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TactiCath™ Contact Force Ablation Catheter Study for Atrial Fibrillation Continued Access Study
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St. Jude Medical, Inc.
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TOCCASTAR

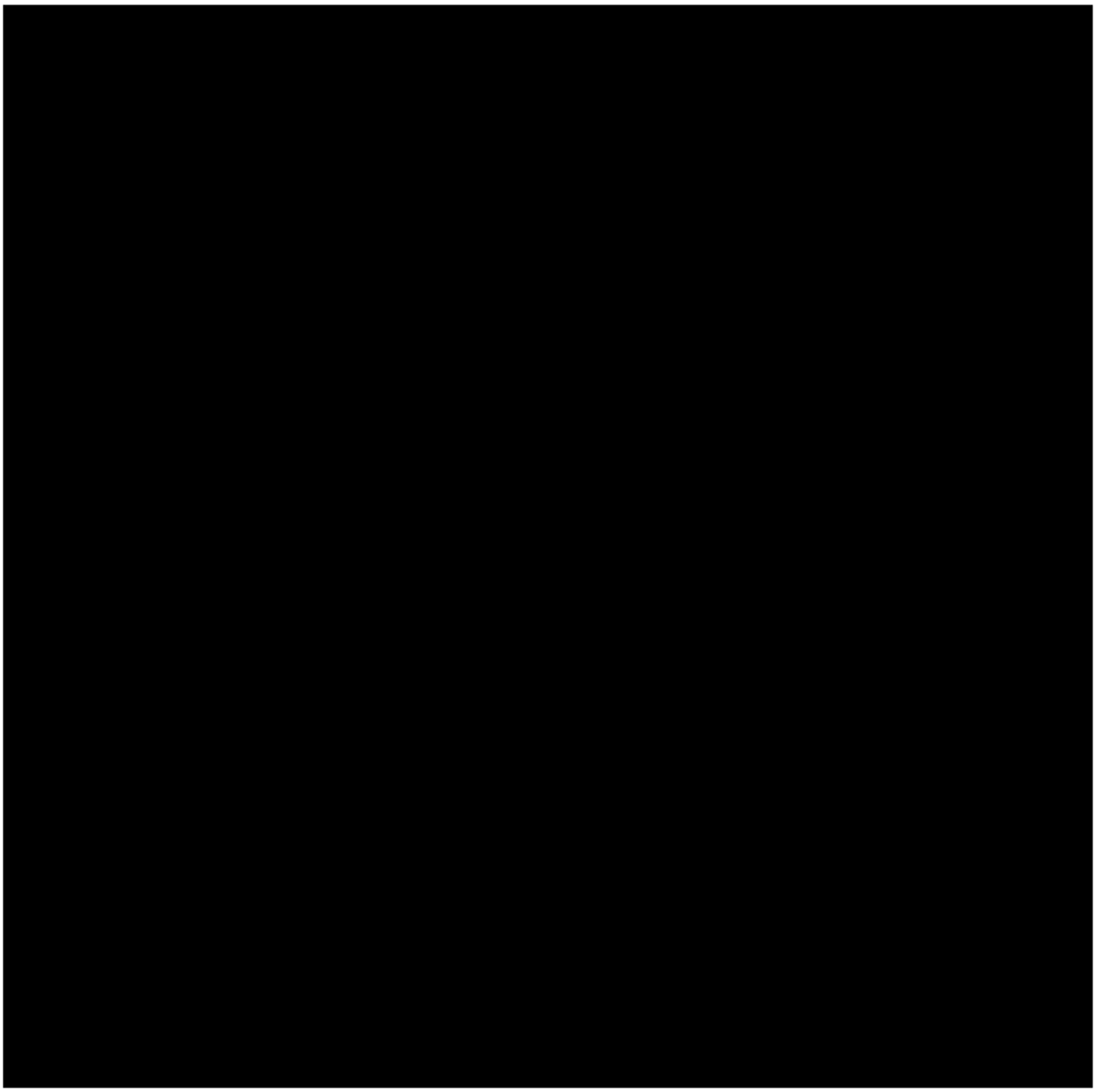
TactiCath® Contact Force Ablation Catheter Study for Atrial Fibrillation

A prospective, randomized, multicenter, interventional study to evaluate the safety and effectiveness of the TactiCath® percutaneous ablation catheter for the treatment of symptomatic paroxysmal atrial fibrillation using contact force assisted irrigated radiofrequency ablation

CLINICAL INVESTIGATIONAL PLAN:	VP-002 527
INVESTIGATIONAL DEVICE:	TactiCath® Set and the TactiCath Quartz Set - a percutaneous catheter and system components for irrigated radiofrequency ablation, incorporating contact force sensing
CIP DATE:	Version H January 21, 2014
SPONSORED BY:	Endosense 42 Chemin du Grand-Puits 1217 Meyrin Geneva Switzerland 41-22-306-1960
MANUFACTURER:	Endosense
CONTRACT RESEARCH ORGANIZATION:	[redacted]

[redacted]

SIGNATURES OF AGREEMENT



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2. CLINICAL INVESTIGATION SYNOPSIS

STUDY TITLE	**TOCCASTAR** **T**actiCath® **C**onta**c**t For**c**e **A**blation Catheter **St**udy for **A**trial Fib**r**illation A prospective, randomized, multicenter, interventional study to evaluate the safety and effectiveness of the TactiCath Percutaneous Ablation Catheter for the treatment of symptomatic paroxysmal atrial fibrillation using contact force assisted irrigated radiofrequency ablation
DEVICE DESCRIPTION	The **TactiCath Set** includes the TactiCath Catheter and the TactiSys® Equipment. The **TactiCath** catheter is a steerable, irrigated percutaneous catheter for endocardial mapping and radiofrequency (RF) ablation, incorporating a tri-axial contact force sensor at the distal tip. The sensor allows precise measurement of the force applied by the catheter to the heart wall in real time. The **TactiSys** Equipment includes the Base Station and Splitter, which provide standard interconnection with commonly used laboratory equipment and is used for processing and display of data. The system displays detailed force information by determining the cross product of axial and lateral force components to obtain the resultant force vector, fully describing the contact force at the point of contact between the catheter and tissue surface.
STUDY DESIGN	TOCCASTAR is a prospective, randomized, multicenter, interventional study to evaluate the safety and effectiveness of the TactiCath Set for the treatment of symptomatic atrial fibrillation (PAF) using contact force assisted irrigated RF ablation. Patients undergoing elective catheter ablation for symptomatic PAF who are refractory or intolerant to at least one antiarrhythmic drug (Class I-IV) will be screened for enrollment. Patients who meet the study entry criteria and sign the patient informed consent form will be enrolled and treated following the 2007 Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS) Expert Consensus Statement on Catheter and Surgical Ablation for Atrial Fibrillation. Eligible patients will be randomly assigned 1:1 to receive treatment with either the TactiCath Set or the control device (the NaviStar® ThermoCool® open irrigated RF ablation catheter manufactured by Biosense Webster, Inc.) Use of three-dimensional (3D) mapping equipment will be required in both treatment groups. Patients will be blinded to treatment assignment. This study aims to demonstrate non-inferiority of the study device to the control device for both safety and effectiveness. After the index procedure, patients will be followed for a total of 12 months for chronic effectiveness assessment, beginning with a 3-month blanking period and ending with a 9-month effectiveness assessment period. During the blanking period, patients may be prescribed a previously ineffective antiarrhythmic drug and undergo up to 2 repeat ablation procedures (up to 10 days prior to end of the blanking period) using the same device specified by the initial randomization. Patients will be evaluated at pre-discharge, at 7 days, at 3, 6 and 12 months post-index procedure and every 6 months thereafter until PMA approval. Patients will be enrolled at up to 30 sites in the United States (US) and elsewhere. A maximum of 50% of patients may be enrolled outside the US.

SUPPLEMENTAL CLINCIAL STUDY	To evaluate the comparative safety of a product evolution (TactiCath Quartz Set) relative to the original TactiCath Set, up to an additional 50 subjects will be enrolled in a supplemental phase to the Toccastar Study. These subjects will comply with the same protocol requirements for patient selection, treatment and follow-up as a roll-in subject; they will not be randomized. Data from the supplemental patients will be reported separately from the randomized population and will not contribute to the primary study endpoints. Please refer to Appendix J (Supplemental Clinical Study) for a description of the supplemental study and specific variance from the randomized protocol, where applicable.
CONTINUED ACCESS STUDY	Continued access to the TactiCath Quartz Set is provided during the regulatory review period for the Pre-Market Application. An additional 150 subjects at the original IDE sites may be enrolled as part of the Continued Access Study. These subjects will adhere to the same protocol requirements for patient selection and treatment with a simplified schedule of follow-up. Subjects enrolled in the Continued Access Study will not be randomized. Data from these subjects will be reported descriptively and separately from the randomized population as well as the Supplemental Clinical Study population. Please refer to Appendix K (Continued Access Study) for a description of the Continued Access Study and specific variance from the TOCCASTAR and Supplemental Clinical Study, where applicable.
OBJECTIVES	**Effectiveness**: To provide valid scientific evidence that use of the TactiCath Set is an effective treatment for symptomatic paroxysmal atrial fibrillation (PAF). **Safety**: To provide valid scientific evidence that use of the TactiCath Set is safe as measured by the incidence of early-onset serious adverse events (SAEs) when compared to the control device.
PRIMARY ENDPOINTS	**Effectiveness** The primary effectiveness endpoint of the study is a non-inferiority comparison of treatment success between the TactiCath Set and the control device as defined by both: • Acute procedural success - electrical isolation of all 4 pulmonary veins (PVs), or in the event of a common PV, the clinical equivalent of all PVs by the end of index procedure • Chronic success - acute procedural success and freedom from recurrence of symptomatic PAF, atrial flutter (AFL), and atrial tachycardia (AT) lasting longer than 30 seconds through 9 months of follow-up after a 3 month blanking period. Re-treatment for AF with ablation or the use of Class I or Class III antiarrhythmic drugs after the blanking period constitutes a treatment failure. **Safety** The primary safety endpoint is a non-inferiority comparison of device-related early-onset primary SAEs between the TactiCath Set and the control device occurring within 7 days of the index procedure or hospital discharge, whichever is later, and diagnosed at any time during the follow-up period.

SECONDARY ENDPOINTS	**Effectiveness** The secondary effectiveness endpoints are related to the use of the contact force sensor and will assess procedural effectiveness superiority of the TactiCath Set over the control device. It is hypothesized that the use of the contact force sensor information will result in added procedural effectiveness through a reduction of: 1. Number of electrically reconnected pulmonary veins following a 30-minute waiting period assessed by entrance block 2. Time to achieve total PV isolation measured from initial application of RF energy to all target vessels isolated 3. Total time of RF application required for full PV isolation **Safety** Incidence of all serious adverse events (SAEs) during the 12-month follow-up period
DESCRIPTIVE ENDPOINTS	**Effectiveness** • Percentage of patients free of symptomatic AF episodes after treatment with combination therapy (previously failed AADs and/or ablation) after 12 months • Percentage of patients free of symptomatic and/or asymptomatic episodes of AF after 12 months • Freedom from AF/AFL/AT at 12 months by 24 hour Holter • Total fluoroscopy time • Number of RF applications • Length of hospitalization • Occurrence of repeat ablations (incidence and time from index procedure) • Use of antiarrhythmic drugs • Quality of life assessment • TactiCath Set contact force data
NUMBER OF PATIENTS	A target of 300 patients (maximum 440) will be randomized. Interim analysis will be conducted when 50% of the patients have completed the 6-month follow-up procedures, and may result in a decision by the data safety monitoring board (DSMB) and Endosense to enroll additional patients. To allow for a period of familiarization with the unique features of the TactiCath Set, each site will be permitted to use the study device in up to 5 patients (roll-in population) who will not contribute data to the primary endpoint analyses. Data from the roll-in population will be reported separately.
TREATMENT SCHEDULE	Eligible patients will be randomly assigned 1:1 to receive treatment with one of the following: • TactiCath Set, or • Control device (the NaviStar® ThermoCool® open irrigated RF ablation catheter manufactured by Biosense Webster, Inc.) Enrolled patients will be evaluated at pre-discharge, at 7 days, at 3, 6, and 12 months post-index procedure and every 6 months thereafter until PMA approval.

INCLUSION CRITERIA	A patient will be eligible for study participation if he/she meets the following criteria: 1. Patient is planned to undergo a catheter ablation procedure due to symptomatic PAF that is refractory or intolerant to at least one Class I-IV antiarrhythmic drug 2. Minimum of one episode of PAF greater than 30 seconds in duration within 12 months prior to enrollment documented by 12-lead electrocardiogram (ECG), Holter monitor, transtelephonic event monitor, telemetry strip, or implanted device 3. Minimum of 3 episodes of PAF within the preceding 12 months documented by patient history 4. Patient is 18 years of age or older 5. Patient is willing and capable of complying unassisted with the study protocol requirements including all specified follow-up visits 6. Patient provides written informed consent prior to enrollment in the study
EXCLUSION CRITERIA	A patient will be excluded from the study if he/she meets any of the following criteria: 1. Persistent or long-standing persistent atrial fibrillation (AF) 2. Patient has had 4 or more cardioversions in the last 12 months 3. Active systemic infection 4. Presence of implantable cardiac defibrillator (ICD) 5. Arrhythmia due to reversible causes including thyroid disorders, acute alcohol intoxication, and other major surgical procedures in the preceding 3 months 6. Myocardial infarction (MI), acute coronary syndrome, percutaneous coronary intervention (PCI), or valve or coronary bypass grafting surgery within preceding 3 months 7. Left atrial diameter > 5.0 cm 8. Left ventricular ejection fraction < 35% 9. New York Heart Association (NYHA) class III or IV 10. Previous left atrial ablation procedure, either surgical or catheter ablation 11. Patient has had a left atrial surgical procedure or incision with resulting scar 12. Previous tricuspid or mitral valve replacement or repair 13. Heart disease in which corrective surgery is anticipated within 6 months 14. Bleeding diathesis or suspected pro coagulant state 15. Contraindication to long term antithromboembolic therapy 16. Presence of condition that precludes appropriate vascular access 17. Renal failure requiring dialysis 18. Known sensitivity to contrast media (if needed during the procedure) that cannot be controlled with pre-medication 19. Contraindication to computed tomography and magnetic resonance angiography 20. Severe pulmonary disease (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces severe chronic symptoms 21. Positive pregnancy test results for female patient of childbearing potential 22. Patient has other anatomic or co morbid conditions that, in the investigator's opinion, could limit the patient's ability to participate in the study or to comply with follow up requirements, or impact the scientific soundness of the study results 23. Patient is currently participating in another clinical trial or has participated in a clinical trial within 30 days prior to screening that may interfere with this study 24. Patient is unlikely to survive the protocol follow up period of 12 months

CRITERIA FOR WITHDRAWAL	All patients are free to withdraw from participation in this study at any time, for any reason, and without prejudice. Patients may be withdrawn from the study when they request early discontinuation or are lost to follow-up. The clinical investigator may terminate a patient from the study at any time for lack of therapeutic effect that is intolerable to the patient, or otherwise considered unacceptable, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the clinical investigator's opinion, to protect the patient's best interest.
ENROLLMENT PERIOD	Enrollment began in the first quarter of 2011 (Q1 2011) and is expected to be complete by approximately Q1 2012.
STUDY DURATION	The total study duration is approximately 24 months: assuming 12 months for patient enrollment and followed by a 12-month follow-up period.
INVESTIGATIVE SITES AND COUNTRIES	Up to 30 sites in the US and elsewhere may participate in the study.

3. INTRODUCTION

3.1 Device Name

The device under clinical investigation is the Endosense TactiCath Set (TactiCath Catheter and TactiSys Equipment).

3.2 Disease State

With a high risk for stroke at 1.6% per year and a primary prevalence of 6 million people, atrial fibrillation (AF) is a one of the biggest treatment challenges for cardiologists today.[2-4]

AF is one of a diverse group of arrhythmias collectively described as supra-ventricular tachyarrhythmia (SVT). In SVT, the trigger originates in the atrium or the atrium is part of the re-entry mechanism for triggering or maintaining the arrhythmia. SVTs vary considerably in their rate and regularity, their clinical manifestations, and the setting in which they occur. These arrhythmias are characteristically abrupt in onset and termination and are often seen in patients who do not have evidence of organic heart disease. Although these disturbances in rhythm are generally not malignant in the short-term, in patients with organic heart disease a rapid atrial rhythm may produce significant hemodynamic complications. In some patients with pre-excitation syndromes combined with an anterograde accessory pathway, there is also a risk of sudden death.

