calendar (or duration) time for completion. The stopping boundaries can be adjusted based on the actual number of events observed at the interim look, rather than information fraction. This method allows flexibility in the monitoring process for accommodating any changes in terms of timing and spacing of the looks or additional examination of the data that is not pre-determined in response to the concerns from the DSMC that may arise during the course of the trial.

The analytic approach that will be used for the interim analyses for assessing treatment differences will be the time-to-event analysis method. The standardized logrank score statistic will be compared with the stopping boundaries at each interim look to draw statistical inference. If the stopping boundary is crossed, then the study will stop for effectiveness.

Judgment concerning the continuation or termination of the study will involve not only the degree of statistical significance observed at the interim analysis, but also the likelihood of achieving significance should enrollment continue to the originally projected sample size. As an aid in this latter assessment, the group sequential analyses outlined above will be supplemented with calculations of conditional power. After approximately 25% of the total number of events have occurred (1st interim look), conditional power (CP) for the primary treatment comparison will be computed and provided to the DSMC as a regular part of the interim study reports. If the CP is less than 0.2, then the study will be stopped for futility.

For example, the anticipated start time for this study is December, 2012 and the expected end of subject enrollment in June, 2014. With 3 years follow-up time, the study is expected to be completed in June, 2017. Interim looks are planned for December 2013, June 2014, December 2014, June 2015, December 2015, June 2016, and December 2016, with a final look in June 2017. The stopping boundaries for effectiveness for these scheduled looks are displayed in Table 6. If the study start time or calendar time for interim looks changes, the operating characteristics will be recalculated based upon actual calendar time of the interim looks and the number of events observed at each look.

Table 6. Operating Characteristics for Group Sequential Design*

Look #	Calendar Time	Information Fraction	Number of Events	Bounds	Incremental Alpha	Cumulative Alpha
1	Dec. 2013	0.22	5	4.6374	0.00000	0.00000
2	June 2014	0.33	9	3.7332	0.00009	0.00010
3	Dec. 2014	0.44	11	3.1913	0.00063	0.00073
4	June 2015	0.56	15	2.8277	0.00192	0.00265
5	Dec. 2015	0.67	20	2.5881	0.00341	0.00606
6	June 2016	0.78	22	2.3477	0.00499	0.01105
7	Dec. 2016	0.89	26	2.2183	0.00639	0.01744
8	June 2017	1	28	2.0507	0.00756	0.02500

* Note: Time-interval related statistical deliverables are subject to change depending on the evolution of the study (e.g. delay in start-up, enrolment delay, …).

13.10 Handling of Missing Data

The primary effectiveness endpoint (time to disease progression) will be conducted in the ITT population. Subjects with missing data will be included in this primary analysis. The following analyses will be used to test the robustness of the analyses results with regards to missing data:

1) Missing data will be censored at their last observation.
2) Missing data will be imputed using multiple imputation. This approach will enable an analysis to be conducted based on the full ITT population. The details of this approach will be provided in the statistical analysis plan.

13.11 Secondary Statistical Analyses of Primary Effectiveness Endpoint

13.11.1 Per-Protocol Analysis

This analysis will be performed in the PP subject population. Propensity score weighting methodology will be applied to adjust for the imbalance of subjects' characteristics between these two groups. Cross-over subjects will be added to the ablation group and the time-dependent covariate will be used to account for the different timing of cross-over. A propensity score weighted Cox proportional hazards model will be used to compare the hazard rate between the two groups at observed death times. Diagnosis analyses will be performed to examine the assumption of proportional hazards. If the proportional harzards assumption is not met, then the interaction effect of time by treatment group and other remedy analyses will be investigated. The adjusted hazard ratio and its 95% confidence intervals will be reported for the two groups. Missing primary effectiveness endpoint data and the associated covariates that will be included in the propensity score modeling will be imputed using the multiple imputation method.

13.11.2 Subgroup Analyses

The primary effectiveness analysis (KM analysis of time to persistent AF/AT) will be performed for the Test Group as randomized and for the Control Group as randomized (excluding cross-over subjects). The cross-over subjects (i.e., continued on their current

AAD or taking a newly prescribed AAD and had an RF ablation procedure) will be analyzed separately as a third group.

- Test Group: randomized to RF ablation to achieve PVI using the CARTO® 3, CARTO® XP or CARTO® RMT System, and THERMOCOOL® Catheter Family
- Control Group: randomized to AAD therapy in accordance with current AF management guidelines[1-4]
- Cross-over Group: Control Group subjects who undergo RF ablation to achieve PVI using the CARTO® 3, CARTO® XP or CARTO® System, and THERMOCOOL® Catheter Family

The median time to persistent AF/AT as well as the 95% confidence intervals will be reported for the three groups. The survival probability and rate of persistent AF/AT at 3 years follow-up as well as the 95% confidence intervals for these three groups will be presented separately.

13.12 Secondary Effectiveness Endpoints Analyses

13.12.1 Rate and Time to Persistent AF/AT at 1 year, 2 and 3 years follow-up by number of ablations

For the secondary effectiveness endpoint, the rate and time to persistent AF/AT (excluding isthmus dependent atrial flutter) at 1 year and 2 years and the rate of persistent AF/AT at 3 years by number of ablations, a KM analysis will be performed to examine the hazard function of persistent AF/AT (excluding isthmus dependent atrial flutter) for the two treatment groups at 1 year follow-up time and 2 year follow-up and 3 year follow-up in the Test Group by the number of ablations. Data will be censored at 1 year and 2 year follow-up in two separate analyses. The analysis will be performed in both the ITT and PP populations. A log-rank test will be used to compare the hazard functions between the two groups at any observed event time. The median time to persistent AF/AT at 1 year and 2 year follow-up as well as the 95% confidence intervals will be reported by the two groups. The survival probability and rate of persistent AF/AT at 1 year and 2 years follow-up as well as the 95% confidence intervals for the two groups will be presented.

The median time to persistent AF/AT at 3 years follow-up as well as the 95% confidence intervals will be reported for the Test Group by the number of ablations. The survival probability and rate of persistent AF/AT at 3 years follow-up as well as the 95% confidence intervals for the Test Group will also be presented by the number of ablations. The KM curves will be plotted and results will be listed as well.

13.12.2 Number of Repeat Ablations and New AAD Drugs

To analyze this secondary effectiveness endpoint, number of repeat ablations and new AAD drugs per subject throughout 3 years follow-up and the number of repeat ablations will be summarized and listed for the subjects who have undergone at least one ablation. In addition, new AAD use will be summarized and listed for the subjects in the two groups by drug category and specific drug. The analyses will be performed in both ITT and PP populations.

13.12.3 Rhythm Throughout 3 Years Follow-up

To analyze this secondary effectiveness endpoint, rhythm (% subjects in sinus rhythm, % subjects with recurrent AF) throughout 3 years follow-up, the number of subjects and percentage of subjects with sinus rhythm and the number of subjects and percentage of subjects with recurrent AF/AT during the 3 year follow-up time will be summarized and listed by the two groups. The analyses will be performed in both ITT and PP populations.

