Hansen Medical

A prospective, single arm study of the Hansen System for introducing and positioning RF ablation catheters in subjects with paroxysmal atrial fibrillation

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Study Information

Study Title	A prospective, single arm study of the Hansen System for introducing and positioning RF ablation catheters in subjects with paroxysmal atrial fibrillation (PAF)
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Intended Use for Clinical Study	The Hansen Medical Sensei® X Robotic Catheter System and Accessories are intended to facilitate manipulation, positioning and control of Hansen Medical's robotically steerable catheters: • for collecting electrophysiological data within the heart atria with electroanatomic mapping and recording systems, using the following percutaneous catheters: the Polaris-Dx™ Steerable Diagnostic catheters made by Boston Scientific Corporation, and the Livewire™ Electrophysiology catheters made by St. Jude Medical, and • for manipulating specified cardiac RF ablation catheters for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three-dimensional mapping systems. This is a premarket IDE study in the United States. Outside of the United States, this is a post market study used according to its intended use per Instructions for Use.
Study Design	A prospective, single-arm, multi-center, US and outside the US (OUS) study to evaluate the safety and effectiveness of the Sensei® Robotic Catheter System and Artisan family of guide catheters for introducing and positioning specified commercially available RF ablation catheters in subjects with symptomatic, drug-refractory paroxysmal atrial fibrillation. Primary safety and effectiveness outcomes must meet pre-established target performance goals. A Bayesian adaptive design is used in the study that allows for interim analyses to be performed initially after 125 subjects have been enrolled and after every 25 subjects thereafter. Stopping rules have been incorporated to evaluate for early success or futility.
Number of Subjects and Investigative Sites	A minimum of 7 and up to 14 US and outside the US (OUS) investigational sites will enroll a minimum of 125 subjects up to a maximum of 250 subjects. Sites may not enroll greater than a predefined number of subjects at each interim analysis without prior

	approval by the Sponsor.
Study Objective	To evaluate the safety and effectiveness of the family of Artisan guide catheters when used to remotely introduce and position commercially available cardiac RF ablation catheters to treat subjects with paroxysmal atrial fibrillation.
Primary Endpoints	Safety: The incidence of Major Complications, including the early onset (within 7 days of the ablation procedure) predefined complications; and the incidence of esophageal injury or pulmonary vein stenosis through day 180. Effectiveness: Chronic Success is defined as: • Freedom from symptomatic atrial fibrillation (AF), atrial flutter, and atrial tachycardia episodes from days 91 - 365 after the initial ablation procedure, as documented by event recording, ECGs, and Holter monitoring. • No use of Class I, Class II ,Class III or Class IV antiarrhythmic medications during days 91 - 365 after the initial ablation procedure with the following exceptions: ▪ Addition of Anti- Arrhythmic (AAD) medication which was previously ineffective for AF and does not exceed the previous historical maximum dosage (24 hour total dose). ▪ Use of Atrioventricular (AV) nodal blocking agents such as beta blockers (BB) and/or calcium channel blockers (CCB) that are maintained at the current dose (does not exceed previous historical maximum dosage (24 hour total dose)). • No more than two additional ablation procedures within 90 days of the initial ablation procedure and no additional ablation procedures after day 90. • No use of a non-study device for ablation of any atrial fibrillation target. Commercially available non-study devices may be used for atrial flutter and atrial tachycardia ablation targets. • No ablation of an atrial fibrillation target made by removing the ablation catheter from the Artisan catheter and manually manipulating the ablation catheter. • Pulmonary vein isolation of at least 3 out of 4 veins confirmed by pulmonary vein entrance block during the last procedure within the blanking period. • No surgical ablation for atrial fibrillation, atrial flutter, or atrial tachycardia within 90 days of the study procedure.

	• No direct current (DC) cardioversion for atrial fibrillation, atrial flutter, or atrial tachycardia within days 91 - 365 after the initial ablation procedure. • No catheter or surgical ablation for atrial fibrillation, atrial flutter, or atrial tachycardia within days 91-365 after the initial ablation procedure.
Secondary Endpoints	Acute Procedural Success: Acute pulmonary vein isolation of at least three out of four veins, as documented by testing entrance block, during the procedure. Chronic Safety: Incidence of Major Complications reported from day 8 through day 365.
Primary Hypothesis	Safety: To determine if the Major Complication rate meets the pre-established target performance goal (TPG) of 16%. H0: $\pi_s \geq 16\%$ vs. H1: $\pi_s < 16\%$, Effectiveness: To determine if the effectiveness rate meets the pre-established target performance goal (TPG) of 54%. H0: $\pi_E \leq 54\%$ vs. H1: $\pi_E > 54\%$, Both primary hypothesis (Safety and Effectiveness) shall be met for study success.
Sample Size	The total sample size will be determined by a Bayesian adaptive design. The trial will enroll a minimum of 125 subjects and up to a maximum of 250 subjects. Interim analyses will be conducted starting after the first 125 subjects are enrolled, and continue every 25 subjects thereafter.
Subject Population	Subjects eligible for study participation must be diagnosed with symptomatic paroxysmal atrial fibrillation refractory to medical treatment, suitable for treatment with RF catheter ablation, meet all inclusion and no exclusion criteria and be willing to comply with all protocol testing and follow-up.
Inclusion Criteria:	1. Subjects with paroxysmal atrial fibrillation who have had two or more spontaneously terminating episodes of atrial fibrillation that last longer than 30 seconds and shorter than 7 days, in the nine months prior to enrollment. At least one episode must be documented with ECG, TTM, Holter monitor, or telemetry. 2. Failure of at least one Class I – IV anti-arrhythmic drug (AAD) for PAF as evidenced by recurrent symptomatic PAF, or intolerable side effects due to AAD. AADs are defined in **Appendix B**. 3. Signed informed consent. 4. Age 18 years or older. 5. Able and willing to comply with all pre-, post-, and follow-up testing and requirements.