SVTs are usually divided into the following 3 groups:

- Supra-ventricular tachycardias (i.e., atrial tachycardia [AT], sino-atrial node re-entry, intra-atrial re-entry, atrioventricular reentrant tachycardias [Wolff-Parkinson-White syndrome], and atrioventricular nodal reentrant tachycardia)
- Atrial flutter (AFL)
- Atrial fibrillation (AF)

Long-term outcomes for symptomatic AF patients treated exclusively with drugs remains poor.[5,6] Treatment of AF using RF ablation or surgery has become increasingly important. Various techniques are being proposed that use ablation in the left atrium.[4]

3.3 Radiofrequency Ablation

Radiofrequency (RF) catheter ablation is a minimally invasive procedure commonly used for more than 20 years to treat most of the recurrent supra-ventricular tachyarrhythmias.[1-3]

Recent advances in the underlying science and technology of ablation for AF have identified the benefits of irrigation and temperature monitoring to control for char formation and reduce embolic risk. A steerable catheter tip provides additional flexibility for catheter placement. These features have been incorporated in the design of the TactiCath catheter.

With the exception of AF, supra-ventricular tachyarrhythmias can be treated by ablation in the right atrium only. For the treatment of AF, an intervention in the left atrium is required.

3.4 Background

The 2006 American College of Cardiology (ACC)/American Heart Association (AHA)/European Society of Cardiology (ESC) guidelines for the treatment of AF recommend catheter ablation as a second-line therapy after a patient has been shown to be refractory or intolerant to at least one Class I or III antiarrhythmic medication.[2] The 2007 Heart Rhythm Society (HRS)/European Heart Rhythm Association (EHRA)/European Cardiac Arrhythmia Society (ECAS) Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation reiterates this recommendation.[3] The 2009 Comparative Effectiveness Review of Radiofrequency Catheter Ablation published by the US Department of Health and Human Services further describes the risks and benefits associated with RF ablation for PAF.[27]

Circumferential electrical isolation of the entire pulmonary vein (PV) musculature is now common practice for patients with paroxysmal atrial fibrillation (PAF) in whom one or more antiarrhythmic agents have failed. This procedure, also known as PV isolation, seeks to block the conduction of arrhythmia triggers originating in PV foci and has become the accepted approach for AF ablation worldwide. The risks for this procedure are known and include complications such as tamponade, stroke, severe PV stenosis, esophageal fistula, major bleeding requiring surgery or transfusion, and death. Based on voluntary international surveys (self-reported results), the currently reported complication rate is 5.9%, with a fatal outcome in 0.1% of patients.[7, 8]

3.5 Rationale for Development of the TactiCath Set

Recent nonclinical research has shown that sufficient contact force between the ablation tip and target tissue is an important determinant of effective lesion creation, although higher contact force increases the risk for complications such as steam pop formation, thrombus formation, and perforations.[9-20] Applying the correct contact force during catheter ablation is important. Insufficient contact force may result in an ineffective procedure as the lesion remains superficial and does not achieve the required lesion depth, thereby permitting electrical reconnection and a resumption of symptoms. Conversely, excessive contact force may result in complications such as perforation of the heart wall, steam pop formation, or esophageal injury. Currently, electrophysiologists generally rely on subjective interpretation of electrocardiograms (ECGs), fluoroscopic images and handling cues to determine how much force to apply at each lesion site. Establishing a stable contact force between the catheter and the endocardial surface remains one of the key challenges in the catheter ablation procedure.

To address this need, Endosense has developed a novel contact force sensor that is embedded in the TactiCath catheter that allows measurement of the tip to tissue contact force during the RF ablation procedure. With the TactiCath Set, the physician is expected to be able to better position the ablation catheter by monitoring real-time contact force information during

mapping and ablation. It is hypothesized that lesions created with an optimal catheter contact force will improve long-term freedom from recurrence in patients.

The topic of contact force sensing during ablation is gaining international attention at an increasing rate as evidenced by the recent 15th Annual Boston AF Symposium (14 – 16 Jan 2010) at which a symposium session dedicated to this topic was presented.[21] The session made clear that in addition to Endosense, other device companies are developing contact force assisted RF ablation catheters to address this need.[22] To date, Endosense is the only company that has conducted a multi-center clinical study of an ablation catheter with an integrated force sensor, the TOCCATA study[23] (Section 3.7).

3.6 Nonclinical Testing of the TactiCath Set

Comprehensive nonclinical testing of the TactiCath Set has been performed to validate and verify the device design in support of the clinical study. Nonclinical testing consisted of functional and procedural testing in both bench and animal laboratory settings.

Additional animal studies unrelated to the Investigational Device Exemption (IDE) submission were previously conducted to characterize parameters for the safe use of the TactiCath Set including evaluations of perforation force, correlation of force with lesion size, and correlation of force with esophageal injury.[9-14,16,17,20]

3.6.1 Investigation of the TactiCath Set in an Animal Model

A study approved by the Institutional Animal Care and Use Committee (IACUC) was performed in GLP-like conditions to assess the safety and effectiveness of the TactiCath Set. Various parameters were assessed in a series of 8 animals including packaging and sterility, catheter deployment and steerability, intracardiac signal quality, compatibility with cath lab equipment, irrigated RF ablation success, force sensor functionality during mapping and ablation and visualization of contact force. The TactiCath system performed to specification while mapping all 4 chambers and delivering lesions to isolate 2 targeted pulmonary veins in each animal which remained isolated after a minimum of one hour. All animals survived the procedure with no significant adverse events such as PV stenosis, esophageal injury, cardiac tamponade, respiratory distress or uncontrollable bleeding.

3.7 Prior Clinical Experience with the TactiCath Set

The TactiCath Set was extensively studied in Europe during the TOCCATA study, which began enrollments in late 2008 and concluded follow-up in early 2010.[23] In this non-randomized, European, safety, performance and preliminary effectiveness study, 21 operators used the TactiCath Set to treat a total of 76 patients (34 AF, 27 AFL, and 15 other supra-ventricular tachycardias). Patients were followed for one year.

The primary safety endpoints of the study were met. The study characterized, for the first time, the wide range of contact forces that are typical in the course of an atrial ablation procedure. Results from the TOCCATA study were successfully submitted in support of an application for CE mark of approval granted in May 2009.

Data from the long-term follow-up of patients enrolled in TOCCATA recently presented at the Cardiostim 2010 meeting[29] describe a correlation between average contact force applied during ablation and freedom from arrhythmia recurrence at 6 months. AF Patients treated with RF ablation whose arrhythmias recurred experienced significantly lower average contact force during ablation than patients without recurrence (14.9g vs. 19.0g, p=0.039).

Unpublished data presented at this meeting updated these results to demonstrate an even more significant difference at 12 months (14.5g vs. 19.5g, p=0.01). These results suggest that a subgroup analysis may be relevant in the TOCCASTAR study to separately report on outcomes for patients with higher average contact force during ablation.

3.8 Supplemental Clinical Study

The initial randomized phase of the TOCCASTAR Study began enrollment in January of 2011 and has completed enrollment as of June 2012. The study data is expected to be submitted in an original PMA in Q3 of 2013.

In November of 2013, an IDE supplement will be submitted to request the further enrollment of up to 50 non-randomized patients using an evolutionary version of the study device known as the TactiCath Quartz Set. This device received CE mark in May of 2012 and has been used in a commercial setting outside the US since June of 2012. Prior to first clinical use in the US, a comprehensive verification and validation study will confirm the operation and robustness of the new device.

The main objective of the Supplemental Clinical Study will be to provide confirmatory evidence regarding the acute safety and effectiveness of the TactiCath Quartz Set in patients with symptomatic PAF. In principle, the TactiCath Quartz Set will provide the same therapeutic and diagnostic functionality to the operator during use as the TactiCath Set. The risks and benefits will also be the same. The new device will be evaluated in an identical patient population (inclusion and exclusion criteria) using the same procedural methodology as the randomized study.

Given the similarities in patient populations, device functionality, and procedural testing requirements, the acute procedural and 30 day safety data from the TactiCath Quartz Set may be compared with data from the TactiCath Set. Therefore, a minimum of 30 days of follow-up data on 50 subjects will be submitted for FDA review, plus any additional follow- up data available at the time of submission. Subjects enrolled in the supplemental study will comply with the same extended follow-up requirements from the randomized study (every 6 months until PMA approval) that will provide additional safety and effectiveness data from the post-assessment period through PMA approval.

Sites that agree to participate in the Supplemental Clinical Study will be required to obtain IRB approval of the Clinical Investigation Plan, Version F and the corresponding Patient Informed Consent. Subjects previously enrolled in the TOCCASTAR Study will not be affected by the protocol revision, however re-consenting of these subjects is at the discretion of the participating site.

Conduct of the Supplemental Clinical Study will conform to the initial randomized TOCCASTAR Study except where indicated. Details regarding the Supplemental Clinical Study, especially with respect to differences from the randomized study, are provided in APPENDIX J.

3.9 Continued Access Study

The last subject enrollment in the TOCCASTAR Study occurred in June 2013. This includes randomized, roll-in and Supplemental Clinical Study subjects. The TOCCASTAR Clinical Study Report was received by FDA on 29 November 2013 thus completing the PMA submission. The TOCCASTAR study submission presented preliminary evidence that the TactiCath Quartz Set is likely to be effective and that no significant safety concerns have been identified for the proposed indication of treatment of drug refractory symptomatic paroxysmal atrial fibrillation.

In January 2014, an IDE supplement will be submitted for continued access to TactiCath Quartz Set for existing investigators during the period of regulatory review of the TOCCASTAR PMA submission. The request will be for enrollment of up to 150 non-randomized patients that will be treated with the TactiCath Quartz Set under the same indication to provide confirmatory evidence of safety and effectiveness. The previous TOCCASTAR clinical protocol (Version F) and Patient Informed Consent will be modified to reflect the addition of the Continued Access Study (Version H). The devices used in the Continued Access Study will be the same as were used during the Supplemental Clinical Study.

Sites that agree to participate in the Continued Access Study will be required to obtain IRB approval of Version H of the Protocol and the corresponding Patient Informed Consent. Subjects already enrolled in the TOCCASTAR Study and the Supplemental Study will not be affected by the protocol revision, however re-consenting of existing subjects is at the discretion of the participating site.

Conduct of the Continued Access Study will conform to the initial randomized TOCCASTAR Study except where indicated. Details regarding the Continued Access Study are provided in APPENDIX K.

3.10 Summary

Based on these considerations, the Endosense TactiCath Set (TactiCath Catheter and TactiSys Equipment) may be a valuable addition to existing technology available to treat PAF and should be further studied in an IDE clinical trial.

4. INTENDED USE AND DEVICE DESCRIPTION

4.1 Intended Use

The TactiCath Set is intended to be used during ablation of PAF to perform PV isolation and to create other lesions as needed to safely and effectively eliminate undesirable arrhythmia triggers and prevent the recurrence of arrhythmia. The embedded contact force sensor provides additional diagnostic information during catheter manipulation to aid in the creation of optimal lesions.

4.2 Device Description

The TactiCath Set[24] includes the TactiCath Catheter and the TactiSys Equipment, which are described below and are illustrated in Figure 1.

Figure 1 Interconnections between the TactiCath Set and related components

4.2.1 Functionality of the TactiCath Set

The TactiCath Set has been designed to perform the following functions in the setting of a clinical electrophysiology laboratory:

- Transmitting cardiac signals for monitoring
- Transmitting pacing signals for electrophysiological study
- Transmitting RF energy to the heart wall
- Objective real time measurement and visualization of the contact force between the catheter tip and the endocardial surface
- Storing and reporting of procedural data collected from the contact force sensor and adjunctive equipment

4.2.2 TactiCath Catheter

The Endosense TactiCath Contact Force Ablation Catheter (version number PN-003 165) is a multi-electrode irrigated catheter with a deflectable tip designed to allow electrophysiological mapping of the heart and, when connected to an RF generator, to transmit radiofrequency current to the catheter tip electrode for the purpose of ablation.

RF generators to be used with TactiCath must be compatible with the functional requirements of TactiCath as specified in the TactiSys User Manual and part of a commercially approved system in the US for performing cardiac ablations.

The catheter tip has an integrated force sensor that, when used with the TactiSys Equipment, allows real-time visualization of the catheter tip contact force.

The TactiCath catheter has the same size as and is designed to be similar to other state-of-the-art open tip irrigated RF ablation catheters. The TactiCath catheter can be integrated into an existing electrophysiology lab and connected with an RF generator, cooling pump, and three-dimensional (3D) imaging systems.

4.2.3 TactiSys Components

The TactiSys Equipment includes the Base Station and Splitter, which provide standard interconnection with commonly used laboratory equipment for data processing and display. The system displays detailed force information by determining the cross product of axial and lateral force components to obtain the resultant force vector, fully describing the force at the point of contact between the catheter and tissue surface.

- **Base Station**
  The Base Station is the principal signal processing unit of the TactiCath Set. It hosts the main piece of software, TactiSoft, which collects the force sensing signal from the catheter tip and computes the force values that are shown on the display.

- **Splitter**
  The Splitter is the interface between the catheter and the Base Station, and between the catheter and the RF generator.
  The Splitter is compatible with the Endosense TactiCath Catheter PN-003 165.

4.2.4 Related Components

The following related components are required to operate the TactiCath Set but are not part of the TactiCath Set:

- RF generator
- Volumetric infusion pump
- Video display

5. STUDY PURPOSE AND OBJECTIVES

5.1 Study Purpose

The purpose of this study is to evaluate the safety and effectiveness of the TactiCath Set when used to treat PAF when compared to an approved control device. Prospective contact force data will be collected and analyzed to evaluate the importance of real-time contact force sensing during the RF ablation procedure.

5.2 Study Objectives

5.2.1 Effectiveness

To provide valid scientific evidence that use of the TactiCath Set is an effective treatment for symptomatic PAF.

5.2.2 Safety

To provide valid scientific evidence that use of the TactiCath Set is safe as measured by the incidence of early-onset serious adverse events (SAEs) when compared to the control device.

6. STUDY ENDPOINTS

The following study endpoints will be evaluated for all patients who satisfy entry criteria, are randomized, and are subsequently enrolled into the study.

6.1 Primary Endpoints

6.1.1 Effectiveness

The primary effectiveness endpoint of the study is a non-inferiority comparison of treatment success between the TactiCath Set and the control device as defined by both:

- Acute procedural success - electrical isolation of all 4 PVs, or in the event of a common PV, the clinical equivalent of all PVs, by the end of index procedure (with the device specified by the randomization arm).
- Chronic success - acute procedural success and freedom from recurrence of symptomatic AF, AFL, and AT lasting longer than 30 seconds through 9 months of follow-up after a 3 month blanking period. Re-treatment for AF with ablation or the use of Class I or Class III antiarrhythmic drugs after the blanking period constitute a treatment failure.

6.1.2 Safety

The primary safety endpoint is a non-inferiority comparison of device-related early-onset primary SAEs between the TactiCath Set and the control device occurring within 7 days of the index procedure or hospital discharge, whichever is later, and diagnosed at any time during the follow-up period. PSAEs that meet the severity criteria described in Table 2 will contribute to the primary safety endpoint only in patients in whom a study device (TactiCath or control) has been introduced.

Hospitalizations solely for arrhythmia recurrence (without coexisting conditions such as thromboembolism, worsening heart failure, etc.) will not be considered primary SAEs.

6.2 Secondary Endpoints

6.2.1 Effectiveness

The secondary effectiveness endpoints are related to the use of the contact force sensor and will assess procedural effectiveness superiority of the TactiCath Set over the control device using a hierarchical closed test procedure. It is hypothesized that the use of the contact force sensor information will result in added procedural effectiveness through a reduction of:

1. Number of electrically reconnected pulmonary veins following a 30-minute waiting period assessed by entrance block
2. Time to achieve total PV isolation measured from initial application of RF energy to all target vessels isolated
3. Total time of RF application required for full PV isolation

6.2.2 Safety

The secondary safety endpoint will evaluate the incidence of all serious adverse events during the 12-month follow-up period.