13.12.4 Factors Associated with AF Disease Progression

To analyze this secondary endpoint, conditions that may be associated with disease progression will be assessed at baseline and throughout the 3-year follow-up period. These targeted parameters include: LA size at baseline and subsequent increase above baseline size; age ≥ 60 years; HATCH score at baseline and subsequent increase above baseline score; hypertension; NYHA Functional Classification of heart disease; diabetes; hyperlipidemia/dyslipidemia; renal insufficiency; and, dementia. A Cox proportional hazards model will be performed to examine the associations of time with disease progression. To document pre-existing diseases, measurable baseline parameters will include age, gender, LA size, AF duration, NYHA Functional Classification of heart disease, HATCH score, blood pressure, lipid profile, renal function and the presence of diabetes and/or dementia. The Cox proportional hazards model will also be used to examine time-varying covariates, based upon each follow-up visit and either as a new onset disorder or a worsened diagnosis since a previous assessment. These analyses will include all follow-up assessments throughout the 3-year study period and measurable parameters will include: LA size; HATCH Score; blood pressure; NYHA Functional Classification of heart disease; diabetes; lipid profile; renal function and, dementia. All analyses will control for treatment assignment. Any significant interactions between treatment effect(s) and covariates will also be examined.

Univariate analysis will be performed to screen for significant factors associated with disease progression at p-value <0.2. Then multivariate analyses will be performed to identify any factors associated with disease progression at p-value <0.05. Model selection methods (e.g., Akaike Information Criteria [AIC], stepwise) will be applied to identify the best set of factors linked to disease progression. The identification of relevant associations provides additional characterization and interpretation of the primary effectiveness outcome. These analyses will be performed in both the ITT and PP populations.

Descriptive statistics will be used to summarize the baseline and follow-up values of LA size, HATCH score, blood pressure, NYHA Functional Classification of heart disease, diabetes, lipid profile, renal function, and dementia by treatment groups. Change-from-baseline will also be summarized and listed. Paired-sample test will be used to test whether the change from baseline values differs from zero (e.g., paired t-test, McNeman's test) within each treatment group. A two-sample comparison of the two groups with respect to changes in these characteristics will be performed using general linear models, including the baseline value as a covariate and assessing treatment group differences.

13.13 Secondary Safety Endpoints Analysis

A key secondary safety endpoint, catheter-related complications (AEs), is limited to subjects who have initiated RF ablation and who are in the safety population. The number and percentage of catheter-related AEs will be summarized and listed overall by Test Group and cross-over patients in the SP and by number of repeat ablations. The number and percentage of catheter-related complications will also be summarized and listed by AE category, causality, anticipated or not, severity and outcome.

Serious catheter-related AEs will be reported by 2 timeframes: acute phase AEs, ablation to ≤ 7 days; and, sub-chronic AEs occurring >7 to 30 days post ablation. Serious AEs will be evaluated by causality and severity, using descriptive statistics.

The number and percentage of adverse drug reactions will be summarized and listed overall, according to Test Group; cross-over; and, Control Group excluding cross-over patients. The number and percentage of adverse drug reactions will also be summarized and listed by drug category and AE category, causality, anticipated or not, severity and outcome.

13.14 Secondary Health Economic Endpoint Analyses

13.14.1 Health Care Utilization

For this secondary health economic endpoint, health care utilization (number and length of hospitalizations and unscheduled cardiovascular-related visits), the total number and length of hospitalizations and unscheduled cardiovascular-related visits will be summarized and listed by treatment groups in the PP population.

13.14.2 Quality of Life

Quality of Life (QoL) status will be compared to baseline at 3 months, 6 months, 1 year, 2 years and 3 years. QoL will be measured by the EQ-5D and AFEQT questionnaires. Descriptive statistics for the baseline and changes-from-baseline measurements of the summary scores of these two measurement scales at follow-up visits will be summarized and listed by treatment groups. The analyses will be performed in the PP population. Paired-sample test will be used to test whether the change-from-baseline values differs from zero (e.g., paired t-test) within each treatment group. A two-sample comparison of the two groups with respect to changes-from-baseline in QoL will be performed using general linear models, including the baseline value as a covariate and assessing treatment group differences.

13.15 Site Heterogeneity

A Breslow-Day test for homogeneity of odds ratios measuring treatment effect on disease progression across site will be conducted at the significance level of 0.15. Sites with less than five subjects will be combined to one mega-site by geographical locations. If the results of the test show evidence of a lack of heterogeneity then the following sensitivity analyses will be performed:

1) The primary effectiveness analysis in the ITT population will be performed using the Cox proportional hazard adjusting for significant site effects.

2) The analysis for the secondary effectiveness endpoint ((factors associated with disease progression at baseline and throughout the 3 years follow-up) will include significant site effects.

3) In the subgroup analysis of the primary effectiveness endpoint (KM analysis of time to persistent AF/AT), the KM analysis will also be performed by site performance (high performing sites versus low performing sites).

13.16 Summary of Secondary Endpoints

Secondary Endpoints – Effectiveness

Effectiveness endpoint 1: Rate and time to persistent AF/AT at 1 year and 2 years, rate of persistent AF/AT at 3 years by number of ablations at 3 years.
Analysis Population: ITT and PP
Analysis Method: KM curve

Effectiveness endpoint 2: Number of repeat ablations and new AAD drugs per subject throughout 3 years follow-up.
Analysis Population: ITT and PP
Analysis Method: Descriptive statistics

Effectiveness endpoint 3: Rhythm (% subjects in sinus rhythm, % subjects with recurrent AF) throughout 3 years follow-up.
Analysis Population: ITT and PP
Analysis Method: Descriptive statistics

Effectiveness endpoint 4: Subject age (≥ 60 years); gender; and comorbidities possibly associated with disease progression, at baseline and throughout the 3-year follow-up period: abnormally large LA; HATCH Score ≥ 1; hypertension; Class 1 – 4 inclusive of NYHA Functional Classification of heart disease; hyperlipidemia/dyslipidemia; diabetes; renal insufficiency; and, dementia.
Analysis Population: ITT and PP
Analysis Method: Univariate and multivariate Cox proportional hazards model

Secondary Endpoints – Safety

Safety endpoint 1: Catheter-related complications (ablation), side effects (AAD).
Analysis Population: Safety Population
Analysis Method: Descriptive Statistics

Secondary Endpoints – Health Economics (HE)

HE endpoint 1: Health care utilization (number and length of hospitalizations and unscheduled cardiovascular-related visits).
Analysis Population: PP population
Analysis Method: Descriptive Statistics

HE endpoint 2: Quality of Life at 3 months, 6 months, 1 year, 2 years and 3 years by EQ-5D and AFEQT Questionnaire and change from baseline.
Analysis Population: PP population
Analysis Method: Descriptive Statistics

14.0 Administrative Responsibilities

14.1 Ethics Committee (EC) / Ethics Board (EB) Information

The protocol and amendments, informed consent form and other applicable study-related documents must be submitted to the appropriate EC and written approval must be obtained and submitted to the Sponsor prior to enrolling any subjects.

Before initiating this study, the Sponsor will work with the investigator to obtain approval from the EC / EB and fulfill any local, applicable requirements for notification to or to obtain approval from competent authorities if necessary. The investigator will obtain written and dated approval from the responsible EC / EB for the study protocol (or amendment[s]) and informed consent before enrollment of subjects. Biosense Webster and the EC / EB must approve in writing any changes to the protocol that affect the rights safety and/or welfare of the subjects, or may adversely affect the validity of the study.

A signed copy of the EC / EB Approval Form and a signed copy of the EC / EB approval letter addressed to the investigator must be submitted to Biosense Webster certifying study approval prior to subject enrollment. Investigators are responsible for submitting and obtaining initial and continuing review (per local regulations) of the study by their EC / EB.

14.2 Informed Consent

The investigator will obtain written and dated approval from the responsible EC / EB for the study ICF. A patient's informed consent must be obtained and documented per institutional, EC / EB, and applicable regulatory requirements.