Exclusion Criteria	1. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause. 2. Previous ablation for atrial fibrillation. 3. Atrial fibrillation episodes that last less than 7 days and are terminated by cardioversion. 4. Previous valvular cardiac surgery procedure. 5. Cardiac artery bypass graft procedure within the previous 180 days. 6. Previous septal defect repair. 7. Expecting cardiac transplantation or other cardiac surgery within the next 180 days. 8. Coronary PTCA/stenting within the previous 180 days. 9. Documented left atrial thrombus on ultrasound imaging (TEE). 10. Documented history of a thrombo-embolic event within the previous 365 days. 11. Diagnosed atrial myxoma. 12. Presence of an implanted ICD. 13. Presence of permanent pacing leads. 14. Significant restrictive, constrictive, or chronic obstructive pulmonary disease or any other disease or malfunction of the lungs or respiratory system with chronic symptoms. 15. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study. 16. Women who are pregnant. 17. Acute illness or active infection at time of index procedure documented by either pain, fever, drainage, positive culture and/or leukocytosis (WBC > 11.000 mm^3) for which antibiotics have been or will be prescribed. 18. Creatinine $\geq$ 2.5 mg/dl (or $\geq$ 221 µmol/L). 19. Unstable angina. 20. Myocardial infarction within the previous 60 days. 21. Left ventricular ejection fraction less than 40%. 22. History of blood clotting or bleeding abnormalities. 23. Contraindication to anticoagulation medicine. 24. Contraindication to computed tomography or magnetic resonance imaging procedures. 25. Life expectancy of less than 1 year. 26. Enrollment in another investigational study. 27. Uncontrolled heart failure (NYHA class III or IV heart failure). 28. Presence of an intramural thrombus, tumor, or other abnormality that precludes catheter introducing or positioning. 29. Presence of a condition that precludes vascular access. 30. Left Atrial size $\geq$ 50mm. 31. INR greater than 3.0 within 24 hours of procedure. 32. Use of amiodarone therapy within the 3 months prior to the

	ablation procedure.
Medical Device	Subjects will be treated with one of the specified commercially available RF ablation catheters within one of the family of Artisan guide catheters controlled by the Sensei® X Robotic Catheter System. The ablation catheter shall be commercially available in the United States, and if used in Europe, the catheter shall be CE marked. The ablation catheter will be used per its instructions for use, although potentially outside its intended use.
Screening/Baseline	• Demographics • Medical history • Physical exam • NYHA Class • CT/MR within 3 months prior to initial ablation procedure to evaluate pulmonary veins and left atrial morphology and dimensions • 12-lead ECG • Labs, including CBC, BUN, serum creatinine (CR), INR*, pregnancy test • Anti-arrhythmic taken within the past 2 years; Anti-platelet or Anticoagulation medication taken within the past 3 months • Echocardiogram – Transthoracic Echocardiogram (TTE) / Transesophageal Echocardiogram (TEE) within 3 months prior to the index procedure to assess cardiac structure, function, LA size and EF • Echocardiogram – Transesophageal Echocardiogram (TEE) within 24 hours prior to the procedure to exclude left atrial thrombus ***Note**: If preferred by the investigator, TEE or ICE within 24 hours or at the onset of the procedure for both structural and thrombus evaluations.*
Intra/post-procedural Testing	• Cardiac echocardiogram prior to the introducing of the ablation catheter (e.g., TEE, TTE, ICE, or IVUS) • Cardiac echocardiogram 5 minutes after removal of the ablation catheter (e.g., TEE, TTE, ICE, or IVUS) • 12-lead ECG prior to leaving EP lab *At Physician discretion the following may be performed:* • Venogram or ICE to determine location, morphology and dimensions of each pulmonary vein • Routine EP study • Cardioversion • Phrenic nerve pacing • Esophageal temperature probe
Follow-up Testing	Pre-Discharge: • 12-lead ECG • Serum creatinine, BUN, CBC

	• Discharge medications (Antiarrhythmic, Anti-platelet and Anticoagulation only) Follow-Up: • Adverse event assessment via phone: 7 days • NYHA classification and adverse event assessment: 30 days, 90 days, 180 days and 365 days • 12-lead ECG will be done at 30 days, 90 days, 180 days and 365 days • Event recorder (for transtelephonic monitoring) issued to subject at the 90 day visit to be in effect through day 365 to document symptomatic recurrence of AF • As of the 90-day visit, asymptomatic transtelephonic monitoring (TTM) is required weekly for 8 weeks and to document symptomatic recurrence of AF • After the weekly TTM for 8 weeks, asymptomatic transtelephonic monitoring is required once per month and to document symptomatic recurrence of AF throughout the end of the study • CT or MR will be required at 180 days to assess PV stenosis. • 24 Hour Holter monitoring at 180 days and 365 days • Cardiac CT or MR at 365 days in subjects showing more than 50% narrowing of a pulmonary vein at the 180 day cardiac CT or MR