6.3 Descriptive Endpoints

6.3.1 Effectiveness

The following parameters will be reported as observational endpoints:

- Percentage of patients free of symptomatic AF episodes after treatment with combination therapy (previously failed AADs and/or ablation) after 12 months

- Percentage of patients free of symptomatic and/or asymptomatic episodes of AF after 12 months
- Freedom from AF/AFL/AT at 12 months by 24 hour Holter
- Total fluoroscopy time
- Number of RF applications
- Length of hospitalization
- Occurrence of repeat ablations (incidence and time from index procedure)
- Use of antiarrhythmic drugs
- Quality of life assessment
- TactiCath Set contact force data
  - Force distribution – distribution of forces employed during ablation per patient procedure
  - Contact force (CF) parameters during ablation including: number of ablations, average CF, standard deviation CF, minimum average CF, maximum average CF, 5th percentile average CF, 95th percentile average CF – correlate CF parameters with recurrence, time to PV isolation, acute success, and other procedural efficiency parameters
  - Force Time Integral (FTI) – correlate FTI with recurrence, time to PV isolation, acute success, and other procedural efficiency parameters
  - Trends – comparison of force data from the first third treated patients with the last third treated patients across and within centers and per operator

6.4 Subgroup Analyses

The primary and secondary safety and effectiveness endpoints will be compared (via superiority testing) between the control group and a subgroup of patients from the TactiCath arm whose average contact force during ablation was ≥ 20 g.

7. STUDY DESIGN

TOCCASTAR is a prospective, randomized, multicenter, interventional study to evaluate the safety and effectiveness of the TactiCath Set for the treatment of symptomatic PAF using contact force assisted irrigated RF ablation.

Patients undergoing elective catheter ablation for symptomatic PAF who are refractory or intolerant to at least one antiarrhythmic drug (Class I-IV) will be enrolled. Patients who meet the study entry criteria and sign the patient informed consent form will be enrolled and treated following the HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation for Atrial Fibrillation.[3]

Eligible patients will be randomly assigned 1:1 to receive treatment with either the TactiCath Set or the control device (the NaviStar® ThermoCool® open irrigated RF ablation catheter manufactured by Biosense Webster, Inc.) Use of 3D mapping equipment will be required in both treatment groups. Patients will be blinded to treatment assignment. This study aims to

demonstrate non-inferiority of the study device to the control device for both safety and effectiveness.

If chronic success is determined to be less than 40% for either the treatment group or the control group, additional exploratory analyses focused on explaining the suboptimal results will be performed.

7.1 Investigational Sites

Up to 30 sites in the United States and elsewhere will be invited to participate in the study. Investigators will be selected from the electrophysiology specialty and will agree to comply with all aspects of the investigational protocol. Use of adjunctive equipment will be limited to devices approved in the US unless approved for use as part of a sub-study.

7.2 Study Population

The trial will be conducted in 300 randomized patients with symptomatic PAF (150 patients per treatment group) who are refractory or intolerant to at least one antiarrhythmic drug (Class I-IV). A maximum of 50% of patients may be enrolled outside the US.

Eligible patients will be included in the study as they become available. Treatments will be randomly assigned (Section 10.2.2). Patients will remain blinded to their treatment assignment throughout the study (Section 10.2.3).

Subjects who sign an informed consent and satisfy all pre-operative entry criteria will be considered for randomization and treatment. Consented subjects who do not satisfy entry criteria are screen failures and will not receive treatment under this protocol. Those screen failures will conclude their participation in the study without further follow-up or data collection activities.

Subjects in whom PVI is contraindicated based on an intra-operative finding such as AVRT/AVNRT will be excluded from the primary endpoint analyses. These subjects will be followed for safety only. Data from these subjects will be reported separately.

7.3 Roll-in Patient Procedures

To allow for a period of familiarization with the unique features of the TactiCath Set, each site will be permitted to use the study device in up to 5 patients that are not randomized in the study, up to 100 total roll-in patients. The roll-in patient population will be screened, consented, and treated with the TactiCath Set, and followed per protocol for 12 months.

Data from patients who participate in roll-in procedures will be excluded from the primary endpoint analyses. Data from the roll-in population will be reported separately in the study report.

7.4 Supplemental Clinical Study Procedures

As a supplement to the original TOCCSTAR Study, up to 50 additional non-randomized patients will be enrolled in a Supplemental Clinical Study. For the purposes of screening, consent, treatment and follow-up, these subjects will be treated identically to the roll-in patient population (with the exception of CT/MR scans that are no longer required). Details regarding the Supplemental Clinical Study procedures are provided in APPENDIX J.

7.5 Continued Access Study Procedures

During the Continued Access phase of the study, up to 150 additional non-randomized patients will be enrolled. These subjects must meet the same enrollment criteria, undergo the same consent process, same treatment and follow-up as the initial randomized TOCCASTAR Study with the following exceptions:

- CT/MR scans are recommended but not required
- Ambulatory monitoring with TTM is no longer required and is replaced with additional instances of Holter monitoring at 3, 6, and 12 months

Details regarding study procedures during the Continued Access Study are provided in Appendix K.

7.6 Study Assessment Intervals

For the purpose of assessing study endpoints, patients will be followed for a total of 12 months after the index procedure beginning with a 3-month blanking period and ending with a 9-month effectiveness assessment period. During the blanking period, patients may be prescribed a previously ineffective antiarrhythmic drug and undergo up to 2 repeat ablation procedures (up to 10 days prior to end of the blanking period) using the device specified by the initial randomization. Enrolled patients will be evaluated according to the HRS/EHRA/ECAS Expert Consensus Statement[3] at pre-discharge, at 7 days, and at 3, 6, and 12 months post-index procedure. After the 12-month follow-up, patients will be contacted periodically (every 6 months until the post market approval (PMA) is granted, and if approved, thereafter according to post-approval requirements) to assess general health and well-being.

Assuming approximately 12 months for patient enrollment and a 12-month follow-up period per patient (including a 3-month blanking period), this study is expected to require approximately 24 months to complete.

When FDA approves a device for commercial use in the United States, they often ask that patients in the clinical trial agree to continue monitoring for several more years to confirm the long-term results of the study. If this occurs, the study will extend for up to 5 years from the time of the initial procedure. FDA has stipulated that informed consent will include participation in the Toccastar study as well as a possible post-approval study that may be specified by FDA at a later date.

7.7 Patient Withdrawal

All patients are free to withdraw from participation in this study at any time, for any reason, and without prejudice.

Patients may be withdrawn from the study for any of the following reasons:

- Patient requests early discontinuation
- Patient is lost to follow-up

The clinical investigator may terminate a patient from the study at any time for lack of therapeutic effect that is intolerable to the patient, or otherwise considered unacceptable, for intolerable or unacceptable AEs, intercurrent illness, noncompliance with study procedures, administrative reasons, or in the clinical investigator's opinion, to protect the patient's best interest.

Patients who request early discontinuation will be considered as having withdrawn consent only after they have signed the Withdrawal of Consent Form. Patients who withdraw consent will receive standard of care treatment.

The clinical investigator will make every effort to collect information about patients who are lost to follow-up.

If a patient is withdrawn before completing the study, the reason for withdrawal (assuming the patient is willing and able to share this information) will be entered on the Study Completion Form. Patients who withdraw before completing the study will be followed only through the date of their withdrawal.

In addition, any comments (spontaneous or elicited) or complaints made by the patient or physician caring for the patient but not involved in the investigation will be documented on the eCRF.

8. CRITERIA FOR ELIGIBILITY

8.1 Inclusion Criteria

A patient will be eligible for study participation if he/she meets the following criteria:

1. Patient is planned to undergo a catheter ablation procedure due to symptomatic PAF that is refractory or intolerant to at least one Class I-IV antiarrhythmic drug
2. Minimum of one episode of PAF greater than 30 seconds in duration within 12 months prior to enrollment documented by 12-lead ECG, Holter monitor, transtelephonic event monitor, telemetry strip, or implanted device
3. Minimum of 3 episodes of PAF within the preceding 12 months documented by patient history
4. Patient is 18 years of age or older
5. Patient is willing and capable of complying unassisted with the study protocol requirements including all specified follow-up visits
6. Patient provides written informed consent prior to enrollment in the study

8.2 Exclusion Criteria

A patient will be excluded from the study if he/she meets any of the following criteria:

1. Persistent or long-standing persistent AF
2. Patient has had 4 or more cardioversions in the last 12 months
3. Active systemic infection
4. Presence of implantable cardiac defibrillator (ICD)
5. Arrhythmia due to reversible causes including thyroid disorders, acute alcohol intoxication, and other major surgical procedures in the preceding 3 months
6. Myocardial infarction (MI), acute coronary syndrome, percutaneous coronary intervention (PCI), or valve or coronary bypass grafting surgery within the preceding 3 months
7. Left atrial diameter > 5.0 cm
8. Left ventricular ejection fraction < 35%
9. New York Heart Association (NYHA) class III or IV (Appendix G)
10. Previous left atrial ablation procedure, either surgical or catheter ablation
11. Patient has had a left atrial surgical procedure or incision with resulting scar
12. Previous tricuspid or mitral valve replacement or repair
13. Heart disease in which corrective surgery is anticipated within 12 months

14. Bleeding diathesis or suspected pro-coagulant state
15. Contraindication to long-term antithromboembolic therapy
16. Presence of condition that precludes appropriate vascular access
17. Renal failure requiring dialysis
18. Known sensitivity to contrast media (if needed during the procedure) that cannot be controlled with pre-medication
19. Contraindication to computed tomography and magnetic resonance angiography procedure
20. Severe pulmonary disease (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces severe chronic symptoms
21. Positive pregnancy test results for female patient of childbearing potential
22. Patient has other anatomic or co-morbid conditions that, in the investigator's opinion, could limit the patient's ability to participate in the study or to comply with follow-up requirements, or impact the scientific soundness of the study results
23. Patient is currently participating in another clinical trial or has participated in a clinical trial within 30 days prior to screening that may interfere with this study
24. Patient is unlikely to survive the protocol follow-up period of 12 months

9. SCHEDULE OF ACTIVITIES

The study began in the first quarter of 2011 (Q1 2011), when the first patient was enrolled. Recruitment of all patients, including roll-in patients, was completed in Q1 2012.

Evaluation of patients enrolled in this study will include all tests and procedures listed in the Schedule of Activities (Table 1). See Appendix K for the study details for subjects enrolled into the Continued Access Protocol.

Table 1 Schedule of Activities

	Baseline	Procedure	Pre-discharge	7 days ± 2 days Telephone	3 months ± 2 weeks	6 months ± 3 weeks	12 months ± 3 weeks	Extended every 6 mos ± 4 weeks
Informed consent	X							
Inclusion/exclusion	X							
Documentation of PAF episodes	X							
Medical history	X							
Thyroid and renal function (standard practice)	X							
PT/PTT or INR	X		X					
Physical examination,vital signs, height, weight[a]	X		X		X	X	X	
Pregnancy test (women of childbearing potential)	X							
12-lead ECG	X		X		X	X	X	
Cardiac medications	X		X	X	X	X	X	
NYHA functional class	X				X	X	X	
Quality of life survey	X						X	X
Randomization	X							
Activated clotting time		X						
Ablation procedure data		X						
Force Sensing data (TactiCath treatment group)		X						
Arrhythmia events	X		X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X[f]
Protocol deviation	X	X	X	X	X	X	X	
TEE (ICE)[b]	X	(X)						
TTE (recommended)[c]	X		(X)					
CT or MRI scan[d]	X				X			
Transtelephonic monitoring[e]					X	X	X	
Holter monitoring							X	
Arrhythmia history								X

Abbreviations: CT = computed tomography; ECG = electrocardiogram; INR = international normalized ratio; MRI = magnetic resonance imaging; NYHA = New York Heart Association; PAF = paroxysmal atrial fibrillation; PT = prothrombin time; PTT = partial thromboplastin time; TEE = trans-esophageal echocardiography; ICE = intra-cardiac echocardiography. NOTES: a.Weight and height will be assessed at baseline only. b.TEE within 24 hrs or ICE at time of procedure to exclude atrial thrombus. c.TTE within 6 mos to measure left atrial dimension. Recommended within 24 hrs post procedure to exclude pericardial effusion. d.Not required for supplemental study subjects. If evidence of stenosis is seen at 3 mos, the investigator may prescribe additional serial scans. e.TTMs weekly for months 4 and 5, monthly for months 6-12, and as needed to document symptomatic episodes. f.survival and hospitalizations only.

10. STUDY PROCEDURES

Cardiac medications and protocol deviations will be recorded from the time of signing the informed consent through the date of study completion or withdrawal.

10.1 Screening and Informed Consent Procedures

When a suitable candidate requiring ablation for PAF presents for consideration for enrollment in the study, the investigator will explain the potential risks and benefits of participation to the patient. Patients will be provided with a copy of the informed consent for review and will be given ample opportunity to read and pose questions they may have about the study. If after review, the patient agrees to participate, the informed consent will be signed by the patient and recorded on a screening/enrollment log. If a patient subsequently fails to meet eligibility criteria, they will be considered a screening failure and may receive standard of care for their condition outside of the study.

10.2 Pre-treatment Procedures

10.2.1 Baseline Evaluations

The following baseline evaluations will be performed for eligible patients within 30 days (or as indicated) prior to the planned treatment procedure.

1. Written informed consent
2. Evaluation of inclusion/exclusion criteria
3. Documentation of 3 symptomatic PAF episodes and one PAF episode > 30 seconds evidenced by ECG tracing (any source) within 12 months
4. Medical history, including demographics, arrhythmia diagnosis, cardiovascular risk factors, cardiac medication
5. Arrhythmia history - patient should be refractory or intolerant to at least one Class I-IV antiarrhythmic drug
6. General physical examination including vital signs, height, and weight
7. Prothrombin time (PT)/ partial thromboplastin time (PTT) or international normalized ratio (INR) following standard clinical practice
8. Blood tests of thyroid and renal function following standard clinical practice
9. 12-lead ECG
10. Determination of the NYHA functional class
11. Quality of life assessment

12. Assessment of atrial thrombus. Either via trans-esophageal echocardiography (TEE) within a period of 24 hours prior to the treatment procedure or, intracardiac echo (ICE) at the time of the procedure in patients currently in normal sinus rhythm with no history of cerebrovascular accident.
13. Location, morphology, and dimensions of PVs using computed tomography (CT) scan or magnetic resonance imaging (MRI) within 60 days (recommended but not required for Supplemental Clinical Study and Continued Access Study subjects)
14. Assessment of left atrial diameter via trans-thoracic echocardiography (TTE) within a period of 6 months prior to the treatment procedure
15. Negative pregnancy test results for female patients of childbearing potential (following the site's usual practice)

10.2.2 Randomization

Patients who complete required baseline evaluations and meet eligibility criteria for the study may be enrolled. Randomization to treatment arm is accomplished by the investigator using an Interactive Web Response System. Patients recruited into the roll-in patient population will not be randomized. (Subjects participating in the Supplemental Clinical Study and Continued Access Study will not be randomized.)

10.2.3 Blinding to assigned treatment

All patients will be blinded to treatment assignment. Study personnel, who may be unblinded, should not disclose any treatment information to the patient prior to unblinding of study data.

10.3 Ablation Procedure

The following procedural requirements apply to all ablation procedures conducted during the study:

1. An approved 3D mapping system will be used in all procedures consistent with device labeling in the case of the control device and with any compatible system in the case of the TactiCath Catheter.
2. If TEE was not performed within the past 24 hours to assess atrial thrombus, an ICE assessment must be performed at the time of the procedure. In case of a positive finding, the procedure will be postponed and the patient placed on anticoagulation until freedom from thrombus can be confirmed.
3. Enrollment, treatment, and peri-procedure follow-up of AF patients will conform to the HRS/EHRA/ECAS Expert Consensus Statement[3] including a treatment strategy to isolate all PVs.
4. A standard treatment scheme of mapping and ablation will be conducted during the interventional procedure followed by confirmation of entry block at 30 minutes after full

isolation of all PVs. In addition, IV isoproterenol (up to 20 μg/min) should be infused to test for both induced non-PV triggers and to elicit latent PV conduction.