Prior to obtaining informed consent, information should be given in a language and at a level of complexity understandable to the patient in both oral and written form by the investigator or designee. Patients should not be coerced, persuaded, or unduly influenced to participate or continue to participate in the study. Patients or their legal representative must be given ample time and opportunity to inquire about details of the study and all questions about the study should be answered to the satisfaction of the patient or their representative.

Prior to participation in the study, the investigator or designated member of the research team will obtain written informed consent from the patient. The background of the proposed study and the potential benefits and risks of the study should be explained to the patient. The patient or legal representative must sign the ICF (see Appendix E) prior to any study-specific exams or tests are provided to them that fall outside of the standard of care. The study's ICF should be signed and personally dated by the patient, or his/her legal representative, and by the person who conducted the informed consent discussion (investigator or designee). If the patient or his/her legal representative is unable to read the study's ICF, a witness should be present during the entire informed consent discussion. After the study's ICF is read to the patient and signed by the patient or his/her legal representative, the witness should also sign it, attesting that informed consent was freely given by the patient or his/her legal representative.

The patient or his/her legal representative must receive a copy of the signed and dated ICF. A copy of the EC/EB -approved ICF for this study must be maintained by each investigator in a designated study administrative file.

14.3 Subject Confidentiality

All information and data sent to Biosense Webster concerning subjects or their participation in this study will be considered confidential. During this study, all representatives of the Sponsor will comply with all in-country privacy laws and regulations regarding contact with subjects, their medical record information, copying of information, and protection of the subject identities. Information and data collected and used in the analysis and reporting of this evaluation will be without identifiable reference to the subject. No information that can be used to identify subjects will be collected. Only authorized Biosense Webster personnel or an appropriately qualified and trained designee, local government authorities or federal agencies (e.g., the U.S. FDA) acting in their official capacities will have access to these confidential files.

14.4 Monitoring the Study

Monitoring will be conducted throughout the course of this study according to the Monitoring Plan.

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

- the rights and well being of the subjects are protected;
- the study is conducted according to Good Clinical Practices (GCP) and FDA 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 randomization procedures are being followed, completion of appropriate source document verification, and identification of and action taken to resolve any issues or problems with the study.

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

14.5 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.

14.6 Management of Protocol Deviations

The investigator may not deviate from the protocol without prior notification and approval from Biosense Webster, Inc. In medical emergencies, prior approval for protocol deviations will not be required, but Biosense Webster clinical operations personnel must be notified within 5 days of the deviation. All protocol deviations will be documented and followed up according to the applicable Standard Operating Procedures (SOPs). All protocol deviations will be monitored closely by the Sponsor or designee(s). Any evident pattern of non-compliance with respect to applicable standards will be cause for the site to be put on probation. If corrective actions are not subsequently undertaken, the site will be asked to withdraw.

14.7 Data Management

Steps taken to assure the accuracy and reliability of data include the selection of qualified investigators and appropriate centers, review of the protocol with the investigator and associated personnel prior to the study start and periodic monitoring visits by Biosense Webster or an appropriately qualified and trained designee.

14.7.1 Data Collection

Electronic Case Report Forms (eCRFs) have been developed to capture the information outlined in this protocol. Data from these eCRFs will be used for the analysis of study outcomes. If modification of study eCRFs is required during the course of this study, Biosense Webster will inform all sites and provide updated information and materials needed for continued study conduct.

14.7.2 Data Reporting

The investigator, or a designated individual, is responsible for recording all data from the study on the eCRFs using source-documents, such as hospital charts. 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.

After completion of study visits, eCRFs should be thoroughly completed without unjustified delay. For AE reporting requirements, refer to the AE Section of this study protocol.

14.7.3 Source Documentation

Data entered on to the eCRFs will be taken from source documentation, such as hospital procedure reports, admission and discharge summaries, and other hospital or investigator office/clinic documents. If no standard hospital or office document exists to capture information that may be unique to this study, a worksheet may be developed to record this information, which shall be signed by the PI at the given site and serve as the source document for unique study data. These worksheet source documents will serve as the basis for monitoring the eCRFs. Electronic subject records will be considered as source documents on the condition that the hospital's database is a validated system. If this is not the case, electronic records must be printed and added to the subject's paper file. A print-out of an eCRF cannot be used as source documentation. It is the obligation of each investigator (or designee) to assure that the medical files and all other possible files, e.g. nursing files, are appropriately completed. The subject's file of each enrolled subject should clearly reflect the status of the subject. The subject's file also should clearly show that this subject is a study participant by entering the following details: study Sponsor (Biosense Webster), protocol number, clinical site, subject number assigned, date of enrolment and a statement that consent was obtained prior to any study specific procedure. The use of a label is allowed to cover this information.
Each follow-up visit needs to be reported in source documents and should at least contain: all AEs, concomitant medication, information on study-related activities per follow-up visit and general status of the subject.

14.7.4 Data Verification and Review

All eCRFs will undergo automated and manual initial inspection for omitted data, gross data inconsistencies, and timeliness of reporting. Periodic analysis of each data field (across cases) will be performed in order to examine the expected distributions of data, and to identify outliers for possible data entry errors.

14.7.5 Final Data Analyses

All exported datasets for analyses will undergo a final data verification procedure. Once all critical data are monitored and the database is locked, the analysis of study data will be performed.

14.7.6 Confidentiality and Protection of Study Files

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

14.8 Publication Policy

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

15.0 Study Management

15.1 Investigator Selection

In order to mitigate the effect of the learning curve, sites experienced with using the CARTO® 3, CARTO® XP or CARTO® RMT System and THERMOCOOL® family of catheters will be selected for the study. Sites will be reflective of real world practice in terms of volume and experience in using these technologies.

Therefore site selection criteria may include but are not limited to:

- At least 100 RF ablation procedures for the treatment of AF performed with the CARTO® XP System, CARTO® RMT or other 3D mapping techniques
- At least 25 RF ablation procedures for the treatment of AF performed with the CARTO® 3 System, CARTO® XP or CARTO® RMT System, and THERMOCOOL® family of catheters
- AF ablation volume will be at least 75 AF ablation procedures performed in 2011 or 2012
- Availability of a study coordinator/fellow to support the logistics of the study
- No other study ongoing at the site that would compete for the same patient population, unless the number of AF ablation procedures justifies conduct of 2 concurrent AF studies and commitment to enrollment targets can be made

15.2 Investigator Training

Training of appropriate clinical site personnel will be the responsibility of the Sponsor. To ensure uniform data collection and protocol compliance, Sponsor personnel will present a formal educational session to the study site personnel including but not limited to reviewing the applicable Good Clinical Practice (GCP) guidelines, the protocol, the eCRF and data collection process, randomization process, and the adverse event and complaint reporting processes.

15.3 Investigator Responsibilities

- Obtain EC/ EB approval, if applicable
- Supply the Sponsor with a current curriculum vitae and that of any colleagues 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, Biosense Webster, Inc.'s Complaints Management Department, the EC / EB) in a timely manner regarding the occurrence of any AEs and/or product malfunctions.

15.4 Sponsor Responsibilities

- Selection of the study investigators
- Selection of appropriately qualified and trained individuals, including monitors, to conduct the study
- Selection of members for the Clinical Endpoint Committee (CEC) and Data Safety Monitoring Committee (DSMC).
- Development and, if applicable, modifications of protocol and eCRFs
- Obtain study contracts with investigators/hospitals, CROs and other involved 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 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

15.5 Clinical Endpoint Committee (CEC)

The Sponsor may consider to assign a Clinical Endpoint Committee (CEC) to adjudicate the primary event outcome.