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1.0 Introduction

1.1 Background

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance, increasing in prevalence with age. AF is often associated with structural heart disease, although a substantial proportion of patients with AF have no detectable heart disease. Hemodynamic impairment and thromboembolic events related to AF result in significant morbidity, mortality, and health care cost. Catheter ablation therapy is widely recognized as a useful modality for patients with cardiac rhythm fibrillation that are refractory to medical and ICD treatment, and is increasingly used earlier in treatment.[1]

Physicians specializing in Interventional Cardiology (IC) and/or Electrophysiology (EP) are often confronted by the need to precisely place and control a variety of therapeutic and non-therapeutic catheters in the cardiovascular space. A variety of shapeable and steerable sheaths and guide catheters have been developed to meet this need. These manually controlled catheters traditionally rely upon the ability of the experienced physician to apply varying amounts of distal curvature via pull wires within a steerable catheter. This tip curvature is then used in combination with insertion and torque to manipulate the distal tip of the catheter in a desired fashion. The manual control over the fine movements of the catheter's distal tip typically has limitations for performing complex mapping, ablation and other therapeutic procedures. Maintaining stable tissue contact at the point of ablation is important in achieving efficient heat transfer to tissues without increasing the power requirement[6], but micro-movement can be difficult to assess. Therefore, stable tissue contact relies on operator skill to exert forces at cardiac tissue that is constantly shifting due to cardio-respiratory movement.[7] Robotic catheter manipulation may be one way to overcome or improve the problem of catheter stability.

In minimally invasive surgery, robotic assisted control of the surgical instruments has helped physicians perform difficult dexterous surgical tasks safely and efficaciously. Robotic remote control of catheters has recently been introduced to assist physicians in the safe, accurate placement of the distal catheter tip during percutaneous cardiac procedures. In ablative procedures it is not known whether improving catheter tip stability has a significant effect on lesion quality compared to the manual approach, but some recent publications of both animal and human studies comparing the Hansen Sensei® Robotic System and Artisan Guide Catheter to manual delivery of the ablation catheter suggest that contact pressure conferred by the robotic system results in improved lesion delivery compared to a manual approach[7] and that the use of robotic manipulation during ablation procedures has an event rate similar to manual manipulation.[10,11,12,13] It has been the convention to deliver energy for up to sixty seconds for slow pathway modification and accessory pathways to produce irreversible tissue necrosis. One study suggested that by 30 seconds, robotic ablation appears to exceed the manual ablation signal attenuation at 60 seconds. The study confirmed that transmural lesions were produced at 30 seconds of robotic ablation. Therefore, it may be possible to use shorter ablation times or lower power settings for robotic approaches. This may in turn reduce the likelihood of complications for example, the risk of

damage to contiguous structures and the risk of steam pop which is most likely to occur after 30 seconds [8] at temperatures greater than 40^0C[7, 9].

Studies have also demonstrated that remote navigation for right and left atrial mapping and radiofrequency ablation for atrial fibrillation and atrial flutter were found to be safe and feasible.[2,3,4,5] In these feasibility studies, remote navigation was shown to have a decrease in procedure time and improved success compared to current manual methods.[2] The Hansen Sensei® X Robotic Catheter System and family of Artisan guide catheters are a remote manipulation system, originally cleared by the FDA in 2007 as a delivery system to facilitate manipulation, positioning and control, for collecting electrophysiological data within the heart atria with electroanatomic mapping and recording systems. Sensei® X and Artisan were first CE marked in 2007 to facilitate the manipulation and precise positioning of percutaneous catheters within the atria of the heart. Although widely used in Europe with approved ablation catheters, in the US marketing and training on the system is limited to the collection of electrophysiological data and mapping. The intent is to achieve US regulatory clearance of the Hansen Sensei® Robotic System and the family of Artisan guide catheters for use with specified, commercially available ablation catheters in subjects with paroxysmal atrial fibrillation.

1.2 Prior Investigations

Table 1 below summarizes the dual-arm Hansen vs. Manual clinical publications. Individual summaries follow in the lettered sections. These investigations were conducted at three hospitals by six physicians - two academic centers in Europe and one community hospital in the U.S. In 538 subjects, the studies found similar rates of acute effectiveness, chronic effectiveness, and serious complications. The studies found significantly lower levels of subject and physician exposure to fluoroscopic radiation when the Hansen System was used.

None of the following Hansen vs. manual clinical investigations was sponsored by Hansen Medical; and, Hansen Medical had no part in the development, execution, or publication of the studies.

Table 1: Hansen Remote vs. Manual Biosense Webster ThermoCool® Positioning in Peer-Reviewed Publications

Parameter	Hansen System	Manual	Total
Total Number of Subjects	270	278	538
Atrial Flutter Subjects	25	25	50
Atrial Fibrillation Subjects	245	243	488
Acute Procedural Success (isolation as defined and reported in each study)	100%	100%	100%
Chronic Procedural Success (as defined and reported within each study)	84%	81%	82%
Fluoroscopy Time (minutes)	37.7 ± 18.7	47.8± 16.9	42.8± 17.7
Safety: Serious Complications *tamponade, groin hematoma, ST elevation, esophageal ulcer*	1.2%	0.8%	1.0%

The following sections summarize each dual-arm publication:

a) Ablation of atrial fibrillation utilizing robotic catheter navigation in comparison to manual navigation and ablation:

Two physicians at St. David's Medical Center, a community hospital in Austin, Texas, used a ThermoCool® catheter to treat 390 subjects; 197 were treated manually and 193 were treated using the Sensei® Robotic System and Artisan Guide Catheter to manipulate the ThermoCool® catheter.[10]

Table 2: Hansen vs. Manual Manipulation of ThermoCool® for Atrial Fibrillation

Parameter	Hansen System	Manual
Number of Subjects	193 135 paroxysmal 55 persistent 6 long-lasting persistent	197 127 paroxysmal 55 persistent 11 long-lasting persistent
Acute Isolation	100%	100%
Procedure Time	3.09 ± 0.82 hours	3.05 ± 0.83 hours
Fluoroscopy Time	48.9 ± 24.6 minutes	58.4 ± 20.4 minutes
Long-term Outcomes (freedom from recurrence)	Overall: 85% at 14.1±1.3 months Paroxysmal: 89.8% 14.2±1.3 months Persistent: 70.9% 14.0±1.2 months Long-Lasting: 100% 14.5±1.4 months	Overall: 81% at 14.1±1.3 months Paroxysmal: 85.2% 14.2±1.3 months Persistent: 72.7% 14.0±1.2 months Long-Lasting: 67% 14.5±1.4 months
Safety	2 (1.0%) pericardial tamponade 1 (0.5%) groin hematoma	1 (0.5%) pericardial tamponade 1 (0.5%) groin hematoma

b) Reduced fluoroscopy during the ablation of atrial fibrillation: benefits of robotic navigation.

Physicians at Hamburg UKE in Hamburg, Germany used an irrigated ablation catheter to treat atrial fibrillation in 60 subjects in a prospective randomized trial; 30 were treated manually and 30 were treated with the Sensei® Robotic System and Artisan Guide Catheter manipulating the irrigated catheter.[11]

Table 3: Steven et al (Atrial Fibrillation)

Parameter	Hansen System	Manual
Number of Subjects	30	30
Acute Outcome: Pulmonary Vein Isolation	100%	100%
Chronic Outcome: Freedom from Atrial Fibrillation at 6 months	73%	77%
Procedure Time	156 ± 44.4 minutes	134 ± 12 minutes
Fluoroscopy Time	9 ± 3.4 minutes	22 ± 6.5 minutes
Physician Exposure Time	7 ± 2.1 minutes	22 ± 6.5 minutes

c) Hansen remote navigation for ablation of paroxysmal atrial fibrillation:

Physicians at IKEM in Prague, Czech Republic used a ThermoCool® catheter to map and treat paroxysmal atrial fibrillation in 38 subjects; 22 of the subjects were treated using the Sensei® Robotic System and Artisan Guide Catheter to manipulate the ThermoCool® catheter and 16 subjects were treated by manually manipulating the ThermoCool® catheter.[12]

Table 4: Hansen Remote vs. Manual Positioning of ThermoCool® for Paroxysmal Atrial Fibrillation

Parameter	Hansen System	Manual
Number of Subjects	22	16
Outcome: freedom from symptoms and recurrence (90 day blanking period)	91% (5 ± 1 month follow up)	81% (9 ± 3 month follow up)
Procedure Time	207 ± 29 minutes	250 ± 62 minutes
Fluoroscopy Time	15 ± 5 minutes	27 ± 9 minutes
RF Duration	1641 ± 609 seconds	2188 ± 865 seconds
Safety	No complications	No complications

d) Hansen Remote vs. Manual Ablation of Atrial Flutter with a ThermoCool® ablation catheter:

Physicians at Hamburg UKE used a ThermoCool® catheter to treat atrial flutter in 50 subjects; 25 were treated manually and 25 were treated with the Sensei® Robotic System and Artisan Guide Catheter manipulating the ThermoCool® catheter.[13]

Table 5: Hansen Remote vs. Manual Positioning of ThermoCool® for Atrial Flutter

Parameter	Hansen System	Manual
Number of Subjects	25	25
Acute Outcome: Bidirectional Isthmus Block	100%	100%
Procedure Time	79.4 ± 30.6 minutes	58.4 ± 17.7 minutes
	learning curve data: 105.3 ± 34.8 min (subjects1-10) 60.6 ± 6.3 min (subjects16-25)	
Fluoroscopy Time	5.8 ± 3.6 minutes	8.2 ± 4.6 minutes
Physician Exposure Time	1.9 ± 1.1 minutes	8.2 ± 4.6 minutes
RF Duration	321.7 ± 214.6 seconds	496.4 ± 213.9 seconds
RF Energy	8279 ± 5767 joules	16308 ± 6870 joules
Safety	No complications	No complications

e) Sensei Study versus Manual Procedures Using a Contact Force Sensing Catheter

A recent article was published regarding the use of the Sensei system with a contact force sensing catheter (Ullah, et al., Comparison of robotic and manual persistent AF ablation using catheter contact force sensing: an international multicenter registry study, Pacing Clin Electrophysiol. 2014 Sep 15. doi: 10.1111/pace.12501). The study compared the use of Sensei with the ThermoCool® SmartTouch catheter to manual procedures performed with the ThermoCool® SmartTouch catheter in patients with persistent atrial fibrillation. The study showed a significant increase in one year freedom from atrial fibrillation in the Sensei group as compared to the manual group (64% versus 36%, p=0.01). The study also showed a 41% decrease in fluoroscopy time in the Sensei group and no significant differences in procedure time or complication rate between the two groups.

f) Current IDE Study:

A current IDE study is being performed per the investigational protocol linked with IDE number G090274.