5. Any prior existing or induced supra-ventricular arrhythmia indicated for treatment with ablation should be treated as part of the PV isolation index procedure unless clinically contra-indicated. Pre-existing or induced typical AFL should be treated with ablation of the cavo-tricuspid isthmus line. If atypical flutter is induced, the decision to ablate is at the discretion of the physician.
6. All ablations in the left atrium must be performed using the device specified by randomization. Use of a different device in the left atrium constitutes an acute treatment failure.
7. In the absence of a clinical or induced arrhythmia, additional ablation lesion sets (e.g., prophylactic linear lesions, ablation of CFAE sites, etc.) should not be performed.
8. PVI may be omitted if contraindicated in the judgment of the investigator in patients presenting with AVRT/AVNRT.
9. In the TactiCath treatment group, contact force data will be provided to the operator and collected throughout the procedure. Intermittent catheter tip contact should be avoided during lesion creation.
10. Ablation should be performed with the minimum power needed in the judgment of the investigator. The maximum RF power during ablation using the TactiCath study device is limited to 40W. Use of the control study device should follow the approved labeling and instructions for use.
11. A multipolar “lasso” type mapping catheter will be deployed in the target vein pre- and post-ablation to monitor PV potentials.
12. Catheters will be irrigated at a continuous rate of 2 ml per minute (ml/min) when not ablating, and during ablation at a minimum of either 17 ml/min (RF power up to 30W) or 30 ml/min.
13. The integrity of the phrenic nerve should be evaluated before and after ablation of the right superior PV. In patients who are breathing spontaneously (not under general anesthesia), observe normal diaphragmatic excursion of the right hemi-diaphragm under fluoroscopy. In patients under general anesthesia, verify phrenic nerve functionality by placing a catheter in the lateral SVC and pacing the phrenic nerve.
14. The lower level of anticoagulation should be maintained at an ACT of at least 300 throughout the procedure, and higher targets (up to 400) may be used as indicated.
15. Physicians are required to use each study device according to labeling and in a manner consistent with their standard clinical practice. In particular, the operator must not adapt or otherwise deviate from ablation technique normally employed when using the control device.

10.3.1 Peri-procedure Safety Recommendations

Consistent with data published in the HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation for Atrial Fibrillation,[3] the following peri-procedure precautions are strongly recommended to minimize risks to patient safety:

- Esophageal temperature monitoring – it is strongly recommended that esophageal temperature be monitored using an esophageal temperature probe at the anatomical location nearest the site of energy delivery.
- Intracardiac echocardiography (ICE) – use of an ICE probe during the procedure to guide septal puncture and to monitor catheter position and manipulation is strongly recommended.
- RF power settings in the TactiCath group – it is generally feasible to increase contact force rather than RF power, if needed, to produce an adequate lesion depth. RF power may be titrated downwards based on increased contact force according to the clinical judgment of the operator. In the TactiCath group, it is recommended that RF ablation be performed at an average contact force of approximately 20 grams.
- Arrhythmia identification – it is recommended that a coronary sinus (CS) catheter be deployed past the Veussen's valve (into the great cardiac vein) to provide arrhythmia identification, linear lesion assessment, etc. Use of a diagnostic catheter in the right atrium (RA) is also recommended.

10.4 Pre-discharge Procedure

Post-interventional medication and treatment will be implemented according to the HRS/EHRA/ECAS Expert Consensus Statement.[3]

The following post-treatment evaluations will be performed within 72 hours (or as indicated) after the treatment procedure and before discharging the patient:

- TTE within 24 hours post-procedure is recommended to exclude pericardial effusion
- General physical examination including vital signs
- PT/PTT or INR following standard clinical practice
- 12-lead ECG
- Recording of any cardiac medications, arrhythmia events, AEs, or protocol deviations

10.5 Follow-up Procedures

For the purpose of assessing study endpoints, patients will be followed for a total of 12 months after the index procedure beginning with a 3-month blanking period and ending with a 9-month effectiveness assessment period. During the blanking period, up to 2 additional RF ablation procedures may be performed (up to 10 days prior to end of the blanking period) and patients may be prescribed previously ineffective antiarrhythmic drugs. Patients indicated for a repeat procedure will be treated according to their initial randomization group.

Patients with treatment failure after the 3-month blanking period (i.e., symptomatic arrhythmia recurrence, re-treatment for AF with ablation, cardioversion for AF/AFL/AT, the use of Class I or Class III antiarrhythmic drugs.) and patients with more than 2 repeat ablations during the blanking period, will be followed per protocol but assessed for safety only.
Subjects who experience a documented symptomatic episode of AF/AFL/AT (lasting longer than 30 seconds) during the 9-month effectiveness assessment period will be classified as a treatment failure. Documentation of the episode by standard 12 lead ECG recording may be shorter than 30 seconds in duration.

Patients who do not experience treatment failure will undergo the following assessments described below at 7 days, at 3, 6, and 12 months post-index procedure, and every 6 months thereafter. Following the conclusion of the study, FDA may require a period of continued follow-up (Post-approval Study) that will last up to 5 years from the time of the initial procedure. Patients who withdraw before completing the study (Section 7.7) will be followed only through the date of their withdrawal.

To avoid deviation from protocol, follow-up procedures must be completed during a window of time specified by the target date (time post-index procedure) and occurring within a fixed number of days/weeks before and after as described below. The schedule for follow-up procedures is determined by the date of the initial ablation procedure. Retreatment at any time will not 'reset the clock' for follow-up.

10.5.1 7-Day Follow-up Procedure

At 7 days post-index procedure (± 2 days) or at hospital discharge, whichever is later, patients will be contacted via telephone by the investigator for a safety assessment. The following data will be collected:

- Cardiac medications
- Arrhythmia events
- Adverse events
- Protocol deviations

10.5.2 3-Month Follow-up Procedure

At 3 months (± 2 weeks) post-index procedure, the following evaluations will be scheduled and data will be recorded:

- Imaging study (CT scan or MRI, consistent with pre-treatment method, recommended but not required for Supplemental Clinical Study and Continued Access Study subjects)
- Physical examination and vital signs
- Cardiac medications
- NYHA functional class
- Arrhythmia events
- Adverse events

- 12-lead ECG
- Protocol deviations

10.5.3 6-Month Follow-up Procedure

At 6 months (± 3 weeks) post-index procedure, the following evaluations will be scheduled and data will be recorded:

- Physical examination and vital signs
- Cardiac medications
- NYHA functional class
- Arrhythmia events
- Adverse events
- 12-lead ECG
- Protocol deviations

10.5.4 12-Month Follow-up Procedure

At 12 months (± 3 weeks) post-index procedure, the following evaluations will be scheduled and data will be recorded:

- 24-hour Holter monitoring (Section 10.8.2)
- Physical examination and vital signs
- Cardiac medications
- NYHA functional class
- Arrhythmia events
- Adverse events
- 12-lead ECG
- Quality of life questionnaire
- Protocol deviations

10.5.5 Extended Follow-up Procedure

At every 6 months (± 4 weeks) following the effectiveness assessment period and until the device is approved, patients will be contacted via telephone by the investigator for a general health assessment. The following data will be collected:

- Adverse events (related to survival and cardiac-related hospitalization)
- Arrhythmia history

10.5.6 Post-approval Study

If deemed necessary by FDA, the requirements for a post-approval study will be specified by FDA at the time of device approval and will likely include periodic contacts with patients to assess general health and well-being.

10.6 Re-ablation Procedure

10.6.1 Retreatment During the Blanking Period

Patients may be re-treated with ablation up to two times during the blanking period but no later than 10 days before the end of the blanking period. Re-treatment during this interval will not constitute a treatment failure and must be performed with the device specified by the initial randomization.

10.6.2 Retreatment After the Blanking Period

Re-treatment after the blanking period will constitute a treatment failure. All re-ablation procedures after blanking must be performed with a commercially available device labeled for use in the US for the treatment of AF, e.g. the control device.

10.7 Imaging for PV Stenosis

If evidence of PV stenosis is seen at the 3-month follow-up when compared to the baseline scan, it is recommended that the subject undergo additional serial CT/MRI scans as deemed clinically appropriate by the investigator.

10.8 Ambulatory Monitoring

Ambulatory monitoring for symptomatic and asymptomatic episodes of AF will be conducted throughout the 9-month effectiveness assessment period.

10.8.1 Transtelephonic Monitoring

Patients will be issued a transtelephonic monitoring (TTM) device one month after the ablation procedure. They will be instructed to transmit an ECG weekly beginning with the 3-month follow-up until 5 months after the index procedure, and then monthly until the end of the study. In addition to these recurring scheduled transmissions, patients will be instructed to record and transmit an ECG coincident with any occurrence of symptoms associated with AF at any time during follow-up. A core laboratory will review each recording and report findings to the investigator.

10.8.2 Holter Monitoring

Patients will be issued a Holter monitor at the 12-month follow-up and instructed to obtain a 24-hour recording. A core laboratory will review each recording and report findings to the investigator.

10.9 Antiarrhythmic Drug Management

10.9.1 Blanking Period

It has been shown that AAD treatment during the 6 weeks after ablation for paroxysmal AF reduces the risk for early recurrence of atrial arrhythmias and the need for hospitalization or cardioversion.[26] It is recommended that any current antiarrhythmic medication be continued following the ablation procedure.

Current AADs may be withdrawn 4-6 weeks after ablation to assess for recurrence of symptoms and the necessity for re-ablation during the blanking period.

If documented symptomatic AF recurs during the 3 month blanking period and the patient requires antiarrhythmic drug therapy, a previously ineffective but tolerated antiarrhythmic drug may be re-initiated to allow for the assessment of its effectiveness when combined with ablation.

10.9.2 Effectiveness Assessment Period

All Class I and Class III AADs will be discontinued at the end of the blanking period. The use of any Class I or Class III antiarrhythmic drug during the effectiveness assessment period will be considered an effectiveness failure. Subjects enrolled in the Continued Access Study may be prescribed previously used Class I or Class III antiarrhythmic drugs.

Beta-blockers, calcium channel blockers or digitalis may be used during the 9-month effectiveness assessment period if prescribed for reasons unrelated to arrhythmia management. Subjects are encouraged to continue their use through the end of the study unless it is determined to be unnecessary or detrimental by the investigator.

Subjects who experience a recurrence of symptomatic PAF after the blanking period (treatment failure) should retry a previously failed AAD before a new medication is prescribed to evaluate the effectiveness of combined ablation and drug therapy.

10.10 Anticoagulant Drug Management

Anticoagulant drug regimen will follow the HRS/EHRA/ECAS Expert Consensus Statement.[3] Warfarin is recommended for all patients following the AF ablation procedure. For patients with a CHADS (congestive heart failure, hypertension, age > 75 years, type 2 diabetes, prior stroke or transient ischemic attack) score ≥ 2, continued use of warfarin is recommended.

10.11 Early Termination Evaluation

No formal early termination procedures will be conducted. Patients who withdraw before completing the study (Section 7.7) will be followed only through the date of their withdrawal.

11. PATIENT BENEFITS AND RISKS

A risk analysis (per ISO 14971) of the medical device has been conducted through appropriate design control and confirmed by nonclinical bench, laboratory, and animal testing to minimize risks to the patient.

11.1 Potential Benefits to Study Subjects

Receiving benefit from participation in the study is not guaranteed. Anticipated benefits to patients may include, but are not limited to, the following:

- Patients who receive treatment with the study device may experience shorter ablation procedure time and improved outcomes, although these objectives may not be demonstrated in this study
- Patients who participate in the study may receive more frequent and/or detailed follow-up than is normally prescribed as standard of care in any given practice
- Overall advancement of medical and scientific knowledge may benefit future patients with similar conditions

11.2 Potential Risks to Study Subjects

Risks to patients enrolled in this study include all those risks currently associated with all electrophysiology diagnostic procedures and RF catheter ablation procedures. The risks of the procedure are related primarily to mechanical injury to the heart and vessels from catheter manipulation and thermal injury due to RF current delivery, including the risk of thromboembolism and myocardial perforation, especially for ablations in the left atrium.

For those procedures where the physician applies sedation or anesthesia, the standard risks of anesthesia also exist and include allergic reactions, pneumonia, aspiration pnuemonitis, atelectesis, prolonged sedation, other medical complications and in very rare cases, death.

Complications associated with the use of the TactiCath Set may be related to the device or the procedure and they may include, but are not limited to the SAEs listed in Table 2 and the other AEs listed in Table 3.

11.3 Clinical Events Committee

An independent standing clinical events committee (CEC) consisting of members not otherwise associated with the trial, while blinded to treatment assignment, will review all SAEs and will adjudicate causality relative to the primary safety endpoints. The mode of operation of the CEC will be defined in a CEC Charter. Contact information for the CEC is provided in Appendix C.

11.4 Clinical Risk Analysis

11.4.1 Increased Risks to Subjects Posed by the Investigation

All patients who are enrolled in the study will undergo pre-procedure testing that is considered standard of care at the participating institution. The investigator is obliged per protocol to perform the ablation procedure in a manner consistent with device labeling and with their standard clinical practice. Subjects may be randomized to receive treatment with the TactiCath Set whose safety has not been assessed in a prospective, randomized trial.

At most participating sites, patient follow-up procedures required per protocol are consistent with standard of care with the possible exception of an additional diagnostic scan at three months post-procedure and the use of diagnostic ambulatory monitoring throughout the follow-up period.

The risks associated with the three month scan are the same as those for the baseline scan. For CT scans, the exposure to x-rays potentially increases the risk for cancer. For MR scans, the exposure to injected contrast agent may cause an allergic reaction. Risks associated with the use of an ambulatory monitor (TTM or Holter) may include abrasion of the skin from the recording electrodes.

The addition of a diagnostic contact force sensor is not expected to introduce new procedural risks. Unexpected failure of this diagnostic feature should not interfere with other functional aspects of the device related to mapping, pacing and RF energy delivery. In the TOCCATA study, [23] patients treated with the TactiCath Set for AF experienced similar or less serious adverse events than the historical control (12% vs. 16.8%, n=34).

In summary, the increased risks to which subjects will be exposed by the investigation are limited to the risk that they may be treated with an unproven device and that they may be exposed to additional follow-up testing as described above.

11.4.2 Manner in Which Risks Will be Minimized

A risk analysis of the TactiCath Set has been conducted according to ISO 14971 Application of Risk Management to Medical Devices. Precautions have been taken to minimize or eliminate risks through appropriate design controls as confirmed by nonclinical bench, laboratory and animal testing. In addition, a multi-center, non-randomized prospective clinical safety and performance study was conducted in Europe, the TOCCATA study.[23] In this study, 76 patients (34 AF, 27 AFL, and 15 other supraventricular tachycardias) were treated with a TactiCath catheter (version number PN-001 065) and followed for one year. The safety endpoints of this study were met and used to support a successful application for CE mark in May 2009.

Patients treated with the study device will undergo an established procedure for which published guidelines exist[1-4] and whose outcomes are documented in the literature.[7-8, 27] The procedural and follow-up requirements and recommendations within this clinical investigational plan reference these guidelines with the intention that patients will be managed consistently.

Risks associated with the three month scans will be minimized by excluding patients from the study with a known contraindication to computed tomography or magnetic resonance angiography.

Risks associated with the ablation procedure will be minimized by requiring operators to assess for atrial thrombus prior to ablation, to employ an approved 3D mapping system, to maintain adequate irrigation and appropriate anti-coagulation, and to monitor for potential injury to the esophagus and phrenic nerve as part of the procedure.

In addition, participating sites have been chosen for their demonstrated proficiency with both 3D mapping systems that will be used (Carto and NavX) and will be trained extensively on the requirements of the protocol. Field clinical engineers trained in the use of the study device and the requirements of the protocol may monitor ablation procedures in the study. Sites will be monitored soon after enrollment begins to identify and address protocol deviations and unsafe practices, if any exist, in a timely manner.

Frequent personal contact with subjects throughout the follow-up period by the investigator and by TTM monitors trained to elicit patient complaints will help identify patients in need of medical care.

11.4.3 Justification for the Investigation

The availability of contact force data during catheter manipulation is intended to guide the safe and effective creation of ablation lesions by providing essential feedback to the operator related to catheter placement.

The TactiCath catheter closely resembles a standard irrigated RF ablation catheter with respect to design, materials and usage. The incorporation of a diagnostic contact force sensor in the distal tip is an incremental feature with potential implications for improved safety and effectiveness. If desired, the force sensor data may be disregarded and the device may be employed similarly to a standard, commercially available RF ablation catheter.

The high rate of arrhythmia recurrence in this population has been shown to be the result of restored conduction between previously isolated pulmonary veins and the left atrium. Patients with recurrence frequently undergo one or more repeat ablation procedures, subjecting them to repeated procedural risks.

Electrical reconnection is believed to result from inadequate lesion formation during ablation. Contact force measured between the ablation catheter tip and the tissue being ablated may be used to position the catheter to produce a sufficiently transmural lesion and theoretically promote better long-term isolation of the PVs.

The TOCCATA study demonstrated safety in a small population (n=76) and showed a correlation between higher contact force and freedom from recurrence. Based on these considerations, the clinical investigation of the TactiCath Set is justified.