15.6 Data Safety Monitoring Committee (DSMC)

An independent DSMC, consisting of 3 physicians, at least one of which must be expert in electrophysiology, will meet according to a defined schedule to review interim analyses of both safety and effectiveness parameters, and for purposes of advising the study sponsor as to whether the study should continue or be suspended/terminated. Telephone conferences may be initiated outside the defined schedule to discuss serious study issues that may have arisen.

16.0 Regulatory / Ethical Considerations

16.1 Basic Principles and Standards

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

- ISO 14155: 2011(E) (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice)

- Declaration of Helsinki
- ICH E6 Good Clinical Practice
- Medical Device Directive 93/42/EC
- MEDDEV 2.12-1 Guidelines on a Medical Devices Vigilance System
- Directive 2001/20/EC and CT-3
- Vaughan Williams Classification of Anti-arrhythmic drugs
- ICH-E2A
- www.medicins.org.uk

16.2 Record Retention and Archiving

Each site will be asked to maintain study records as instructed by local requirements. The Sponsor will maintain study records according to the applicable Biosense Webster procedure.

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Appendices

Appendix A: Description and Analysis of Risks

The incremental risk associated with use of a saline-irrigated electrode catheter rather than a standard electrode catheter is small. The larger RF lesion size produced with this catheter may increase pain (during the procedure) associated with RF applications and may increase the risk of cardiac rupture. Increased pain, however, can be managed with intravenous analgesics. Additionally, use of the cooled electrode tip catheter may reduce procedural time, fluoroscopy time and increase procedural success by increasing lesion depth and by minimizing coagulum formation, which necessitates repeated removal and re-deployment of the ablation catheter. While the ability to cool the electrode-tissue interface allows the use of higher power than with a conventional 4mm electrode, RF power in the range of 30-40 watts is often adequate. For any given power setting, the power delivered to the tissue is similar to that used with a 4mm electrode.

Radiofrequency current may cause occlusion of a coronary artery, either by direct thermal damage, spasm, or thrombosis. Experience at numerous centers suggests that the risk of coronary occlusion is less than 0.5%.[47, 48] Coronary artery occlusion could produce myocardial infarction (MI), angina or death. Should occlusion of a coronary artery occur for any reason, the investigator will attempt to restore coronary blood flow through pharmacological, catheter and/or surgical intervention, as medically indicated.

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

A thrombus may form on the ablation electrode during the application of radiofrequency current without any change in impedance. The thrombus might become dislodged and embolize to produce a stroke, MI, or other ischemic injury. The risk of an embolus is reduced by quickly terminating the application of current after an impedance rise, which limits the size of the coagulum on the electrode. Probably the most important aspect of the THERMOCOOL® family of catheters is the near absence or very low likelihood of thrombus formation during RF.

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

Cardiac perforation may result from catheter manipulation or application of radiofrequency current (risk is <1%).[47, 48] This may result in cardiac tamponade and may require percutaneous pericardial drainage or surgical repair. Significant hemodynamic compromise can result in neurologic injury or death. An increased risk of cardiac perforation may be associated with the use of a saline-irrigated electrode catheter due to its ability to create a larger, deeper RF lesion. This risk is greatest in a thin walled chamber (i.e., RA, LA, or RV); however, the risk of perforation related to a deep steam pop is reduced if RF energy is not delivered perpendicular to the wall at power above 35 or 40 watts. If the lesion is deeper, the risk of steam pop is higher above 35-40 watts.

Injury to a cardiac valve may result from catheter manipulation or the application of radiofrequency current (risk <1%).[47, 48, 49] This may produce valvular insufficiency and possibly necessitate valve replacement surgery.

The application of RF current along the posterior left atrium can result in thermal injury to the esophagus and the formation of an atrio-esophageal fistula. This is a very rare (0.04%) but severe complication of RF ablation that may require surgical intervention or result in permanent impairment.[49] Reducing power at sites in close proximity to and/or avoiding sites directly over the esophagus may reduce the risk of thermal injury.

Injury to the phrenic nerve may occur as a result of RF application in the region of the right pulmonary veins. The reported incidence of phrenic nerve injury varies from 0% to 0.48% when RF energy is used for catheter ablation. Prior to ablation in the region of the RSPV, investigators are encouraged to perform precautionary measures, such as evaluation of proximity to the phrenic nerve and pacing maneuvers.

Radiation exposure during fluoroscopic imaging of catheters may result in an increase in the lifetime risk of developing a fatal malignancy (0.1%) or a genetic defect in offspring (0.002%).[50-52]

The risk of pulmonary AEs (e.g., pulmonary vein stenosis, thrombus and hypertension), associated with an AF ablation procedure targeting the pulmonary veins, is considered small (<4%).[49, 53-59]

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

- Allergic reaction to the local anesthetic, sedatives, x-ray dye, heparin, protamine, or other agents administered during the procedure (risk <1%).[60-64]
- 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%).[47, 48] This may produce hemorrhage, hematoma or ischemic injury to an extremity or major organ.
- Hemorrhage as a result of anticoagulation (risk <0.5%), which may require transfusion.[47, 48]
- Infection, either at the catheter insertion site or systemically, including endocarditis and septic emboli (risk <0.5%).[47, 48, 49] This risk can be minimized by using standard aseptic technique and by the use of antibiotic agents when indicated.

Minimization of Risks:

The criteria for subject selection, methods, personnel, facilities, and training that have been specified for this study are intended to minimize the risk to subjects undergoing this procedure. Subjects will be screened carefully prior to enrollment in the study to confirm compliance with the study inclusion and exclusion criteria.

Participating investigators will be experienced and skilled in performing electrophysiology studies, intracardiac mapping, and ablation of AF with the use of the RF ablation catheters. Procedures will be performed in electrophysiology laboratories, with the assistance of skilled nurses and technicians. The laboratory will contain sufficient resuscitative equipment and facilities to manage any potential complication. Cardiac surgical facilities, as well as a qualified cardiovascular surgeon, will be available during the ablation procedure in the event that surgical intervention becomes necessary.

Ablation procedures with the THERMOCOOL® family of catheters will be performed according to the product Instructions for Use, including but not limited to instructions regarding indications and contraindications for using these devices.

Precautions:

Invasive electrophysiological evaluation and catheter ablation may impart some degree of risk to the patient. The risk of serious complications is generally related to the severity of cardiac disease. The degree of risk of the electrophysiological and catheter ablation procedures and the potential benefit of the treatment of symptomatic PAF should be determined by a qualified physician. Failure to observe all contraindications, warnings, and precautions, as listed in the Instructions for Use may result in procedural complications. Procedural complications include: cardiovascular injury or perforation with or without cardiac tamponade, pulmonary embolus, tricuspid regurgitation, MI, bleeding at the catheter insertion site, sepsis, and death.

Potential Benefit:

The direct benefit for patients undergoing radiofrequency catheter ablation is the potential elimination of AF episodes. It is furthermore expected that quality of life will improve and less frequent hospitalization will be required. The information gathered during the conduct of this study may be of benefit in the future for the treatment of patients with atrial fibrillation.

Appendix B: Guidelines and Restrictions for the ATTEST Protocol Regarding Cross-over from the Drug (Control) Group

1. Guidelines and principles for cross-over are to be followed by the investigator as laid down in this document and in the protocol.

2. It is the intent of the Sponsor and organizers of this study that cross-over be significantly reduced from published rates quoted in previous drug versus ablation trials.