The original protocol, Revision A dated December 21st 2009 was not approved by the FDA. In response, Revision B, dated March 19th 2010 was presented to the FDA along with responses to the non-approval letter on March 23rd 2010. Sections of the protocol that were updated were: Study Design, Chronic Procedural Success, Statistical Hypotheses, Safety, Major Adverse Event Definitions, Study Definitions, Sample Size Determination and Power Analysis, Acute Procedural Success, Effectiveness- Chronic Procedural Success, Study Design and Statistical Considerations, Clinical Event Committee, Primary Hypothesis, Primary Endpoints, Data Safety Monitoring Committee, Study Procedure, Secondary Endpoints, Randomization, Prior Investigations, Poolability, Training of Clinical Investigators, Pre-Procedural Evaluation, Study Procedure: Post Procedural Care, Core Laboratory Data Analysis, Additional Analyses, Follow-up Evaluation, Inclusion and Exclusion Criteria, Table 7: Schedule to Study Assessments, Figure 4: Remote versus Manual Introduction and Positioning of the ThermoCool Catheter, and Appendix B: Classes of Anti-Arrhythmic Drugs (Vaughn-Williams Classifications). As a response to Revision B, conditional approval was granted on April 22nd 2010.

Protocol Revision C, dated May 6th 2010 was updated to address the FDA responses to the Conditional Approval Letter. Protocol Revision C was submitted to the FDA on May 11th 2010. Sections that were modified in Revision C includes: Primary Safety Endpoints, Secondary Chronic Safety Endpoints, Primary Safety Endpoint, Study Information, Major Adverse Event Definitions, Sample Size Determination and Power Analysis, Acute Procedure Success, Secondary Effectiveness Endpoint- Acute Procedural Success, Inclusion and Exclusion Criteria, System Training, Study Procedure, Study Definitions, Holter Monitoring and Event Recording, Primary Effectiveness Endpoint, Analysis of Endpoints, and Poolability.

Another conditional approval letter was provided in response to previous submissions, on June 11th 2010.

Protocol Revision D, dated September 7th 2010, addressed and was submitted along with the IDE Conditional Approval Letter responses submitted on September 14th 2010. The sections in Revision D were: Justification for Sample Size, Study Procedure, Training of Clinical Investigators, Study Definitions, Poolability and Essential Documents for Study Start.

Protocol Revision E, dated September 30th 2010, was in response to interactive communications with the FDA, but mainly administrative updates were made.

On October 15th, 2010, the clinical study was unconditionally approved as a response to the September 14th 2010 submission.

Protocol Revision F, dated April 28th 2011, was submitted to the FDA along with the IDE Annual Report. Revision F, was also updated to remove the requirement of cardiac enzyme testing.

Protocol Revision G, dated May 29th 2012, was submitted along with the IDE Annual Report. Updates in Revision G were mainly administrative.

Protocol Revision H, dated April 23rd 2013, was submitted to the FDA as a modified study plan, and received conditional approval on May 24th 2013. The study was changed from a randomized control study versus manual use of the NaviStar ThermoCool catheter to a single arm, target performance goal based study.

Protocol Revision I, dated June 28th 2013, was submitted to the FDA, responding to the questions listed in the Conditional Approval Letter; full study approval was granted on August 7th 2013. Inadvertently, another Protocol Revision I was submitted to the FDA but dated July 25th 2013. The only clinical site to have submitted the June 28th 2013 Revision I to their IRB was Texas Cardiac Arrhythmia Research Foundation. The protocol Revision I dated July 25th 2013 addresses questions the FDA noted about the 2013 Annual Report. Protocol Revisions noted in the June 28th 2013 submission are contained within and superseded by the July 25th 2013 revision. The initial revision had updates to: Study Information, Study Design, Secondary Endpoints, Secondary Safety Endpoints, Justification for Sample Size, Data Analysis, Poolability, Patient Withdrawal and Missing Data, Assignment of Subject Identification Number, Study Procedure, Table 8: Study Definition of Time Points, Holter Monitoring, Data and Safety Monitoring Board, Study Definitions, Appendix C: Clinical Study Informed Consent Template, Appendix G: Case Report Forms (CRFs), and Appendix L: Major Complication Definitions. The later revision contained the addition of esophageal temperature monitoring, addition of PPI (proton pump inhibitors) for 4 weeks post procedure, clarification of death and atrio-fistula FDA reporting.

Protocol Revision J, dated July 24, 2014, was submitted to the FDA to implement changes in the way in which the use of antiarrhythmic drugs were evaluated in the study. The changes were intended to make the evaluation of AAD use equivalent to the way in which the data were analyzed in the previous IDE study for the Biosense Webster NaviStar ThermoCool Catheter. Several other administrative changes were included.

Protocol Revision K, dated August 26, 2014, was submitted in response to minor questions and clarifications from the FDA on Revision J.

Protocol Revision L, dated October 30, 2014, expanded the study to use commercially available cardiac RF ablation catheters meeting a set of identified specifications to the study. The inclusion of additional RF ablation catheters enables the use of the EnSite mapping system in addition to CARTO. The protocol was also updated to address the poolability analysis to be performed for the different ablation catheters. In addition, the protocol was updated to clarify when a clinical report may be submitted for early success and when a final clinical study report will be completed.