11.4.4 Description of Patient Population

A pre-defined sample of patients prescribed for PAF will be enrolled such that a statistically valid result may be obtained. In general, the distribution of age and gender is expected to reflect the incidence of PAF in the US and Europe with mean age in the mid to upper 50s and approximately one third female subjects.

Per protocol, all subjects will have failed one or more anti-arrhythmic medications and will have symptoms during AF. Thus, the patient population being studied will be indicated for further treatment with ablation according to published guidelines.

11.4.5 Adverse Events

The definitions for adverse events, adverse device effects and unanticipated adverse device effects are provided in section 12.1 of the protocol. A tabulation of adverse events and the criteria that will be used to assess severity is provided in section 12.2 of the protocol. Potential adverse events that may be associated with the ablation procedure are provided in section 12.3 of the protocol. Sponsor and investigator obligations for reporting adverse events are described in section 12.4 of the protocol.

11.5 Conclusion

An extensive Risk Analysis and Risk Mitigation plan has been implemented to minimize any residual risk of the TactiCath Set to the patient.

Hands-on training opportunities will be provided for operators who are unfamiliar with the study device. These may include simulations, using the study device in the nonclinical setting, or the observation of clinical use of the study device by experienced operators.

We believe that the availability of catheter contact force information during a procedure may convey a benefit to the patient and outweigh any potential residual risk.

12. ADVERSE EVENTS

12.1 Definitions

12.1.1 Adverse Events

An AE is defined as any untoward medical occurrence in a patient. This definition does not imply that there is a relationship between the adverse event and the device under investigation.

An AE will not be reported if it existed at enrollment and continued unchanged thereafter unless the event worsened considerably and required additional medical or pharmacological treatment. Investigators in this study are required to report all AEs except for the following:

- **Standard follow-up or exacerbation of pre-existing conditions unrelated to the cardiovascular system** including diabetes, cancer/tumors, multiple sclerosis, allergies, osteoporosis, arthritis, emphysema, vision or aural problems and rectal polyps.

- **Physical trauma determined to be unrelated to the ablation procedure** including pain due to musculoskeletal injuries, muscle aches due to over-exertion, joint degeneration, tendonitis and bursitis and burns from external causes.

- **Newly developed disease or illness unrelated to AF, the ablation procedure, a study device or the drugs used to treat cardiovascular illness** including gastrointestinal ulcers, hemorrhoids, immune system deficiencies like HIV or AIDS, infectious diseases like hepatitis or herpes viruses, neurological/psychological disorders such as Alzheimer's, Parkinson's, dementia, obsessive/compulsive or eating disorders. Other illness, if clearly isolated from the cardiovascular disease, including jaundice unrelated to systemic infection, infection in extremities unrelated to the procedure, bacterial infection or cellulitis.

- **Common ailments unrelated to the cardiovascular system, the ablation procedure, a study device or the drugs used to treat cardiovascular illness** including common headache, muscle pain, food poisoning, superficial infections, rashes, warts, shingles, constipation, eczema, hernias, upper respiratory infections or influenza.

12.1.2 Adverse Device Effects

An ADE is defined as any untoward and unintended response to a medical device. This definition includes any event resulting from insufficiencies or inadequacies in instructions for use or deployment of the device. This definition also includes any event that is a result of user error.

12.1.3 Serious Adverse Events

All SAEs will be reported. An SAE is defined as any event that

1. Leads to death,
2. Leads to serious deterioration in the health of a patient that:
   a. Results in a life-threatening illness or injury,
   b. Results in a permanent impairment of a body structure or a body function,
   c. Requires in-patient hospitalization or prolongation of existing hospitalization,
   d. Results in medical or surgical intervention to prevent permanent impairment to a body structure or a body function.
3. Leads to fetal distress, fetal death, or a congenital abnormality or birth defect.

12.1.4 Serious Adverse Device Effects

A serious adverse device effect (SADE) is defined as an ADE that results in any of the consequences characteristic of an SAE or that may lead to any of these consequences if suitable action is not taken or intervention is not made or if circumstances are less opportune.

12.1.5 Unanticipated Adverse Device Effects (United States sites only)

An unanticipated ADE is defined as any SADE on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death has not been previously identified in nature, severity, or degree of incidence in the CIP or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

12.2 Primary Serious Adverse Events

Primary serious adverse events (PSAEs) related to the use of a study device (TactiCath or control) are defined as having occurred within 7 days of the ablation procedure or prior to pre-discharge, whichever is later, and diagnosed at any time during the follow-up period.

PSAEs that meet the severity criteria described in Table 2 will contribute to the primary safety endpoint only in patients in whom a study device has been introduced. Hospitalizations solely for arrhythmia recurrence (without coexisting conditions such as thromboembolism, worsening heart failure, etc.) will not be considered primary SAEs. PSAEs include but are not limited to:

Table 2 Primary Serious Adverse Events

Primary Serious Adverse Event	Severity Criteria
Atrial perforation	Visible (either with radiographic and/or ultrasonagraphic imaging and/or direct visualization) movement of ablation catheter, needle or sheath through the atrial wall as evidenced by bleeding and the need for pericardial drainage or surgical intervention
Death	Adverse event resulting in patient death
Diaphragmatic paralysis	Change in baseline diaphragmatic function as evidenced by elevation of a hemi-diaphragm above its normal position or loss of normal respiratory excursion but not due to a pulmonary process such as atelectasis and persisting longer than the end of the procedure
AV block	New, persistent 2nd or 3rd degree AV block not attributable to a vasovagal reaction or

	medication effect and requiring permanent pacing
Gastroparesis	Gastroparesis as a result of ablation requiring intervention or hospitalization
Hospitalization (initial or prolonged)	Adverse event leading to new hospital admission or extension of initial hospital stay beyond expected timeframe due to ablation procedure-related cause. Excludes hospitalization solely for arrhythmia recurrence.
Left-atrial-esophageal fistula	Creation of a direct communication (fistula) between the left atrium and esophagus necessitating surgical intervention or resulting in permanent impairment (e.g. due to hemorrhage or septic emboli)
Myocardial Infarction	Requires 2 of the following 3 criteria: • Elevation of biochemical markers of myocardial necrosis (preferably troponin) • Ischemic Symptoms • Development of pathologic Q waves on the ECG or persistent ECG changes indicative of ischemia (ST segment elevation or depression)
Pericarditis	Pleuritic chest discomfort associated with either pericardial rub and/or ECG changes that requires or prolongs hospitalization
Pneumothorax	Identification of air in the pleural space which either prolongs hospital stay (for observation) or requires surgical intervention or chest tube placement
Pulmonary edema	Pulmonary alveolar fluid accumulation accompanied by typical symptoms (dyspnea), physical findings (rales, hypoxemia), radiologic findings, and response to diuretic therapy and requiring hospitalization
Stroke	Brain disorder involving loss of brain functions (that persists for > 24 hours) that occur when the blood supply to any part of the brain is interrupted as determined by the consulting neurologist
PV stenosis	Severe (≥ 70%), or complete occlusion of a PV, even in the absence of symptoms

Tamponade	Pericardial effusion of sufficient size to cause hemodynamic compromise and requiring drainage based on hypotension, echocardiographic findings or other clinical factors
Thromboembolism	Deep vein thrombosis or pulmonary embolism
Transient ischemic attack	Acute episode of temporary (< 24 hrs.) and focal loss of cerebral function of vascular (occlusive) origin as determined by the consulting neurologist
Vascular access complications	Vascular access complication requiring surgical repair, blood transfusion (e.g., groin hematoma, AV fistula) or significant intervention such as thrombin injection (e.g., pseudoaneurysm)

12.3 Procedure and Device Related Adverse Events

Adverse events that occur in conjunction with the ablation procedure (most also listed in the TactiCath Set Instructions for Use) are listed below in Table 3. These AEs will contribute to the secondary safety endpoint in all enrolled patients. AEs will be classified as primarily related to the procedure or to the device. Device related SAEs and SAEs whose origin is unclear will be reported to the CEC for adjudication as potential PSAEs.

Table 3 Adverse Events Associated with Radiofrequency Ablation

Procedure Related	Possibly Device Related
Air embolism	X
Cardiac perforation	X
Cardiac thromboembolism	X
Cerebrovascular attack	X
Chest pain/discomfort	X
Complete AV block	X
Coronary artery dissection	
Coronary artery spasm	X
Coronary artery thrombosis	X
Gastroparesis	X
Hemothorax	
Myocardial Infarction	X
Pericardial effusion	X
Pericarditis	X
Phrenic nerve injury	X

Pneumothorax	
Pseudoaneurysm	
Pulmonary edema	X
Pulmonary embolism	
Pulmonary vein stenosis	X
Tamponade	X
Thrombosis	
Transient ischemic attack	X
Valvular damage	X
Vascular access complications	
Venous Thromboembolism and vasovagal reactions	
Ventricular tachyarrhythmia	X

12.4 Handling and Reporting of Adverse Events

Patients will be carefully monitored during the study for possible AEs. Any AE will be followed to a satisfactory resolution, until it becomes stable, or until it can be explained by another known cause(s) (i.e., concurrent condition or medication) and clinical judgment indicates that further evaluation is not warranted. All findings relevant to the final outcome of an AE must be reported in the patient's medical record.

The clinical investigator will attempt to assess the involvement of the investigational device in the AE. All observations and clinical findings, including the nature, severity, and relationship, will be documented on the appropriate eCRFs.

In case of death, the clinical investigator must make every effort to obtain a copy of the autopsy report and/or death certificate and transmit this to Premier Research Group Limited (Premier Research). The patient's private information shall be concealed prior to transmittal to Premier Research.

The clinical investigator will report all SAEs and ADEs to Premier Research by telephone or fax within **7 days** at the number provided by Premier Research. The clinical investigator will provide a detailed written report within **14 days.**

Premier Research will discuss with the clinical investigator and the safety advisory committee (as applicable), all ADEs and SAEs and coordinate appropriate actions, in particular their notification to other clinical investigators and to the appropriate regulatory agencies as applicable.

For any event where there is a suspicion that the device is involved, Endosense may request that the clinical investigator return the device (when possible) for investigation at Endosense's laboratory. Endosense will provide a procedure for cleaning and preparation as well as special kits for the return of used and potentially bio-hazardous materials.

12.4.1 European Reporting Obligations for European Investigators

All SAEs must be reported to the IEC as per local regulations.

All SADEs must be reported by both the clinical investigator and Premier Research to the CA as per national regulations and in accordance with the applicable sections of Medical Devices Directive 93/42/EEC and ISO 14155.

12.4.2 United States Reporting Obligations for United States Investigators

All SAEs must be reported to the IRB who approved the study **within 7 days** (or sooner if so specified by local IRB policy).

All SADEs and UADEs must be reported by Premier Research to the Food and Drug Administration (FDA) **within 10 days** after Premier Research is first made aware of the event. Reporting to the FDA will be consistent with 21 CFR Part 812.150.

12.5 Early Termination or Suspension of the Clinical Investigation

An independent data safety monitoring board (DSMB) comprised of members not otherwise associated with the trial will convene periodically to assess overall study safety. The DSMB will make recommendations regarding suspension of the study on the basis of predefined conditions related to the incidence of AEs. The mode of operation of the DSMB will be defined in a DSMB Charter. Contact information for the DSMB is provided in Appendix D.

The DSMB can use the decision rules described in Appendix A as a reference. However, the DSMB can make its own recommendations based on aggregated information. The DSMB and Endosense will decide if the suspension of the study will be followed by a termination.

13. DATA QUALITY ASSURANCE

The study described in this CIP will be implemented according to the local regulatory requirements (FDA, EU) and GCP. All procedures not described in this protocol will be performed according to approved written Standard Operating Procedures (SOPs) unless otherwise stated.

Steps to assure the accuracy and reliability of data include the selection of qualified clinical investigators and appropriate study sites, review of CIP procedures with the clinical investigator and associated personnel prior to the study, and periodic monitoring visits by Premier Research. Premier Research will review data for accuracy and completeness during and after on-site monitoring visits, and any discrepancies will be resolved with the clinical investigator or designees as appropriate.

13.1 Case Report Forms

The electronic case report forms (eCRFs) contain confidential material. Specific training on the completion of eCRFs will be provided to the clinical investigator and other site personnel

as appropriate. The clinical investigator is responsible for the accuracy and completeness of data reported on eCRFs.

The clinical research associate (CRA) will periodically verify the data entered onto the eCRFs against source documents to ensure data integrity, accuracy, and completeness of the data prior to locking the eCRFs for tabulation of study endpoint data.

13.2 Monitoring Procedures

Premier Research monitors will conduct site visits to the study facilities to monitor the study and ensure compliance with the CIP, GCP, and applicable regulations and guidelines.

The clinical investigator agrees to allow these monitors and other authorized Endosense representatives access to the clinical supplies dispensing and storage area and to study documentation for the above mentioned purpose and agrees to assist the monitors in their activities, if requested. Requests by regulatory agencies to inspect the study sites may be made. The clinical investigator agrees to allow inspectors from regulatory agencies to review records and to assist the inspectors in their duties, if requested.

Source documents include the physician or hospital patient records that are maintained at the study site. In most cases, the source documents will be the physician or hospital patient chart. In some cases, the source documents may be electronic. In both cases, the information captured on the eCRF must match the information in the chart or electronic source document. Periodically, the Premier Research monitor or Endosense representative will visit the study site for the purpose of directly comparing the data in the eCRF with the source. The clinical investigator agrees to make source documents (hard copy or electronic) available for this purpose.

It is the clinical investigator's responsibility to ensure accurate completion of the eCRFs and to approve the eCRFs. The clinical investigator or a designated sub investigator recognized by the IEC or IRB has the authority to sign eCRFs. These electronic signatures serve to attest that the information contained in the eCRF is accurate and true.

13.3 Data Management

The standard procedures for handling and processing records will be followed per GCP and Premier Research's SOPs.

A comprehensive Data Management Plan will be developed including a Data Management Overview, Database Contents, annotated eCRF, Pre-Entry Review List, Self-evident Correction Conventions, Query Contacts, and Consistency Checks.

14. INVESTIGATIONAL PRODUCT TRACEABILITY AND RECORDING

Device accountability will be maintained during the study. Each site will document all used and unused devices received, stored, dispensed, and returned to Endosense as applicable. Inventory records will be periodically monitored by the CRA.

14.1 Device Complaints and Malfunctions

Device complaints may reflect any deficiencies related to the study device, instructions for use, operator's manual, or other product-related documentation.

Device complaints may or may not involve a clinical event. If the device complaint is based on a clinical event, the event must be recorded as an adverse device effect (ADE) as outlined in Section 12.1.2 of this clinical investigational plan (CIP).

14.2 Complaint Reporting

If any study device complaints occur (e.g., instructions for use, operator's manual, or other product-related documentation), the clinical investigator will document the complaint(s) using the appropriate form(s).

15. ETHICS

15.1 Declaration of Helsinki

The study will be conducted according to the guidelines established in the Declaration of Helsinki. Patients will be free to withdraw from the study at any time without prejudice to their subsequent treatment.

15.2 Institutional Review Board or Independent Ethics Committee Approval

This study will be conducted in compliance with the Declaration of Helsinki and its amendments and the applicable regulations of the country in which the study is conducted.

A properly constituted, valid Institutional Review Board (IRB) or Independent Ethics Committee (IEC) must review and approve the CIP, the investigator's informed consent document, and related patient information and recruitment materials before the start of the study.

15.3 Informed Consent

Informed consent shall be obtained in writing and documented before a patient is enrolled in the clinical investigation in accordance with the principles of Informed Consent, according to the Declaration of Helsinki, Good Clinical Practice (GCP), 21 Code of Federal Regulations (CFR) Part 50, the Medical Devices Directive 93/42/EEC, and International Organization for Standardization (ISO) 14155-1, Chapter 6.7.1.

It is the responsibility of the clinical investigator to ensure that written informed consent is obtained from the patient (or legally acceptable representative) before any activity or procedure is undertaken that is not part of routine care.

15.4 Patient Identification and Confidentiality

Patient identification and confidentiality will be ensured according to the terms and definitions in ISO 14155-1, Chapter 6.5. This includes but is not limited to the following:

1. Patients will be identified on all eCRFs by a unique reference code including the patients' initials.

2. ECRFs are confidential documents and will only be available to Endosense (including delegates, such as CRAs) the clinical investigator, the biostatistician, and if requested, to the advisory committee and regulatory authorities. Selected ECRFs will also be available to the independent clinical lab responsible for collecting and entering the results of ambulatory monitoring tests (Appendix F). The principal clinical investigator for each center will maintain, as part of the investigation file, a list identifying all patients entered into the trial.