3. The crossing over from the drug group undermines the tenets of equipoise that are intended in: (a) the study's collective inclusion/exclusion criteria for all subjects; (b) the eligibility of all subjects at study onset to be randomized to either treatment group; and, (c) the intended balance of AF severity, drug history, concurrent illnesses (HATCH score severity), demographics, and other characteristics, such that legitimate statements might be made in comparing the outcomes of medical management versus ablation therapy. The nature and conditions for cross-over from the Control (AAD therapy) Group to the Test (PVI) Group, in a randomized controlled study, are not well understood and are multi-factorial. Thus, any assumptions that subjects crossing over reflect the general demographics, disease severity, and extent of disease progression within either study group at randomization cannot be held with certainty.

4. One could justifiably argue that those most likely to suffer severe side effect reactions from AAD therapy might be those who take their drugs sporadically, take drugs sometimes too close together (shortened inter-dose time interval), suffer rebound effects from resumption of drugs after a drug holiday, and who do not heed the warnings of physicians/pharmacists about mixing drugs for AF/AT with those for other chronic diseases. One might further argue that those with heightened disease progression, as noted in published literature, would be among the oldest in their randomized study group and that their baseline HATCH scores are likely to be high as well, which is consistent with elderly patients. If one or more of these assumptions are true, those most likely to seek cross-over from the drug group would be among the aforementioned, resulting in a relatively younger, healthier, and more compliant group of subjects remaining in the drug group over the whole 3 year study period. In this context, extensive cross-over certainly would erode equipoise.

5. The recognized reasons for patients not doing well on drug therapy are as follows:

    a. Patients failing to take the medication as prescribed – called "non-adherence":
        i. Missed days (drug holidays) – recurring <u>disease symptoms or sudden drug-related side effects, if drug rebound effect, after resuming medication.</u>
        ii. Irregular timing, resulting in low concentrations of active drug at some points or too high concentrations of active drug when medication is taken at close intervals (may manifest as side effect problem).
        iii. Medication dropout – patient takes no drug but does not share this information with his/her physician – unexpected <u>disease progression.</u>
    b. Patient cannot tolerate medication, even if compliant with prescribed regimen (side effects):
        i. Sensitivity to the prescribed AAD.
        ii. Concurrent prescribed medications for other chronic diseases are contraindicated for the particular AAD prescribed.

6. When a subject complains to his/her Investigator about the medication and requests a cross-over to receive ablation, the Investigator will have little idea of the root cause of the subject's medication-related problem.

A cross-over management algorithm[h] could be used to help sort out disease progression issues from drug-related problems.

7. The following guidelines should be addressed by each investigator, prior to making a decision on a subject:

REASON TO INDUCE CROSS-OVER	REASON TO AVOID CROSS-OVER
1. Severe symptoms of AF in the absence of evidence that the subject was not taking the prescribed medication and consensus that further medication would be unsuccessful. 2. Severe side effects or AF symptoms, evidence of adherence to the prescribed AAD regimen, and no other drug options to which to switch the subject.	1. Evidence that the subject did not take the medications as prescribed and/or took concurrent incompatible medications for other chronic diseases – this subject should undergo Medication Management[i] and then return to the hospital 3 weeks later for re-evaluation. 2. Evidence not sufficiently strong to merit cross-over, in the minds of the Investigator..

[h] *A copy of this algorithm will be available to investigators in this trial as a reference guide to managing subjects with difficulties with their prescribed AAD.*

[i] *Medication management includes reviewing all medications taken and an attempt to identify drugs with possible incompatibility with AAD medication(s); review and manage drug taking routine: timing - warning about taking drugs too close together or too far apart; warning about drug holidays and dangers; discuss taking with or without food, as prescribed; coach to use robust routines (taking pills same time each day); pill organizers; and/or recruitment of family to assist subject.*

Appendix C: Justification for AF Disease Progression Rate Estimates

1. Introduction

The study of Atrial Fibrillation Progression Trial (ATTEST) is to determine whether early RF ablation intervention using the CARTO® 3 System, CARTO® XP or CARTO® RMT System and THERMOCOOL® Catheter family in the paroxysmal AF (PAF) population delays or prevents progression of AF compared with conventional drug therapy (either rate or rhythm control) using current AF management guidelines. The rates of disease progression at the 3 year follow-up for the ablation group and drug group were estimated at 5% and 25% respectively. This document is to justify these estimates using DerSimonian and Laird meta-analysis method.[1]

2. Methodology

The weighted noniterative DerSimonian and Laird random effects model was used to synthesize information from relevant literature studies. In this approach, we assume that there is a distribution of treatment effects and utilize the observed effects from individual studies to estimate this distribution. This approach estimates the magnitude of the heterogeneity, and assigns a greater variability to the estimate of overall treatment effect to account for this heterogeneity. The approach allows for treatment effects to vary across studies and provides an objective and more conservative method for weighting.

3. Literature Search

An independent research group (S2 Statistical Solutions) conducted a literature search on AF disease progression outcomes, according to a prospective work plan. Published studies (1990-2011) were searched via PubMed, and unpublished studies were sought from abstracts and presentations at recent professional meetings. Fifty studies meeting inclusion criteria were identified, of which 4 compared catheter ablation to medical treatment. Details of these comparative studies are shown in Tables C1 and C2.

4. Meta-Analysis Results

The four comparative studies have different follow-up time. Their disease progression rates at 3 years follow-up are estimated assuming a linear increase of subjects with disease progression over time. The study characteristics and disease progression rates for the ablation arm are summarized in Table C1. The weighted estimate for disease progression of ablation treatment at 3 years follow-up combining the four comparative studies, using non-iterative weighted DerSimonian and Laird random effects model,[1] is 5.6% with the 95% interval of 0.4% - 47.9%.

Table C1. Literature Studies for Ablation Arm

Author	Study Design	AF Type at Baseline	Follow-up time (months)	Disease Progression Rate at Study Follow-up Time	Disease Progression Rate at 3 Year Follow-up Time	95% CI
Santinelli 2009 (APAF)	RCT	Paroxysmal to persistent/ permanent	48	1% (1/99)	1% (1/99)	(0.0% – 5.5%)
Dabrowski 2010	Comparative (non-RCT)	Paroxysmal to persistent/ permanent	12	0% (0/6)	0% (0/6)	(0.0% - 45.9%)
De Vos 2010	Comparative (non-RCT)	Paroxysmal to persistent/ permanent	12	6.5% (4/61)	19.7% (12/61)	(10.6% - 31.8%)
Pappone 2008	Comparative (non-RCT)	Paroxysmal to persistent/ permanent	60	0% (0/11)	0% (0/11)	(0.0% - 28.5%)

The four comparative studies have different follow-up time. Their disease progression rates at 3 years follow-up are estimated assuming a linear increase of subjects with disease progression over time. The study characteristics and disease progression rates for the drug arm are summarized in Table C2. The weighted estimate for disease progression of drug therapy at 3 years follow-up combining the four comparative studies, using non-iterative weighted DerSimonian and Laird random effects model,[1] is 26.4% with the 95% interval of 14.8% - 42.6%.