Protocol Revision M, dated December 11, 2014, is the current revision. It further specifies the list of commercially available cardiac RF ablation catheters by trade name and model. The specification of the catheters resulted in minor modifications to the IFU and CRFs.

As mentioned previously, the study was unconditionally approved by FDA in October 2010 as a randomized study. Fifty two subjects were enrolled in the randomized study at seven sites over a 2.5 year period. Thirty five subjects were enrolled in the treatment arm and were treated using the

Hansen System with the ThermoCool® catheter. Seventeen subjects underwent manual delivery of the ablation catheter during the treatment procedure in the control arm using only the ThermoCool® catheter.

In March 2013, enrollment in the current study was suspended to seek FDA approval for a modified study design and investigational plan. The study was re-initiated using a modified design and protocol (Rev H) after conditional IDE approval was granted by FDA. Currently, 61 subjects have been enrolled in the Target Performance Goal (single arm) study.

An interim analyses is planned to assess the primary safety and effectiveness endpoints once 125 subjects have been enrolled. There have been no reported unanticipated adverse events experienced by the study subjects. Four annual IDE progress reports have been submitted and accepted by the FDA. These reports have described study enrollment progress, subject demographics, procedure description, protocol deviations, and reported adverse events. Table 6 provides an enrollment overview of the current IDE status.

Table 6: Current ARTISAN IDE Study Status

ARTISAN AF IDE Study	
Number of Investigational Sites	**10**
Number of Subjects Enrolled in the Single-Arm Study	**74**

1.3 Advantages and Disadvantages

Studies have shown that catheter ablation is a safe and effective treatment option for patients with atrial fibrillation, despite the inherent risks.[2, 3] The Hansen System, including the family of Artisan guide catheters, provide the potential for enhanced navigation, control and stability of tissue contact at the point of ablation over manual manipulation of a commercially available ablation catheter when used in subjects with atrial fibrillation.

The Sensei® X Robotic Catheter System and the family of Artisan guide catheters are CE marked to facilitate manipulation and precise positioning of percutaneous catheters within the atria of the heart. As reflected in a wide body of literature, pulmonary vein isolation procedures and subject demographics in Europe are representative of procedures and demographics in the United States. Literature review of ablation cases done in Europe with the Sensei® X Robotic Catheter System and Artisan Guide Catheter used to manipulate marketed catheters show a similar event rate to standard percutaneous cardiovascular and ablation procedures.[10,11,12,13]

The Sensei® X Robotic Catheter System, family of Artisan guide catheters, and accessories are 510(k) cleared to facilitate manipulation, positioning and control of both the Polaris DX and Livewire Steerable electrode catheters for mapping within the atria of the heart. To date, over 14,000 commercial procedures have been performed using the Sensei X Robotic Catheter System and family of Artisan Guide Catheters to manipulate catheters within the atria of the heart.

The Sensei® X Robotic Catheter System and family of Artisan guide catheters were extensively tested for the CE mark and 510(k) clearance. Full risk analyses have been conducted for the Hansen System for navigating a commercially available ablation catheter.

The primary risks associated with use as proposed in this study are not necessarily associated with the Hansen System, but are inherent in performing any interventional electrophysiological or ablation procedure. These risks include major adverse cardiac events (MACE) as listed in section 8.0 Risk Analysis. The MACE rates associated with the use of the Hansen System are not anticipated to be greater than those associated with manual positioning of intra-cardiac ablation catheters.

1.4 Alternatives

Alternative therapy for symptomatic paroxysmal atrial fibrillation includes the following:

- Pharmacological therapy for rate and/or rhythm control,
- Electrical cardioversion,
- Surgical intervention to create atrial lesions,
- Implantable devices to control heart rate,
- Ablation therapy with approved guide catheters.

1.5 Additional Information

Even though the Hansen System is only used to position a therapy catheter and does not provide therapy, the FDA Guidances for Industry and Staff – *Cardiac Ablation Catheters Generic Indication for Use* and *Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation* have been referenced during the formation of this proposed study. Because the ThermoCool® catheter was initially used in the study within its indication, labeling for the ThermoCool® catheter has also been referenced for creation of the study protocol. The investigational plan also references the *2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for subject Selection, Procedural Techniques, Subject Management and Follow-up, Definitions, Endpoints, and Research Trial Design.*

2.0 Purpose

2.1 Study Purpose

The purpose of this clinical study, in the United States, is to demonstrate that the family of Artisan guide catheters controlled by the Sensei® X Robotic Catheter System can safely and effectively introduce and position a commercially available RF ablation catheter for the treatment of subjects with paroxysmal atrial fibrillation. This is a post market study outside the United States, with the Artisan catheters and Sensei X System used according to CE mark and per Instructions for Use.

This study will gather data to assess the following primary study endpoints:

1. The Major Complication rates including acute events through seven days (as defined in this investigational plan) and the incidence of esophageal injury and pulmonary vein stenosis through day 180.
2. The Chronic Success rate from day 91 through day 365.

2.2 Study Objective

To evaluate the safety and effectiveness of the family of Artisan guide catheters when used to remotely introduce and position specified commercially available cardiac RF ablation catheters to treat subjects with paroxysmal atrial fibrillation.

3.0 Device Description

3.1 Device Name

Hansen Medical Sensei® X Robotic Catheter System and the family of Artisan guide catheters.