16. REGULATORY REQUIREMENTS

16.1 Compliance With Regulations Applicable to Clinical Trials

The study will be conducted according to the laws, regulations and administrative provisions relating to the implementation of GCP in the conduct of clinical trials, as applicable by national legislation and European Union (EU) Directives, including 93/42/EEC, ISO 14155-1, ISO 14155-2, 21 CFR Part 812, and local regulations where applicable.

16.2 Competent Authority Notification

When required, Endosense will provide notice to the Competent Authority (CA) that the clinical trial is scheduled to begin and obtain regulatory clearance whenever required by national law.

Any applicable notifications or submissions must also be made to the relevant CA regarding data protection.

17. CHANGES TO THE CIP OR RELATED PROCEDURES

This CIP cannot be altered or changed except through a formal CIP amendment, which requires the written approval of Endosense.

The CIP amendment(s) must be signed by the clinical investigator and approved by the IRB or IEC before implementation. The CIP amendments will be filed with the appropriate regulatory agency(s) having jurisdiction over the conduct of the study.

Note: Substantial changes may require approval from the FDA, IRB, IEC, and the CA prior to implementation.

18. DEVIATIONS FROM THE CIP

Any deviation from the CIP must be recorded along with an explanation for the deviation. The clinical investigator will report each deviation to Endosense. Significant deviations will be reported to the IEC or IRB within the appropriate deadlines stipulated by the appropriate regulatory agency(s) and according to local SOPs.

Significant deviations are defined as those impacting or potentially impacting patient safety, enrollment of non-eligible patients, and any deviation that significantly compromises the outcome of the study.

Note: Where relevant, the Competent Authorities should be informed.

19. GENERAL CONSIDERATIONS

19.1 Discontinuation of the Study

Endosense reserves the right to discontinue this study for safety or administrative reasons at any time. In such events, patients will be followed to assess safety through the entire planned follow-up period.

19.2 Use of Information and Publication

All information concerning the TactiCath Set, Endosense operations, patent applications, manufacturing processes, and basic scientific data supplied by Endosense or Premier Research to the clinical investigator and not previously published, is considered confidential and remains the sole property of Endosense. The eCRFs also remain the property of Endosense. The clinical investigator agrees to use this information for purposes of study execution through finalization.

The information developed in this study will be used by Endosense in connection with the continued development of the TactiCath Set and thus may be disclosed as required to other clinical investigators or government regulatory agencies.

Publication or other public presentation of the TactiCath Set data resulting from this study requires prior review and written approval of Endosense according to the TOCCASTAR Publication Policy. Abstracts, manuscripts, and presentation materials should be provided to Endosense for review at least 30 days prior to the relevant submission deadline.

20. REFERENCES

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21. APPENDICES

APPENDIX A ..... Statistical Methods

A.1 Determination of Sample Size

A.1.1 Assumptions

[redacted]

A.1.2 Non-inferiority Margins

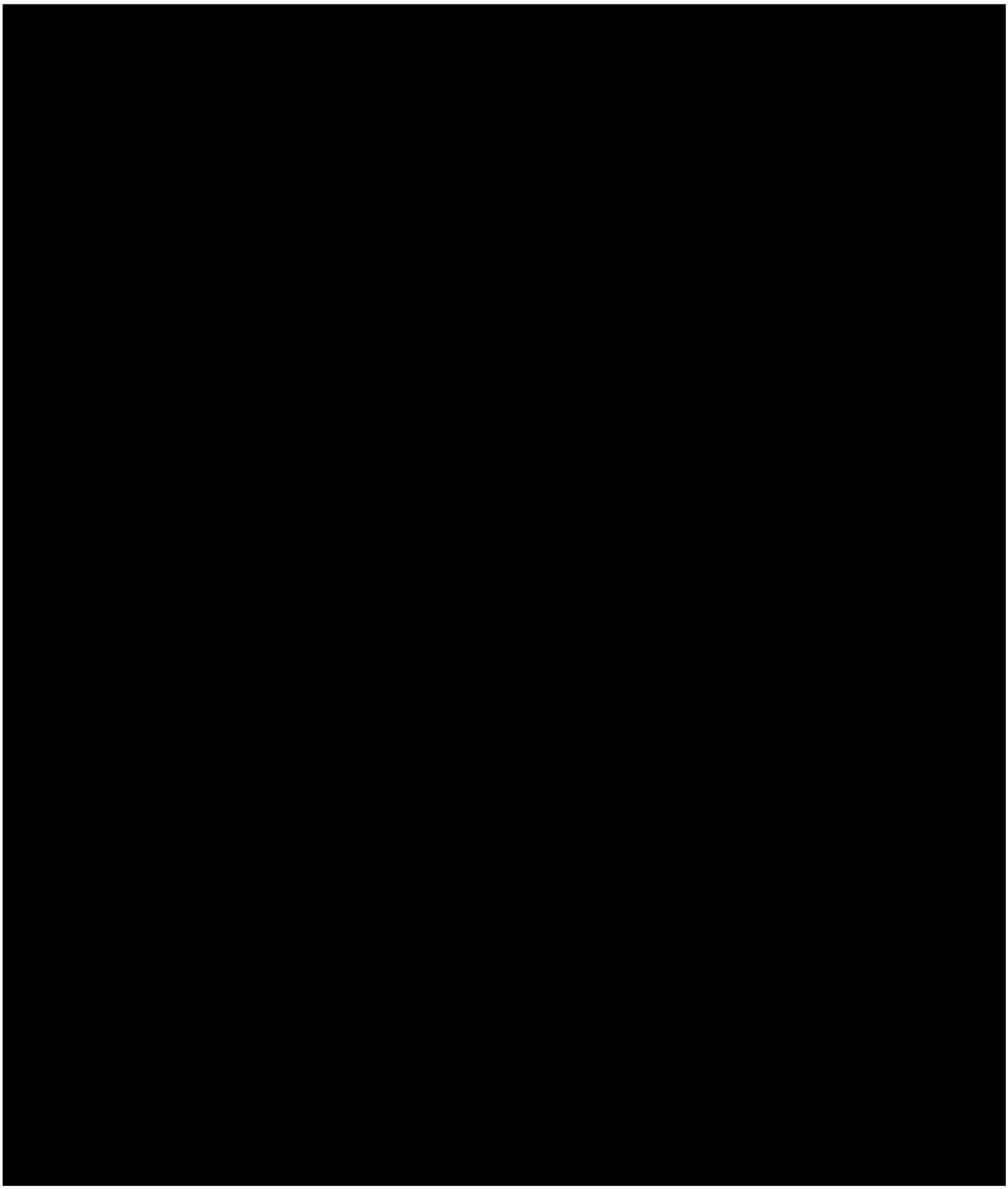
[redacted]

A.1.3 Sample Size

[redacted]

[redacted]

A.2 Interim Analyses



[redacted]

A.3 Randomization and Blinding

Patients will be randomly assigned 1:1 to receive treatment with either the TactiCath Set or the control device (NaviStar® ThermoCool® Catheter manufactured by Biosense Webster, Inc.) Roll-in patients will not be randomized. Use of 3D mapping equipment will be required in both treatment groups. The randomization schedule will be computer generated using a permuted block algorithm and will randomly allocate the randomization numbers. The randomization numbers will be assigned sequentially through an Interactive Web Response System as patients are entered into the study. The randomization schedule will be stratified by site. Each site is expected to have approximately 10 to 20 patients.

All patients will be blinded to treatment assignment. Study personnel, who may be unblinded, should not disclose any treatment assignment information to the patient prior to unblinding of the study data to all study-related personnel.

A.4 Patient Characteristics

In general, patient demographics and baseline characteristic variables will be summarized descriptively by treatment group and overall. Continuous variables will be summarized in terms of descriptive statistics including the mean, standard deviation (SD), minimum, maximum, and quartiles. Categorical variables will be summarized in terms of frequencies and percentages.

Demographic variables will include age, gender, race, ethnicity, height, and weight. Baseline patient characteristics will include the following:

- Medical history
- Baseline physical examination and ECG
- Baseline thyroid and renal function
- Baseline PT/PTT or INR
- Baseline and concomitant medication
- Documentation of arrhythmia events and cardiac medication

Data collected during the procedure, including activated clotting time and ablation procedure data will be summarized. Descriptive statistics for these quantities, including the mean, SD, minimum, maximum, and quartiles, will be provided by treatment group.

The TTE/TEE will be performed at baseline and pre-discharge, and data will be summarized in 3 categories: normal, abnormal - not clinically significant, and abnormal - clinically significant.

The remaining patient characteristic variables will be summarized descriptively by treatment group and overall (continuous variables: mean, SD, minimum, maximum, and quartiles; categorical variables: frequencies and percentages).

A.5 Analysis

A.5.1 Analysis Populations

This study will have the following 4 planned analysis populations.

- The full analysis (FA) population will include all randomized patients.
- The modified intent-to-treat (MITT) population will include all randomized patients in whom a study device was introduced and PVI was attempted.
- The safety population (SAF) will also include all randomized patients in whom a study device was introduced.
- The per-protocol (PP) population will include all patients in the FA population who do not have major protocol deviations that will compromise the effectiveness or safety evaluation of the study device. Lists of major protocol deviations and of patients excluded from the PP population will be provided prior to database lock and unblinding.

A.5.2 Effectiveness

A.5.2.1 Primary Analysis

The primary effectiveness endpoint of the study is a non-inferiority comparison of treatment success assessment as defined by both:

- Acute procedural success - electrical isolation of all 4 PVs, or in the event of a common PV, the clinical equivalent of all PVs, by the end of index procedure (with the device specified by the randomization arm)
- Chronic success – acute procedural success and freedom from recurrence of symptomatic AF, AFL, and AT lasting longer than 30 seconds through 9 months of follow-up after a 3 month blanking period. Re-treatment for AF with ablation or the use of Class I or Class III antiarrhythmic drugs after the blanking period constitute a treatment failure.

The one-sided 95% lower confidence limit will be calculated using the normal approximation method for the difference between the 2 treatment groups (P_t - P_c) based on the PP population. If the 95% lower confidence limit is > -15%, non-inferiority is demonstrated in terms of effectiveness. Median time to treatment failures and probability of treatment failures at 12 months will be estimated using the Kaplan-Meier method, and two-sided 95% confidence intervals will be provided. Sensitivity analysis will be provided for the FA and MITT populations.

If chronic success is determined to be less than 40% for either the treatment group or the control group, additional exploratory analyses on effectiveness outcomes will be performed. The analyses will focus on explaining the suboptimal results or poor device performance. Effectiveness outcomes (including acute procedural success, chronic success at 12 month, free of symptomatic AF after 12 months, free from AF/AFL/AT at 12 month by Holter) will be examined by baseline characteristics and by study sites. Baseline characteristics will include age group, relevant medical condition at time of procedure, disease history, hypertension and heart failure. Site variation may include experience of operator, experience

of site, number of operators, percentage of patients who received re-ablation during the study, and ablative technique.

A.5.2.2 Secondary Analyses

The following secondary effectiveness endpoints are related to the use of the contact force sensor and a formal superiority test will be performed comparing the TactiCath Set to the control device using a hierarchically closed test procedure. It is hypothesized that the use of the contact force sensor information will result in added procedural effectiveness through a reduction of number of electrically reconnected pulmonary veins, time to achieve total PV isolation, or total time of RF application. These endpoints will be tested sequentially, conditional on the success of reaching the non-inferiority primary effectiveness objective in the order they appear below, using a one sided, $\alpha = 0.025$ test based on the PP population. Subsequent endpoints will be tested only if the prior endpoint(s) are superior.

1. Number of electrically reconnected pulmonary veins following a 30-minute waiting period assessed by entrance block
2. Time to achieve total PV isolation measured from initial application of RF energy to all targeted vessels isolated
3. Total time of RF application required for full PV isolation calculated from data paired within investigative site and weighted based on the number of enrollments per site.

Secondary endpoint one will be tested using the Wilcoxon rank sum test. Secondary endpoints 2 and 3 will be tested using the log rank test. Patients without full PV isolation will be censored. Sensitivity analysis may be provided for the FA and MITT populations.

A.5.2.3 Descriptive Analyses

The other effectiveness endpoints, listed in Section 6.3.1, will be collected and will be summarized descriptively based on the PP population. Continuous variables will be summarized in terms of descriptive statistics including the mean, SD, minimum, maximum, and quartiles. Categorical variables will be summarized in terms of frequencies and percentages.

A.5.3 Safety

The primary safety endpoint is a non-inferiority comparison of device-related early-onset primary SAEs between the TactiCath Set and the control device occurring within 7 days of the index procedure or hospital discharge, whichever is later, and diagnosed at any time during the follow-up period. A complete list of primary SAEs is provided in Table 2.

Hospitalizations solely due to recurrence of AF/AFL/AT (i.e., without coexisting conditions such as thrombo-embolism, worsening of congestive heart failure, etc.) do not count towards primary safety. PSAEs that meet the severity criteria described in Table 2 will contribute to the primary safety endpoint only in patients in whom a study device (TactiCath or control) has been introduced.

The one-sided 95% upper confidence limit will be calculated using the normal approximation method for the difference between the two treatment groups (P_t - P_c) based on the SAF population. If the 95% upper confidence limit is < 9%, non-inferiority is demonstrated in terms of safety. Sensitivity analysis will be provided for the FA and PP populations.

The secondary safety endpoint includes the incidence of all SAEs during the 12-month follow-up period. The secondary safety endpoint will be summarized descriptively based on the safety population and all enrolled patients, including the roll-in patients.

Other safety data, e.g., 12-lead ECG, physical examination, vital signs, NYHA functional class, will be collected throughout the study, and will be summarized descriptively based on the SAF population.

A.6 Subgroup Analyses

In addition to the analyses described in Section A.5, the primary and secondary effectiveness and safety endpoints will also be compared between the control group and a subgroup of patients from the TactiCath arm whose average contact force during ablation is ≥ 20 g. To examine comparability, baseline tables will be displayed showing the contact force subgroups (≥ 20 g vs. < 20 g) as well as the overall treatment group.

The primary effectiveness endpoint and the primary safety endpoint in these subgroups will be examined using exploratory statistical analyses and summarized with descriptive statistical measures. Secondary effectiveness and safety endpoints will be analyzed using the same methods as described in Section A.5.2.2 and Section A.5.3 and also summarized with descriptive statistical measures. No p-values associated with statistical tests or conclusions regarding statistical significance of findings will be reported.

An analysis of primary and secondary endpoints will also be performed by gender subgroups (gender analysis).

A.7 Poolability of Data

The primary justification for poolability across centers is made on the basis that there is a uniform study protocol with well-defined inclusion/exclusion criteria and that centers will be uniformly monitored to verify protocol compliance. Centers located outside the United States have been assessed for participation using the same selection criteria as in the United States and will utilize the identical protocol and procedures in their conduct of the study.

Poolability will be evaluated and justification for pooling data will be provided before combining data. Study variables that are potentially related to study endpoints will be identified prior to database freeze for the interim analysis, and statistical analysis will examine the homogeneity of demographic and procedural covariates across centers and geographical regions. Center effect and interaction between treatment and center will be considered in the subgroup analyses and secondary analyses on the primary endpoints to

examine possible site to site variations using multivariate analysis methods. A p-value of ≤ 0.15 will be considered having significant treatment-by-center interaction. The primary effectiveness and safety endpoints will be summarized by center. In these analyses, small centers may be combined based on size, center characteristics and geographical regions. Sensitivity analysis will be performed to verify robustness of the statistical model by different center pooling algorithms.

A.8 Missing Data

For the primary effectiveness analysis, patients who terminated the study prematurely before experiencing a treatment failure will not be considered a treatment success at 12 months. Patients whose participation in the study is terminated due to reasons clearly unrelated to the study device (lost to follow-up due to patient relocation, death due to causes unrelated to the study devices, etc.) may also be excluded from the denominator, and thus will not be considered treatment failures. An expert medical panel while blinded to the individual patient's treatment arm will adjudicate exclusion of patients from the primary effectiveness analysis. The decision will be made prior to obtaining the database snapshot for the interim analysis, and prior to database lock for the final analysis.

Sensitivity analysis will be provided as described below:

1. All early terminations, regardless of reason for termination will be considered treatment failures.
2. All early terminations, regardless of reasons for termination will be excluded from the denominator. The analysis will be carried out in patients who have either completed the 12-month follow-up period or have experienced chronic failures.
3. Worst-case analysis will be used to impute failures for missing observations from the TactiCath group and to impute successes for missing observations from the control group.
4. Propensity scores will be used to assess the comparability of the two study groups after exclusion of protocol deviations in the PP population.
5. Tipping point analysis will be used to replace missing data with values so that the p-value is equal to significance level.