Table C2. Literature Studies for Drug Therapy

Author	Study Design	AF Type at Baseline	Follow-up time (months)	Disease Progression at Study Follow-up Time	Disease Progression at 3 Year Follow-up Time	95% CI
Santinelli 2009 (APAF)	RCT	Paroxysmal to persistent/ permanent	48	2% (2/99)	1.5% (1.5/99)	(0.0% - 3.9%)
Dabrowski 2010	Comparative (non-RCT)	Paroxysmal to persistent/ permanent	12	10% (15/148) Subgroups: Parox to perm: 0% (0/79) Pers to perm: 20% (15/75)	30.4% (45/148)	(23.1% - 38.5%)
De Vos 2010	Comparative (non-RCT)	Paroxysmal to persistent/ permanent	12	15% (174/1158)	45.1% (522/1158)	(42.2% - 48.0%)
Pappone 2008	Comparative (non-RCT)	Paroxysmal to persistent/ permanent	60	53% (24/45)	25.5% (14/45)	(14.7% - 39.0%)

5. Conclusion

Our point estimates using the DerSimonian and Laird random effects meta-analysis method[1] for disease progression rates at 3 years follow-up in the ablation arm and drug arm are 5.6% and 26.4% respectively, which are consistent with the physicians' estimates of 5% and 25% for ablation and drug therapy in the new study. Therefore, the published literature and experience in AF disease progression support our estimates of disease progression rate at 3 years follow-up and fully support the study design of a randomized trial testing whether early ablation treatment delays or prevents disease progression from paroxysmal AF to persistent or permanent AF compared with drug therapy.

Reference

1. DerSimonian R and Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials 1986; 7:177-188.

Appendix D: Safety Provisions - Drug Regulations

Countries for which the Attest study is subjected to national drug regulations (EudraCT number: 2012-002338-35, if applicable) the following provisions are applicable in addition to Section 12 of the protocol.

Definitions:

Suspected Unexpected Adverse Reaction (Directive 2001/20/EC and CT-3)**:**

An suspected unexpected adverse reaction (SUAR) is an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorized product).

A SUSAR is defined as an event meeting the definition of a suspicion of SUAR and Seriousness definition (medicines).

To determine if an Serious Adverse Reaction of an AAD is expected or unexpected, Biosense Webster will refer to a list of SmPc's (e.g. www.medicines.org.uk).

ATC	Class*	Name	Control
C07AA05	II	Propranolol	Rate
C07AA07	III	Sotalol	Rate/Rhythm
C07AB02	II	Metoprolol	Rate
C07AB03	II	Atenolol	Rate
C07AB04	II	Acebutolol	Rate
C07AG02	II	Carvedilol	Rate
C07AB12	NA	Nebivolol	Rate
C07AB07	II	Bisoprolol	Rate
C08DB01	IV	Diltiazem	Rate
C08DA01	IV	Verapamil	Rate
C01AA05	V	Digoxine	Rate
C01BA01	Ia	Quinidine	Rhythm
C01BC04	Ic	Flecainide	Rhythm
C01BD01	III	Amiodarone	Rhythm
C01BD07	III	Dronedarone	Rhythm
C01BC03	Ic	Propafenone	Rhythm
C01BD04	III	Dofetilide	Rhythm
C01BG07	Ic	Cibenzoline	Rhythm

* Vaughan Williams Classification of Anti-arrhythmic drugs

Investigator responsibilities:

AAD related SUSAR's shall be reported by the Investigator to Biosense Webster immediately but not later than 24 hours of awareness.

NOTE: Pharmacovigilance reporting of events coming forth from drugs which are authorized medicinal products, shall be reported to the marketing authorization holder, unless otherwise indicated by institutional policies, EC / EB (or equivalent) policies, and local regulations.

Biosense Webster responsibilities

Drug related events

Any SUSARs must be handled and reported by Biosense Webster to the appropriate authorities (e.g., competent authorities) as well to the ECs / EBs (or equivalent) according to the prevailing regulations per country.

Biosense Webster shall perform standard expedited reporting to participating CAs, ECs / EBs and Investigators, unless otherwise indicated by national regulations:

Event Type	**Timelines**
SUSAR fatal or life-threatening	7 days (after the sponsor was first aware of the reaction) 8 days (any relevant additional information shall be sent within 8 days of the report)
SUSAR (other)	15 days

Biosense Webster shall not report adverse reactions related to other drugs than AAD's (non-IMP) received by the subject and without interaction with the AAD (IMP).

Appendix E: Informed Consent Form Template

Master Template Informed Consent Form, subject to change on country and/or site level upon need/request of local regulations. Site- and/or country-specific Informed Consent Forms require review and approval from the applicable EC or EB prior to its use in the ATTEST study.

PATIENT INFORMATION

subject's Name: _____ subject's Number: _____

STUDY NAME: ATTEST

STUDY TITLE: Atrial Fibrillation Progression Trial (ATTEST)

INVITATION

You are invited to take part in a research study because you suffer from Paroxysmal Atrial Fibrillation. Atrial fibrillation is an abnormal heart rhythm; the atria of the heart don't contract normally, but rapidly and irregularly. In general, the heart keeps its vital ability to pump the blood around because the ventricles are still working effectively, but irregularly. Paroxysmal AF means that episodes happen occasionally and self-terminate in less than 7 days without medical intervention.

Before you decide to participate, it is important for you to understand why the research is conducted and what is expected from you. Please read the following information carefully and take time to decide whether or not you wish to participate. **Your participation to this clinical study is completely voluntarily. You have the right to decline participation without providing further clarification. Your decision not to participate to the study has no impact on your further medical treatment.**
Do not hesitate to ask questions if there is anything that is not clear or if you would like more information.

Principal Investigator's name
Hospital name
Telephone number
Fax number

This research project is sponsored by Biosense Webster Inc, a Johnson & Johnson company.

WHAT IS THE PURPOSE / OBJECTIVE OF THE STUDY?

The goal of this study is to evaluate the progression toward persistent atrial fibrillation after undergoing radiofrequency (RF) ablation with a catheter from the THERMOCOOL® Catheter Family when used with the CARTO® 3, CARTO XP® or CARTO® RMT System (Biosense Webster, Inc.) compared to drug therapy.

Persistent atrial fibrillation is a more chronic form of the illness, characterized by atrial fibrillation sustained beyond 7 days, or lasting less than 7 days but necessitating cardioversion (a medical procedure by which the cardiac arrhythmia is converted to a normal rhythm, using electricity or drugs).

During an ablation, radiofrequency energy is used to destroy heart cells in order to treat an abnormality in the electrical conduction system of the heart. These abnormal electrical impulses can cause arrhythmia.

The aim of ablation is to restore and maintain normal heart rhythm, relieve symptoms associated with atrial fibrillation, and reduce the risk of stroke. Stroke is a cerebrovascular accident or sudden interruption of the blood supply to a part of the brain by occlusion of a blood vessel by a blood clot. These blood clots may be formed in the chambers of the heart during atrial fibrillation.

Radiofrequency ablation is performed in the left upper chamber of the heart known as "left atrium". Several studies have shown that electrical stimuli, that originate from the pulmonary veins (= blood vessels bringing blood from the lungs to the left atrium) trigger atrial fibrillation. Therefore, these veins have to be isolated electrically from the rest of the left atrium. This means that the electrical impulses that are generated in the pulmonary veins will be interrupted before they reach the heart, thereby eliminating the atrial fibrillation and related symptoms.

Atrial fibrillation can also be treated with drugs. Your physician will discuss the different treatment strategies with you.

STUDY TREATMENTS:

During this trial, we will compare radiofrequency (RF) ablation with standard of care drug therapy. Standard of care drug therapy means the treatment you would most likely receive if you were not participating in this clinical trial and if you would not be eligible for catheter ablation.

The ablation technology used is CARTO® 3, CARTO® XP or CARTO® RMT System-guided RF Ablation using a catheter from the THERMOCOOL® Catheter Family.

This technology uses a computer system to make a 3D image of your heart. Based on this image, your doctor will decide how to isolate the pulmonary veins. The THERMOCOOL® Family of Catheters use a single electrode to ablate, so only one lesion (destruction of tissue) will be created at a time. This electrode is cooled by the flow of saline solution coming through little holes at the tip of the catheter. During this ablation procedure your study doctor will assess the fluid status, determine if diuretics are necessary, and treat you accordingly. Diuretics are drugs used to increase the excretion of water from the body. If there is too much build up of fluid inside your body, diuretics will help to eliminate this via the urine.