3.2 Principles of Operation

The Hansen Medical device consists of two primary components, the Sensei® X Robotic Catheter System and the family of Artisan guide catheters (remotely controlled steerable guide catheters). The physician remotely directs the movement of the Artisan Guide Catheter with the Sensei® X Robotic Catheter System.

The Sensei® X Robotic Catheter System is an electronically controlled mechanical system for remotely controlling the family of Artisan guide catheters. The Sensei® X Robotic Catheter System is comprised of a physician workstation, an electronics rack, and a subject side Remote Catheter Manipulator (RCM). The system allows the clinician to direct the catheter tip to a desired intra-cardiac location based on visual feedback from 3-D electroanatomic maps, fluoroscopic images and Intra-Cardiac Echocardiography (ICE) images while seated at the remote workstation. The RCM electromechanically manipulates the steerable guide catheter in response to commands received from the physician through a special three-dimensional joystick called the Instinctive Motion Controller (IMC) at the physician workstation (Figure 1).

Figure 1: Sensei® X Robotic Catheter Control System

The family of Artisan guide catheters consists of the Artisan and the Artisan Extend Guide Catheters (Figure 2). Each guide catheter is a conventional pull-wire actuated open-lumen guide catheter. The inner lumen is 8F diameter and the guide catheter fits through a standard 14F hemostatic introducer sheath. The guide catheters attach to the RCM (Figure 3) through a sterile drape barrier and the RCM in turn actuates the catheter pull-wires in response to commands from the physician seated at the workstation. The Artisan and Artisan Extend are guide catheters and do not have therapeutic or diagnostic capabilities on their own.

The Artisan was originally cleared with the Sensei® Robotic Catheter System under 510(k) K052480 in May, 2007 and CE marked in September 2006. The Artisan Extend, cleared under 510(k) K122275 in August, 2012 and CE marked in February, 2013, is an extension to the Artisan family of guide catheters. The navigation capabilities of these catheters are identical. The difference between the two catheters is the proximal flush assembly that remains outside of the body throughout the procedure and is the hemostatic introduction point for commercially available catheter-based devices.

Figure 2: Distal Tip Articulation of The Family of Artisan Guide Catheters

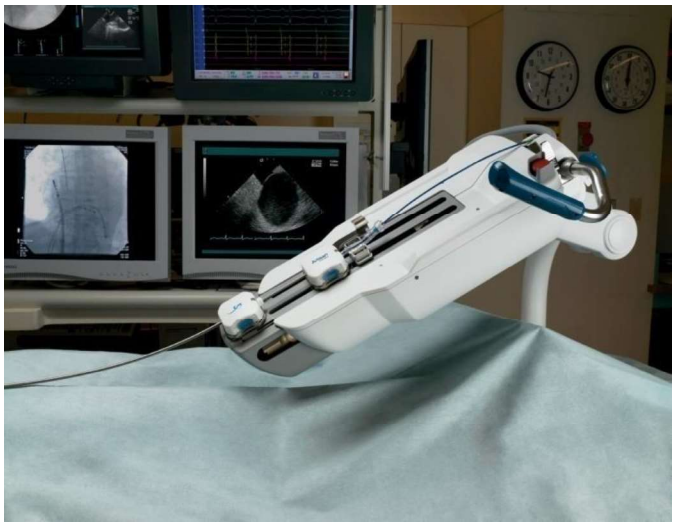

Figure 3: Artisan Catheter Attached to the RCM

The Sensei® X system also has a feature called *IntelliSense*, cleared under 510(k) K073225, that provides the physician with information about the relative level of contact force being applied through the family of Artisan guide catheters. The feature uses force sensors at the proximal opening of the Artisan Guide Catheter to grip the mapping catheter. The output from the force sensors is presented to the physician at the Sensei® X workstation in grams on an instantaneous analog graphic scale, on a running strip-chart scale and via a light, non-directional buzz on the IMC that increases as the reading increases. A sample of the IntelliSense output scale on the workstation screen is shown in Figure 4.