For time to treatment failure and probability of treatment failure at 12 months by the Kaplan-Meier method, patients who terminated early prior to failure will be censored at time of discontinuation and will include all patients. The same rule will apply to the primary safety analysis. Patients who terminated the study prematurely without experiencing any primary SAEs will not be considered as having any primary SAEs during the course of the study. Other missing data will not be imputed.

Compliance with TTM requirements will be characterized in terms of actual vs. expected number of recordings per patient, and overall compliance for each arm of the study. Patients with major protocol violations (which may include non-compliance with TTMs) will be excluded from the PP population.

APPENDIX B ..... Principal Investigator

The principal investigator for the TOCCASTAR study will be

APPENDIX C.....Clinical Events Committee

[redacted]

The [redacted] has established a standing Clinical Events Committee (CEC) under the guidance of the [redacted]. The CEC will be responsible for adjudicating all serious adverse events reported during the study, as identified and submitted by Endosense, or its designee.

This committee is comprised of 3 to 5 physicians with experience in clinical trial event adjudication, including at least one physician with expertise in each area of the study, who are not participants in the study and who meet regularly throughout the study to adjudicate events in an ongoing fashion. The CEC members are chosen based on their clinical expertise and have no association with any trial for which they adjudicate events. The CEC is blinded to treatment assignment during all deliberations. Three voting members comprise a quorum.

The CEC drafts and agrees upon its working charter for each study prior to performing any work. This includes explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. The CEC Administrator will prepare the CEC Manual of Operations (MOP) based on this information and the CEC MOP will serve as the guideline for adjudication for the specific trial under review.

Clinical events related to the primary endpoints are identified by the sponsor and submitted to [redacted] for review. After review of the identified events by [redacted], support documentation for identified events is obtained from the site, if necessary, and a summary is written to describe the significant details of the event. These summaries, with appropriate support documentation, are presented to the physician members of the CEC. The results of the adjudications are entered into the Complications database after the CEC meeting. The Complications database is specifically created within the overall study database and is used in the preparation of DSMB reports, as well as in all analyses of endpoint results.

CEC meetings are held approximately 3 times per month at [redacted]. As documentation of the CEC meeting and each event under review, [redacted] provides to Endosense relevant supporting documentation and/or meeting minutes. The format of the information will vary depending on whether or not [redacted] is involved with event narration.

APPENDIX D.....Data Safety Monitoring Board

[redacted] will manage Data Safety and Monitoring Board (DSMB) services for this study. [redacted] will generate a DSMB charter, for approval by the DSMB. Endosense and [redacted] will identify DSMB members, which will include 3 experts in clinical electrophysiology and ablation as voting members as well as a qualified statistician and medical monitor as non-voting members. [redacted] will negotiate and execute confidentiality and consulting agreements with the members.

[redacted] will provide a dataset to the statistician who is not a member of the project team for analysis. The independent statistician will generate the unblinded tables and listings needed for generation of the DSMB report. The report will undergo independent medical review by a [redacted] physician before being distributed.

FDA will be notified in the event that the DSMB recommends any changes to the study protocol, procedures or informed consent document.

APPENDIX E ..... Core Laboratory Services

All transtelephonic monitoring (TTM) tracings, 24-hour recordings from Holter monitors, and select computed tomography (CT)/magnetic resonance imaging (MRI) scans (those with a preliminary finding of moderate (50% – 70%) or severe (> 70%) PV stenosis) will be manually over-read by board-certified cardiologists/electrophysiologists at prespecified intervals. Findings will be communicated to the investigator and the sponsor. [redacted]

[redacted]

APPENDIX F ..... Ambulatory Monitoring Services

Ambulatory monitoring will be conducted by a vendor staffed with qualified caregivers including nurses who are trained to accurately elicit patient complaints and physicians who perform and approve the reading of ECGs. Subjects are typically issued the transtelephonic monitoring (TTM) device when discharged from the hospital after training by the local study nurse. They are instructed to transmit an ECG according to a well-defined schedule over the next 12 months. They may transmit additional ECGs anytime they experience symptoms. The collection of ECG data is accompanied by a report of the patient's health status and well being (including symptoms) obtained over the telephone.

TTM and Holter services will be provided by:

[redacted]

<u>The Use of Protected Health Information (PHI) by [redacted]</u>

Ambulatory monitoring is an integral part of the TOCCASTAR Study Clinical Investigational Plan and is essential to the study endpoints. The use of PHI is normally provided by patient informed consent strictly for the purpose of compliance with protocol-defined follow-up. A patient information form is used to provide [redacted] with the subject's name and telephone contact information should a follow-up call be required.

- Subject information is protected by restricted access to study files via unique user ID and passwords for all operators, tracking of all authorized and unauthorized login attempts and password expiration schedules.
- All [redacted] employees are trained on GCP (Good Clinical Practices) and HIPAA (Health Insurance Portability and Accountability Act) guidelines. Training records are available upon request.
- [redacted] is bound by contract with the study sponsor to protect the privacy and confidentiality of all study data and reports.
- Data subsequently forwarded to investigators, the sponsor and clinical core labs are fully de-identified of PHI.
- [redacted] will only contact patients directly if a patient has failed to report in a timely way or has specifically requested [redacted] to do so.

APPENDIX G..... New York Heart Association Classes

NYHA Class	Criteria
I	No symptoms and no limitation in ordinary physical activity. Shortness of breath when walking, stair climbing, etc.
II	Mild symptoms (mild shortness of breath and/or angina pain) and slight limitation during ordinary activity.
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity (e.g., walking short distances, approximately > 20 – 100 meters). Comfortable only at rest.
IV	Severe limitations. Experiences symptoms even while at rest, mostly bedbound patients.

Abbreviation: NYHA = New York Heart Association

APPENDIX H.....Quality of Life Survey

The Atrial Fibrillation Effect on Quality of Life survey, also known as the AFEQT[28] questionnaire, is a responsive measure of quality of life specifically for atrial fibrillation. It is a reliable, validated questionnaire that evaluates Health Related Qualify of Life (HRQoL) across three domains: symptoms, daily activities, and treatment concerns. It is composed of 20 questions scored on a seven point Likert scale that takes approximately five minutes for the subject to complete. The questionnaire is scored for the following results: global AFEQT score and subscale functional scores (treatment concerns, daily activities and symptoms.)

Higher overall AFEQT scores indicate the subject has no limitations while a lower score indicates increased to extreme difficulty affect on quality of life due to atrial fibrillation. The Treatment Satisfaction Score indicates how well the subject feels their current treatment regimen is working, the higher the score, the more satisfied with the treatment. AFEQT will be administered to subjects at the baseline visit and at the 12-month post-procedure visit.

APPENDIX I ..... List of Abbreviations

3D	three-dimensional
ACC	American College of Cardiology
ADE	adverse device effect
AE	adverse event
AF	atrial fibrillation
AFEQT	Atrial Fibrillation Effect on Quality of Life survey
AFL	atrial flutter
AHA	American Heart Association
AT	atrial tachycardia
CA	Competent Authority
CFAE	complex fractionated atrial electrogram
CEC	clinical events committee
CFR	Code of Federal Regulations
CHADS	congestive heart failure, hypertension, age > 75 years, type 2 diabetes, prior stroke or transient ischemic attack
CIP	clinical investigational plan
CRA	clinical research associate
CT	computed tomography
DSMB	data safety monitoring board
ECAS	European Cardiac Arrhythmia Society
ECG	electrocardiogram
eCRF	electronic case report form
EHRA	European Heart Rhythm Association
ESC	European Society of Cardiology
EU	European Union
FA	full analysis
FDA	Food and Drug Administration
FTI	Force Time Integral
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HCRI	Harvard Clinical Research Institute
HRS	Heart Rhythm Society
IACUC	Institutional Animal Care and Use Committee
ICD	implantable cardiac defibrillator
ICE	intracardiac echocardiography
IDE	Investigational Device Exemption

IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
ISO	International Organization for Standardization
MI	myocardial infarction
MITT	modified intent-to-treat
MRI	magnetic resonance imaging
NaviStar® ThermoCool® Catheter	NaviStar® ThermoCool® open irrigated RF ablation catheter
NYHA	New York Heart Association
PAF	paroxysmal atrial fibrillation
PCI	percutaneous coronary intervention
PMA	premarket approval
PP	per-protocol
Premier Research	Premier Research Group Limited
PT	prothrombin time
PTT	partial thromboplastin time
PV	pulmonary vein
Q3 2010	third quarter of calendar year 2010
Q3 2011	third quarter of calendar year 2011
RF	radiofrequency
SADE	serious adverse device effect
SAE	serious adverse event
SAF	safety
SD	standard deviation
SOP	Standard Operating Procedure
TEE	trans-esophageal echocardiography
TTE	trans-thoracic echocardiography
TTM	transtelephonic monitoring
UADE	unanticipated adverse device effect
US	United States
W	Watts

APPENDIX J.....Supplemental Clinical Study

J.1 INTRODUCTION

The TactiCath Set composed of the TactiCath catheter and the TactiSys contact force visualization equipment (described in IDE G100230 submitted to FDA on August 13, 2010 and fully approved on May 17, 2011) is currently being evaluated in the TOCCASTAR clinical study. Completion of patient enrollment occurred in June 2012. A total of 317 subjects (300 randomized and 17 roll-in) have been enrolled at 17 sites. The PMA is expected to be ready for submission to FDA in Q3 of 2013.

In parallel to the IDE evaluation in the United States, the TactiCath Set has been approved for commercial use in Europe and in Australia. To date, no device-related complications were reported under the applicable post-market vigilance reporting regulatory systems.

The company has developed a new catheter version along with new contact force visualization equipment called the TactiCath Quartz Set, based closely on the TactiCath Set devices. The indications for use remain unchanged, as does the catheter basic design. Improvements are made to materials and components. This evolution will improve manufacturability and increase reliability for the TactiCath catheter. Changes in TactiSys will improve usability and integration with the EP lab environment. The company introduced the TactiCath Quartz Set in the European market in June 2012.

To compile evidence of the comparative safety of the TactiCath Quartz Set and to clinically evaluate proposed enhancements to the user interface, Endosense proposes to conduct a Supplemental Clinical Study with the TactiCath Quartz Set in the US. Clinical data regarding acute safety and effectiveness of the TactiCath Quartz Set in patients with PAF will be compared to that of the TactiCath Set from the pivotal TOCCASTAR Study to confirm comparable clinical performance of the two systems.

J.2 INTENDED USE AND DEVICE DESCRIPTION

J.2.1 Intended Use of the TactiCath Quartz Set

The intended use of the TactiCath Quartz Set is the same as the TactiCath Set as described in Section 4.1.

J.2.2 Device Description – TactiCath Quartz Set

The TactiCath Quartz Set developed by Endosense consists of the:

- TactiCath Quartz open irrigated radiofrequency (RF) ablation catheter
- TactiSys Quartz Equipment, the contact force visualization system.

The TactiCath Quartz Catheter is connected to the TactiSys Quartz Equipment. The TactiSys Quartz is connected to a general-purpose computer (PC) on which Endosense TactiSoft

software will be installed. The TactiSys Quartz Equipment refers to the combination of the TactiSys Quartz and TactiSoft. Each of the TactiCath Quartz and TactiSys Quartz Equipment has been subjected to full verification and validation.

J.2.3 Functionality of the TactiCath Quartz Set

The functionality of the TactiCath Quartz Set is identical to the TactiCath Set as described in Section 4.2.1.

J.2.4 Evolution from TactiCath Catheter to TactiCath Quartz Catheter

The basic design from the TactiCath catheter (currently under IDE evaluation) remains essentially unchanged. However, a modification of the force sensor has been implemented for enhanced stability, reliability and manufacturability.

The basic design of the TactiCath Quartz body (shaft concept, handle, proximal cable, electrical and optical connectors) is equivalent to the current generation TactiCath. Minimal changes have been made with respect to functionality and materials that are in direct contact with the patient. The manner in which the catheter is used by physicians has not changed.

The change to the force sensor technology is the main design difference between the TactiCath and the TactiCath Quartz. Modifications to the force sensor include:

[redacted]

J.2.5 Evolution from TactiSys to TactiSys Quartz Equipment

[redacted]

[redacted]

J.3 STUDY PURPOSE AND OBJECTIVES

J.3.1 Study Purpose

The purpose of the Supplemental Clinical Study is to evaluate the acute clinical safety and effectiveness of the TactiCath Quartz Set to verify that the new design performs comparably to the initial design.

The TactiCath Quartz Set includes hardware design modifications intended to improve manufacturability and to increase reliability as well as minor enhancements to the user interface intended to promote improved usability and safety. These enhancements do not introduce any new design features that would be expected to measurably impact clinical performance compared with the original design.

J.3.2 Study Objectives

J.3.2.1 Effectiveness

To provide comparative acute effectiveness data on the treatment of symptomatic PAF relative to the TactiCath Set.

J.3.2.2 Safety

To provide comparative acute safety data on the incidence of early-onset SAEs relative to the TactiCath Set.

J.4 STUDY ENDPOINTS

Outcomes from the Supplemental Clinical Study will be summarized descriptively.

J.5 STUDY DESIGN

J.5.1 Justification for the Investigation

The main objective of the Supplemental Clinical Study will be to provide confirmatory evidence regarding the acute safety and effectiveness of the TactiCath Quartz Set in patients with symptomatic PAF. In principle, the TactiCath Quartz Set will provide the same therapeutic and diagnostic functionality to the operator during use as the TactiCath Set. It is anticipated that the risks and benefits will also be the same. The new device will be evaluated in an identical patient population (inclusion and exclusion criteria), using the same procedural methodology from the TOCCASTAR study.

Prior to first clinical use, a comprehensive verification and validation study will confirm the operation and robustness of the new features included in the device.

Given the similarities in patient populations, device functionality, and procedural testing requirements, the acute procedural and 30 day safety data from the TactiCath Quartz Set may be compared with data from the TactiCath Set. Therefore, a minimum of 30 days of follow-up data on 50 subjects will be submitted for FDA review in the original PMA, plus any additional follow- up data available at the time of submission. Subjects enrolled in the supplemental study will comply with the same extended follow-up requirements from the original study (every 6 months until PMA approval) to provide additional safety and effectiveness data from the post-assessment period through PMA approval.

J.5.2 Scope of Study

Up to 10 sites participating in the TOCCASTAR Study will be asked to also participate in the Supplemental Clinical Study. Investigators will likewise be chosen from the current group of TOCCASTAR investigators. Sites will be required to seek approval of the Clinical Investigational Plan and Patient Informed Consent (Version F) as a prerequisite to enrollment.

Up to 50 subjects will be enrolled in a non-randomized manner and treated identically to the roll-in patient population except as described in Section J.7.

J.5.3 Study Assessment Intervals

For the purpose of assessing acute comparative performance, patients will be followed for a minimum of 30 days, after which subjects will continue follow-up according to the Schedule of Activities (Table 1) with one exception. To comply with current standard of care at the participating institutions, CT and MR scans are recommended but not required for the supplemental study patients only.

The supplemental study is intended to provide confirmation that the device and procedure related complications assessed at 30 days are comparable to the experience with the randomized TactiCath subjects. The supplemental study also allows for subjects to be followed for a total of 12 months (3 months blanking period followed by 9 month effectiveness assessment period).

J.5.4 Clinical Investigational Plan

We propose to study the primary safety and acute effectiveness of the TactiCath Quartz Set in the Supplemental Clinical Study with the following key features (relative to the current randomized study):

- Single arm, non-randomized study
- Identical inclusion and exclusion criteria for subjects
- Identical procedural testing requirements during the index procedure
- Identical data collection requirements in the acute study phase
- Identical follow-up requirements for 12 month (excluding CT/MR scans)
- 30 day safety outcome assessment on 50 patients (descriptive summary comparing randomized and supplemental study subjects)
- Extended follow-up every 6 months until time of PMA approval
- Study restricted to sites who are already participating in the TOCCASTAR Study

J.6 CRITERIA FOR ELIGIBILITY

Subject eligibility is identical to the initial randomized study as described in Section 8 CRITERIA FOR ELIGIBILITY.

J.7 STUDY PROCEDURES

Procedures required in the Supplemental Clinical Study are identical to those specified in Section 10 STUDY PROCEDURES of the randomized study with the following exceptions:

1. Subjects enrolled in the Supplemental Clinical Study will not be randomized. All subjects will be treated with the TactiCath Quartz Set.