This study is a Prospective, Multi-center, Randomized (1:1), Controlled, Two-arm, Open-label Clinical Study.
A **Prospective** study follows over time a group of individuals who have a similar medical condition.
Multi-center: Approximately 330 patients in up to 50 hospitals in Europe, and/or Asia and/or North America will be enrolled in this study.
Randomized (1:1) means that you will be assigned randomly (by chance like flipping a coin) to a treatment group (RF ablation or drug therapy). This will be done via a computerised system. You have an equal chance to be in the RF ablation group then in the drug therapy group.
Two-arm: two types of treatment will be compared during this study.
Open-label means that the researcher knows the full details of the treatment and so will you.

ALTERNATIVE TREATMENTS:

You do not have to participate in this study in order to be treated for your condition; your treatment will not differ much whether you decide to take part in the study or not. You may thus choose not to take part in the study and have the same treatment as the study treatments. By taking part in the study you help the medical community in better understanding the effect of both treatments for atrial fibrillation.

WHAT IS EXPECTED FROM ME WHEN PARTICIPATING IN THIS STUDY?

If you agree to take part in the study, you are asked to strictly follow the instructions from your physician i.e. with respect to the planned visits and study procedures. For this study to be a success it is important that you remain in the treatment group that you have been assigned to during the entire duration of the study. Your physician might take a decision to treat you with a different treatment then the treatment you have been assigned to if clinically necessary.

The duration of your participation in the study will be approximately 3 years. During this period you will have to visit the hospital at least 6 times. Your physician will also call you by telephone approximately 3 times during the study to check how you are doing and which medications you are taken. The entire study will take approximately 4.5 years to finalize.

The following visits and study procedures are planned during this research study. All procedures performed during the study are done as standard of care.

During the screening period (prior to the procedure/start drug therapy):

- Transesophageal Echocardiogram (TEE): an ultrasound device is passed into the esophagus (the swallowing tube) and is positioned directly behind the heart to provide more accurate pictures of your heart. This test is standard and necessary to make sure there are no blood clots in your left atrium before the ablation procedure. This test will be performed within 48 hours before the procedure. This test will not be performed if you are randomized to the drug therapy group.
- Transthoracic Echocardiogram (TTE): An echocardiogram uses ultrasound waves to map a picture of the heart. A device is moved around your chest to obtain images of your beating heart. It's a simple and painless test that provides valuable information about a heart with an arrhythmia.
- Questionnaire(s): The physician may ask you to complete 1 or 2 questionnaires. These questionnaires ask some general questions about your quality of life and frequency and severity of symptoms related to your arrhythmia

During the ablation procedure (only applicable if you are randomized to the RF ablation group):

- The first step of a radiofrequency ablation procedure is the placement, via the groin, of several types of catheters into your heart to record the electrical activity from areas that may be starting or maintaining the atrial fibrillation. Fluoroscopy, which is a type of light x-ray, will be used to help guide the placement and movement of the catheters. Your groin will be numbed to make the procedure more comfortable. You may also be given medications to help you feel more relaxed, or asleep, depending upon the doctor's choice. Some of the catheters will need to be positioned into the left side of your heart. To reach the left side, a small puncture is made in the area of the heart that separates the left from the right atrium, called the septum. These catheters may also be used to pace (delivering pulses of electric current) your heart in different regions.
- Then energy will be applied to electrically isolate these pulmonary veins. These areas have recently been shown to trigger atrial fibrillation. This procedure may last several hours.
- At the end of the ablation procedure, your heart may once again be paced to verify that the areas in the heart that were targeted have been successfully ablated. After completing the ablation procedure, you will be monitored and remain in the hospital for a few days.

After the procedure and before discharge another Transthoracic Echocardiogram (TTE) will be performed.

Approximately **3 months** after the procedure/enrolment to drug therapy you will visit your

clinic and you may be asked to complete the same questionnaire(s) as the one(s) completed before the procedure/dosing.

As from this visit you will be asked to record your heart rhythm on a regular basis, and also when you are experiencing symptoms possibly related to your arrhythmia. You will receive a Transtelephonic monitoring (TTM) device. This is a small device that you will take home with you and keep with you all the time. You will put this device on your chest to measure your heart rhythm. This procedure is simple, painless and will only take a few minutes. After the recording, you will need to send your recording via a telephone. Someone at the hospital will explain you how to do this.

You will have to record your heart rhythm and send it via telephone during the entire study (3 years of follow-up). If you progress toward persistent atrial fibrillation, you will no longer need to record your heart rhythm
6 months after the procedure/dosing you will visit your clinic and you may be asked again to complete the same questionnaire(s) about your quality of life and frequency and severity of symptoms related to your arrhythmia (the same questionnaire(s) as you completed before the procedure/dosing and at the 3-month follow-up visit).

Approximately **9 months, 1.5 year and 2.5 years** after the procedure/enrolment to drug treatment your physician will call you to check how you are doing, which medications you are taken and how the TTM transmission of your heart rhythm is going.

Approximately **1 year, 2 years and 3 years** after the procedure/enrolment to drug treatment you will visit your clinic to have the following assessments:

- 1 or 2 questionnaire(s) (the same questionnaire(s) as you completed before).
- Transthoracic Echocardiogram (TTE): the same examination as at the start of the study will be performed.

If you progress toward persistent AF before the end of the study, you will continue to be followed by your physician as per his standard of care but you will not have to attend all the last follow up visits of the study. You will only need to visit your clinic a last time for the 3 year follow-up visit and have the assessments done as described above.

During each follow-up visit / follow-up phone call, your medication and any adverse events you may have had will be recorded. There will also be some information collected on certain medical conditions during the study, for example diabetes, hyperlipidemia/dyslipidemia (too much cholesterol in your blood), kidney function and dementia. Other questions that will be addressed are about your adherence to the drug therapy - how well you take your medication as prescribed by the physician.

WHAT ARE THE ANTICIPATED INCONVENIENCES, SIDE EFFECTS AND RISKS?

There are risks associated with both ablation procedure and drug therapy. These risks do not differ as what you would experience outside the study since these treatments do not deviate from your doctor's standard procedure.

Previously identified risks with an ablation procedure are described below and are common to all catheter ablation procedures for atrial fibrillation.

- Catheters will be inserted into your blood vessels. The insertion of catheter(s) in the vein or the artery could cause different complications such as bleeding and infection.
- Catheters inserted in the left atrium could cause blood clots or air embolism (air bubbles) resulting in stroke, heart attacks or perforation of the wall of the heart. A perforation can possibly result in blood effusion (blood escaping) in the pericardium (the membrane enclosing the heart) and tamponade (accumulation of blood in the

pericardium, preventing the heart from expanding fully and finally causing the heart to stop pumping).
- Paralysis of the phrenic nerve, which could cause shortness of breath.
- Narrowing of the pulmonary veins.
- Atrio-esophageal fistula, a passage created between the heart and the esophagus, is a severe complication of AF ablation but is very rarely seen.
- During the ablation procedure, you may feel discomfort or a burning sensation in your chest. Sedation will be proposed and the known side effects associated with anesthesia will be explained to you.

If any of the known or unforeseen risks occur, it is possible that other interventions may be necessary, such as angioplasty to open an obstructed coronary artery, surgery in case of a damaged heart valve or perforation of the heart, implantation of an artificial pacemaker, or other interventions not listed here. An angioplasty is a widening of narrowed arteries, by inserting a balloon in the narrow part and then inflating it. The balloon will be removed after the procedure. In some cases, a stent (tube) can be positioned in the artery to keep it open more effectively.

Previously identified risks associated with drug therapy are listed below. As per standard, risks identified with the drug treatment are described in the patient leaflet included in the pack of your medicine. If you have any questions about these leaflets, you should discuss this with your doctor, pharmacist or nurse.

- Risks of rate control drugs: Hypotension, heart block (disease in the electrical system of the heart), bradycardia (slow heart beat), asthma, heart failure (the inability of the heart to supply sufficient blood flow to meet the needs of the body), constipation.
- Risks of rhythm control drugs: photosensitivity (sensitivity of the skin to a light source), pulmonary toxicity, polyneuropathy (neurological disorder that occurs when many peripheral nerves throughout the body malfunction simultaneously), bradycardia, torsades de pointes (a specific, rare variety of ventricular tachycardia, a fast heart rhythm, that originates in one of the chambers of the heart), impaired liver function, thyroid dysfunction, eye complications, heart failure, glaucoma (an eye disorder in which the optic nerve suffers damage, permanently damaging vision in the affected eye(s)), urinary retention (the lack of ability to urinate), ventricular tachycardia (a fast heart rhythm, that originates in one of the chambers of the heart).
- Risks of anticoagulation: the most common side effects associated with anticoagulant therapy are itching, rashes, easy bruising, increased bleeding from injuries and purplish spots on the skin. Purplish skin spots are caused by small amounts of bleeding under the skin. Bruising tends to be more severe when taking anticoagulants, and bleeding from wounds can be difficult to stop.

CAN I PARTICIPATE IN MULTIPLE STUDIES?

Participation in multiple studies may be hazardous to you. If you are already participating in other studies please inform your physician fully.

WHAT ARE THE POSSIBLE BENEFITS OF TAKING PART?

The major benefit of undergoing radiofrequency catheter ablation and/or drug treatment for atrial fibrillation is the potential elimination of symptomatic AF episodes. It is furthermore expected that the quality of life will improve and less frequent hospitalization is needed. Also, your participation will allow us to gather information on the use of different technologies and treatments, which may be beneficial for the treatment of other patients with atrial fibrillation.

DO I HAVE TO TAKE PART?

Your participation is voluntary. It's up to you to decide whether or not to take part in this study. No one can make the decision for you. You can withdraw from this study at any time and without giving a reason. A decision not to participate or to withdraw at any time during the study, will not affect the quality of the standard care you receive. It will not have any effect on your further treatment. You may thus choose not to take part in the study and still have the

same treatment for your arrhythmia as the study treatments (RF ablation or drug therapy) as both are part of daily practice.

If you decide to withdraw, the information already collected may still be used.

If you accept to participate in this study, you will receive this information form to keep and you will be asked to sign the last page for consent.

The study doctor can stop your participation in this study at any time for one of the following reasons:

- You do not follow the instructions for participation in the study;
- Your further participation in the study appears to be harmful to you;
- At a later stage, it becomes clear that you do not meet the study criteria;
- The sponsor stops the study everywhere, or just in this hospital for reasons other than the ones listed above, and unknown at this moment.

If the study is stopped prematurely, your physician will make sure you continue to have the best possible treatment.

WHAT IF RELEVANT NEW INFORMATION BECOMES AVAILABLE?

Sometimes, new information becomes available about the treatment that is being studied during the course of the study. If this happens, your doctor will inform you and will discuss whether you want to continue your participation in the study or not. If you decide not to carry on, your doctor will make sure you receive the best medical treatment available. If you decide to continue, you will be asked to sign an updated consent form.

WHO SHOULD NOT TAKE PART IN THIS STUDY?

Patients who do not fulfil the criteria to enter in the study should not participate. Your doctor will check if you are suitable to participate in this study.

- **Pregnancy**

Pregnant women, lactating women or women planning to become pregnant during the study, are not allowed to participate.

WHAT IN CASE OF STUDY RELATED PERSONAL INJURY - INSURANCE?

If you incur damage which is connected to this study, this damage will be compensated by the sponsor of this study to you or your rightful claimants (family) in accordance with the [COUNTRY] law concerning experiments on the human person of [DATE].You do not have to prove someone's fault.
The sponsor has contracted an insurance policy with ACE European Group limited Policy n° [policy number] to cover the risk and the damage, which would follow from the study. You or your rightful claimants can sue the insurer [COUNTRY] directly.

FINANCIAL COMPENSATION

The sponsor, Biosense Webster Inc., pays your study doctor and/or hospital to carry out this study. There will be no financial benefit to you; you will not receive any money as payment or compensation for taking part in this trial.

ANTICIPATED COSTS RELATED TO MY STUDY PARTICIPATION

There will be no additional costs for you if you are taking part in this study.

PROTECTION OF YOUR PRIVATE LIFE

Your identity and your participation to this study will be treated strictly confidential. You will not be identified by name or in any other identifying manner in files, results or publication concerning this study. The Investigator will encode your personal data to ensure that your identity shall remain secret at all times.

According to the good clinical practice guidelines, your medical records will, insofar as this relates to the study, be examined by representatives of the sponsor or the subsidiaries of the sponsor and by the regulating authorities, in order to check the study data and study examinations and in order to assure that the information is accurate. Your identity remains secret since personal information will only be designated by a unique patient number (therefore coded).

The sponsor might use your personal information for other research purposes. Only coded personal information will be used for this purpose.

Your personal information might be transferred to regulation authorities (locally and/ or abroad), to the ethics committee and to other doctors and / or organizations which cooperate with the sponsor. Your personal information might also be transferred to other branches of the sponsor in this country and in other countries where the rules concerning data management might be different or less strictly followed. The sponsor will apply the same rules concerning data protection within the legal framework of the countries concerned.
Your personal information will be processed and analysed electronically (in the computer) or manually in order to determine the results of this study. You have the right to ask the study doctor which data are collected about you in the context of the study and what the purpose of that collection is. You also have the right to request the study doctor to give you access to your personal information and to correct it if necessary. The protection of personal data is legally established in the Law of [DATE] concerning the protection of private life.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by US Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If you consent to the participation in the study, this implies that you also consent to the use of your coded medical data for the abovementioned purposes and to the transfer of them to the abovementioned persons and/ or bodies.
If your participation in the study is terminated early, your initial approval will allow for the data, relating to your inclusion in the study, to be used.

ETHICS COMMITTEE and COMPETENT AUTHORITIES

The hospital's <local Ethics Committee> has given a favorable opinion to start this research project. The Competent Authority of your country has been notified, and where applicable, approval has been requested and obtained.

INFORMED CONSENT FORM

- I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care being affected.

- I confirm that I have read and understood the information sheet. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

- I agree that relevant personal data will be used for the purpose of this clinical investigation.

- I understand that all documents belonging to my medical file will remain strictly confidential. I also understand that my medical notes may be looked at by:
    - The responsible individual from the Sponsor or a representative
    - Regulatory authorities
    - Members of the Ethics Committee

  I give permission for these individuals to have access to my records.

- I agree/disagree that my general practitioner will be informed of my participation in this study (please circle 'agree' or 'disagree')

- I agree to take part in the above-mentioned study and will strictly comply with study procedures.

- I receive a copy of the patient information and signed informed consent form.

Name patient	**Signature patient**	**Date**
Name legal representative or witness (if applicable)	**Signature witness**	**Date**
Name physician taking informed consent	**Signature physician**	**Date**