2. CT and/or MR scans are recommended but not required (either pre-procedure or at 3-month follow-up).

J.8 PATIENT BENEFITS AND RISKS

Benefits and risks are identical to those described in Section 11 except for those risks that have been reduced by the elimination of the CT and MR scans in the study. In addition, the TactiCath Set continues to be used safely in a commercial setting outside of the US having now exceeded 2500 units worldwide. Data resulting from both company and investigator sponsored research has resulted in over 30 peer reviewed publications and presentations that have reported on potential benefits associated with contact force sensing with TactiCath.

J.9 ADVERSE EVENTS

The definitions and reporting requirements related to adverse events, serious adverse events and UADEs are identical to those described in Section 12. Only serious adverse events related to safety will be referred to the Clinical Events Committee for adjudication for subjects enrolled in the Supplemental Clinical Study. I.e., arrhythmia recurrence resulting in a "treatment failure" will not be adjudicated for an effectiveness endpoint determination.

J.10 OMISSIONS

Unless specifically described in APPENDIX J, all other aspects of study conduct in the Supplemental Clinical Study will be the same as in the initial randomized study as described in the body and appendices of this Clinical Investigational Plan.

APPENDIX K..... Continued Access Study

K.1 INTRODUCTION

The TactiCath Quartz Set PMA was submitted to FDA in Q4 of 2013. While the marketing application is under regulatory review, St Jude Medical proposes to conduct a Continued Access Study of the TactiCath Quartz Set in the US. The study will report clinical data regarding acute safety and effectiveness of the TactiCath Quartz Set in patients with PAF.

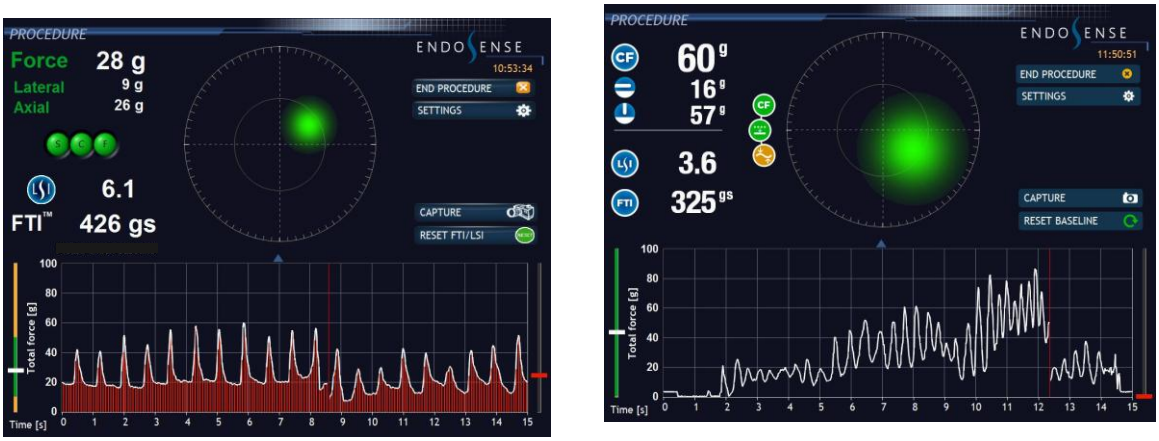
K.2 DEVICE DESCRIPTION

The TactiCath Quartz Catheter and TactiSys Quartz Equipment are described in Section J.2 above. Changes to the TactiSoft Graphical User Interface (GUI) software are described in Section K.2.1 below.

K.2.1 TactiSoft Software

TactiSoft v4.3.1.0 will be used in the Continued Access Study. It is essentially the same as v4.3.0.0 that was used in the Supplemental Clinical Study as shown in Figure 4. The main functionalities are identical, however several minor modifications were made to conform to findings from a Usability Study of human factors of the user interface.

Figure 4 Procedure Screen Example TactiSoft v4.3.0.0 (left) and 4.3.1.0 (right)



Changes implemented in the TactiSoft v4.3.1.0 GUI include:

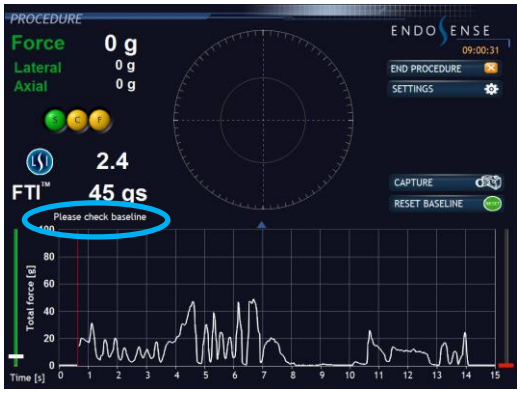
"Please check baseline" message appearance frequency reduced:

This message appears in response to the detection of a possible offset in the contact force reading. In an engineering study, it was found that the threshold for detection could be safely reduced to improve specificity (thereby avoiding false positives) without compromising the detection of true positive offsets.

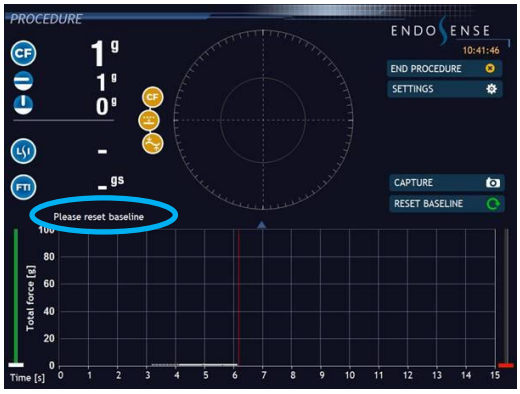
"Please check baseline" message replaced with "Please reset baseline" upon initial use:

An initial baseline reset is required upon first use of a TactiCath catheter. The "please check baseline" message that appeared was identical to the message that might appear during later use for different reasons and may have contributed to a user error. The new message has been implemented to clarify the initialization requirement that should improve user comprehension and recognition. *(See example below.)*

Figure 5 "Please reset baseline" message



TactiSoft v4.3.0.0



TactiSoft v4.3.1.0

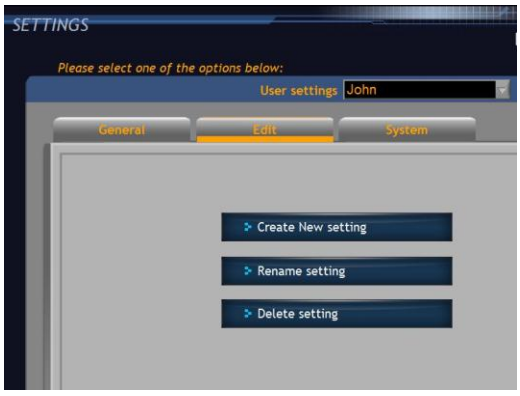
"Please check irrigation" message replaced with "Please check baseline":

In the previous TactiCath catheter design, an irrigation failure could cause a force drift during ablation causing the "Please check irrigation" message to appear in response. Owing to design improvements in the current version of the catheter, irrigation failure during ablation will no longer cause a drift in the contact force. To avoid user error and mitigate the risk of delayed therapy caused by a catheter change, the irrigation message has been replaced by the more appropriate "Please check baseline" message.

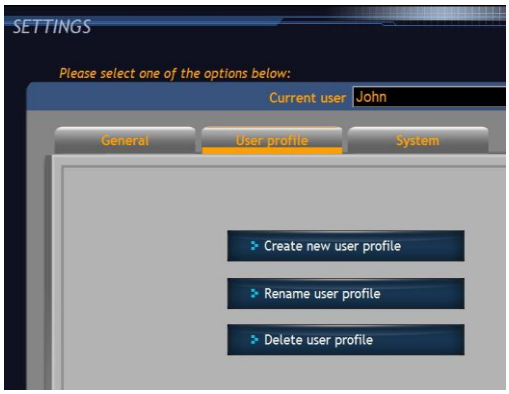
"Settings" menu - Improved wording and button operation:

The summative usability test revealed common user errors associated with navigating the settings screens due to ambiguous labels and inconsistent up/down button behavior. The wording and operation of certain buttons and labels have been improved to better correlate with the button function. *(See example below.)*

Figure 6 Settings Menu



TactiSoft v4.3.0.0



TactiSoft v4.3.1.0

Use of pictograms in procedure screen:

This change has been implemented as an additional change beyond the opportunities of improvement identified during usability testing. The primary intention of this change was to improve readability of the contact force information displayed and to better group numerical and graphical contact force indicators, respectively. The addition of pictograms instead of words or letters allows the use of a uniform user interface in the multilingual international environment, especially with respect to contact force reading and stability indicator in the TactiSoft procedure screen.

K.3 STUDY PURPOSE AND OBJECTIVES

K.3.1 Study Purpose

The purpose of the Continued Access Study is to provide access to the TactiCath Quartz Set during the regulatory review period to collect confirmatory evidence of safety and effectiveness.

K.3.2 Study Objectives

K.3.2.1 Effectiveness

To collect acute effectiveness data on the treatment of symptomatic PAF with the TactiCath Quartz Set.

To collect chronic effectiveness data on the treatment of symptomatic PAF with the TactiCath Quartz Set.

K.3.2.2 Safety

To collect acute safety data on the incidence of early-onset SAEs relative to the TactiCath Quartz Set.

K.4 STUDY ENDPOINTS

Outcomes from the Continued Access Study will be summarized descriptively.

K.5 STUDY DESIGN

K.5.1 Justification for the Investigation

The Continued Access Protocol will provide ongoing physician access to the TactiCath Quartz Set and its use under the same indication to provide confirmatory evidence of the safety and effectiveness of the TactiCath Quartz Set in patients with symptomatic PAF.

K.5.2 Scope of Study

Up to 10 sites in the US currently participating in the TOCCASTAR Study will be invited to participate in the Continued Access Study. Investigators will likewise be chosen from the current group of investigators. Sites will be required to seek approval of the Clinical Investigational Plan and Patient Informed Consent (Version H) as a prerequisite to enrollment.

Up to 150 subjects will be enrolled in a non-randomized manner and treated identically to the Supplemental Clinical Study population except as described in Section K.7.

K.5.3 Study Assessment Intervals

The Continued Access study is intended to provide confirmation that the device is safe and effective for the treatment of PAF in subjects followed for a total of 12 months (3 months blanking period followed by 9 month effectiveness assessment period).

K.5.4 Clinical Investigational Plan

We propose to study the primary safety and acute effectiveness of the TactiCath Quartz Set in the Continued Access Study with the following key features (relative to the TOCCASTAR study):

- Single arm, non-randomized study
- Identical inclusion and exclusion criteria for subjects
- Identical procedural testing requirements during the index procedure
- Identical data collection requirements in the acute study phase
- Follow-up requirements do not include CT/MR scans and TTM monitoring.
- Safety and Efficacy outcomes reported descriptively
- Study restricted to sites who are already participating in the TOCCASTAR Study

K.6 CRITERIA FOR ELIGIBILITY

Subject eligibility is identical to the initial randomized study as described in Section 8 CRITERIA FOR ELIGIBILITY.

K.7 STUDY PROCEDURES

Procedures required in the Continued Access Study are identical to those specified in Section 10 STUDY PROCEDURES with the following exceptions:

1. Subjects enrolled in the Continued Access Study will not be randomized. All subjects will be treated with the TactiCath Quartz Set.
2. Subjects enrolled in the Continued Access Study will not receive ambulatory monitoring via TTM devices. TTM monitoring is replaced by 48-hour holter recordings at 3- and 6-months post procedure, and 72-hour holter recording at 12-months post procedure.
3. CT and/or MR scans are recommended but not required (either pre-procedure or at 3-month follow-up).
4. Subjects may take previously failed antiarrhythmic medications after the blanking period.

Table 4 Schedule of Activities for Continued Access Study

	Baseline	Procedure	Pre-discharge	7 days ± 2 days Telephone	3 months ± 2 weeks	6 months ± 3 weeks	12 months ± 3 weeks	Extended every 6 mos ± 4 weeks
Informed consent	X							
Inclusion/exclusion	X							
Documentation of PAF episodes	X							
Medical history	X							
Thyroid and renal function (standard practice)	X							
PT/PTT or INR	X		X					
Physical examination,vital signs, height, weight[a]	X		X		X	X	X	
Pregnancy test (women of childbearing potential)	X							
12-lead ECG	X		X		X	X	X	
Cardiac medications	X		X	X	X	X	X	
NYHA functional class	X				X	X	X	
Quality of life survey	X						X	
Activated clotting time		X						
Ablation procedure data		X						
Force Sensing data		X						
Arrhythmia events	X		X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X[f]
Protocol deviation	X	X	X	X	X	X	X	
TEE (ICE)[b]	X	(X)						
TTE (recommended)[c]	X		(X)					
CT or MRI scan[d]	X				X			
Holter monitoring[e]					X	X	X	
Arrhythmia history								X

Abbreviations: CT = computed tomography; ECG = electrocardiogram; INR = international normalized ratio; MRI = magnetic resonance imaging; NYHA = New York Heart Association; PAF = paroxysmal atrial fibrillation; PT = prothrombin time; PTT = partial thromboplastin time; TEE = trans-esophageal echocardiography; ICE = intra-cardiac echocardiography. NOTES: a.Weight and height will be assessed at baseline only. b.TEE within 24 hrs or ICE at time of procedure to exclude atrial thrombus. c.TTE within 6 mos to measure left atrial dimension. Recommended within 24 hrs post procedure to exclude pericardial effusion. d.Not required for CAP study subjects. If evidence of stenosis is seen at 3 mos, the investigator may prescribe additional serial scans. e.48 hour Holter recording at 3, 6 months and 72 hour recording at 12 months. f.survival and hospitalizations only.

[redacted]

K.8 PATIENT BENEFITS AND RISKS

Benefits and risks are identical to those described in Section 11 except for those risks that have been reduced by the elimination of the TTM in the study. These risks are somewhat offset by the increased holter monitoring at 3, 6, and 12 months post-procedure. In addition, the TactiCath Quartz Set continues to be used safely in a commercial setting outside of the US having now exceeded 1500 units worldwide. Data resulting from both company and investigator sponsored research has resulted in over 30 peer reviewed publications and presentations that have reported on potential benefits associated with contact force sensing with TactiCath.

K.9 ADVERSE EVENTS

The definitions and reporting requirements related to adverse events, serious adverse events and UADEs are identical to those described in Section 12. Adverse Events will be reported to St Jude Medical.

K.10 CLINICAL EVENTS COMMITTEE

A successor Clinical Events Committee (CEC) will be created to assume responsibility for reviewing all Serious Adverse Events reported in the Continued Access Study. This committee is comprised of 3 to 5 physicians with experience in clinical trial event adjudication, including at least one physician with expertise in each area of the study, who are not participants in the study and who meet regularly throughout the study to adjudicate events in an ongoing fashion. The CEC members are chosen based on their clinical expertise and have no association with any trial for which they adjudicate events. The CEC is blinded to treatment assignment during all deliberations. Three voting members comprise a quorum.

The CEC drafts and agrees upon its working charter for each study. This includes explicit rules outlining the minimum amount of data required, and the algorithm followed in order to classify a clinical event. A CEC Manual of Operations (MOP) is prepared based on this information and the CEC MOP will serve as the guideline for adjudication for the specific trial under review.

Only serious adverse events related to safety will be referred to the Clinical Events Committee (CEC) for adjudication for subjects enrolled in the Continued Access Study, i.e. arrhythmia recurrence resulting in a “treatment failure” will not be adjudicated for an effectiveness endpoint determination.

K.11 PROTOCOL DEVIATIONS

Deviations from the Continued Access Protocol will be reported to St Jude Medical via eCRF.

K.12 AMBULATORY MONITORING

Ambulatory monitoring via Holter monitors will be provided and over-read by a qualified vendor or core lab to ensure quality of monitors and readings.

K.13 OVERSIGHT

Data management and monitoring of conduct for the Continued Access Study will be the responsibility of St. Jude Medical. Clinical investigator agrees to permit St Jude Medical, and its representatives, access to all clinical supplies, source documents, study data, eCRF and other study documents. St. Jude Medical assumes the right to discontinue the study for safety or administrative purposes. St. Jude Medical also assumes all rights regarding use of information and publication.

K.14 OMISSIONS

Unless specifically described in APPENDIX K, all other aspects of study conduct in the Continued Access Study will be the same as in the TOCCASTAR study as described in the body and appendices of this Clinical Investigational Plan.