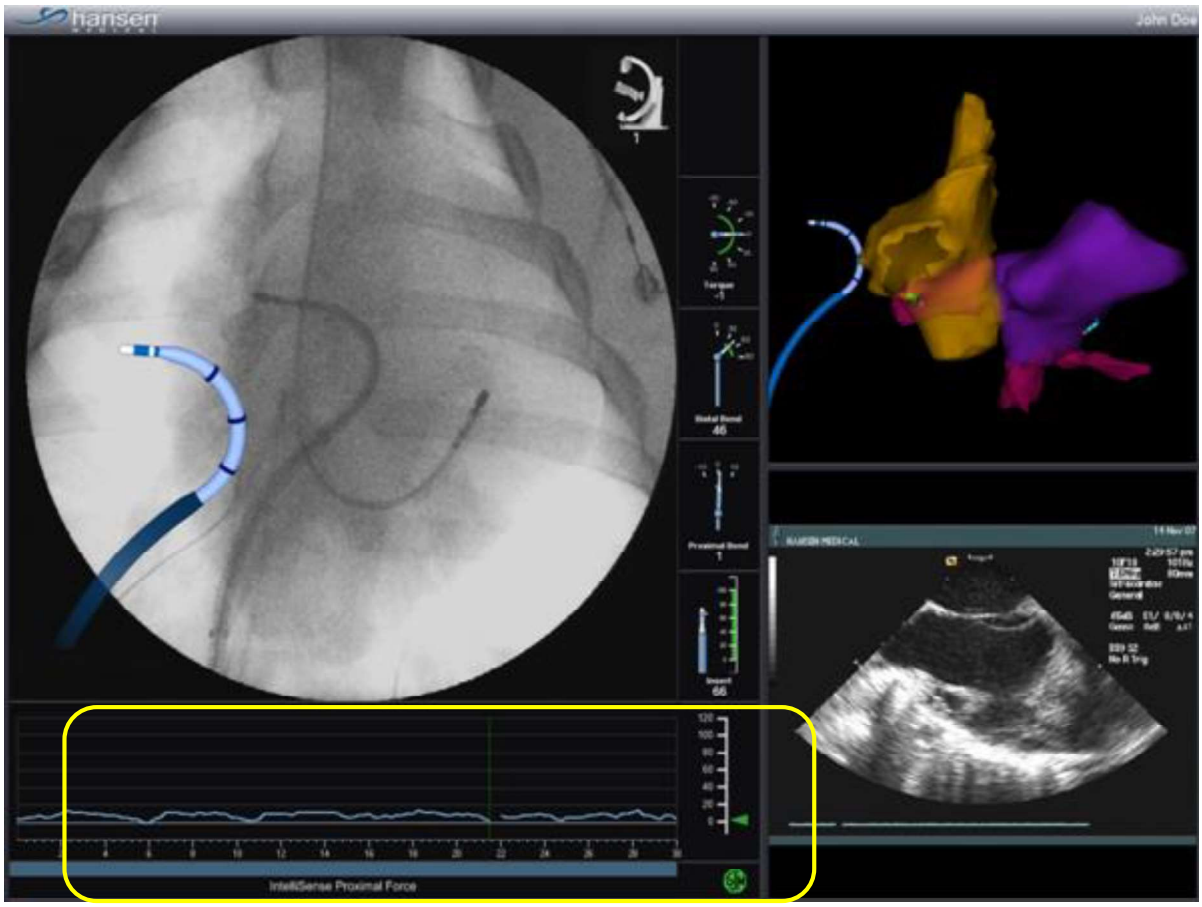

Figure 4: IntelliSense Displays (highlighted in yellow)

3.3 Intended Use

No changes are being made to the Sensei® X Robotic Catheter System or the family of Artisan guide catheters to execute this proposed IDE study. Data from this proposed IDE clinical study will be used to support a submission to extend the intended use to include introducing and positioning of specified commercially available RF ablation catheters for use in subjects with paroxysmal atrial fibrillation in the United States.

3.4 Ablation Catheters

The Sensei X Robotic Catheter System and Artisan guide catheters will be used in this study with commercially available cardiac RF ablation catheters that meet the following specifications[1]. The following catheters will be used in the study: the Biosense Webster ThermoCool,(NaviStar, SmartTouch and Celsius), St. Jude Medical Safire, and the Boston Scientific Blazer II. If the ablation catheter does not meet the specifications below, it should not be used in the study.

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[1] Catheters evaluated through bench testing included the Biosense Webster NaviStar ThermoCool, Biosense Webster Celsius ThermoCool, Biosense Webster ThermoCool SmartTouch, St. Jude Medical CoolPath, St. Jude Medical Safire BLU, St. Jude Medical Safire, and the Boston Scientific Blazer II.

- Commercially available radiofrequency cardiac ablation catheter
- Irrigated tip catheter
- Compatible with CARTO or EnSite Velocity mapping systems
- Compatible with an 8Fr sheath
- Working length ≥110
- Compatibility with multi-plane deflectable sheaths
- Symmetrical tip bending performance. This is observed by setting the ablation catheter in the neutral/straight position and attempting to manually deflect the tip in multiple planes. If the bending performance is symmetrical, the catheter can be used.

The investigator may choose which ablation catheter is to be used for ablation treatment, as long as the catheter meets the specifications listed.

4.0 Labeling

Copies of Instructions for Use for the Hansen Medical Sensei X System and the family of Artisan guide catheters are provided in Appendix I.

5.0 Study Design

This is a prospective, single-arm, multi-center, US and OUS study to evaluate the safety and effectiveness of the family of Artisan guide catheters with the Sensei® X Robotic Catheter System for introducing and positioning one of a set of specified commercially available ablation catheter in subjects with paroxysmal atrial fibrillation. Up to 14 investigational sites will participate in this study to enroll a minimum of 125 and up to a maximum of 250 subjects.

Interim analyses will be conducted starting after the first 125 subjects are enrolled, and continuing every 25 subjects thereafter. At each interim analysis, enrollment may be stopped for expected success or for futility. If there is at least 95% probability that both the safety and effectiveness analysis will meet the success criteria if enrollment stops at the current sample size and all patients are followed to the 12-month endpoint, then enrollment will stop early for expected success. Up to three additional interim analyses will be performed: after full enrollment and at 3 and 6 months after full enrollment to assess the criteria for an early declaration of success. If there is at least 99.9% probability that both the safety and effectiveness analyses will meet the success criteria after all enrolled subjects are followed to the 12-month endpoint, and if a minimum of 80 and 100 patients have complete follow-up for the effectiveness and safety endpoints, respectively, then the trial will declare early success. A clinical study report can then be prepared for submission to the FDA.

Subsequently, the final analysis will occur when the 12-month follow-up is complete for all enrolled subjects. An updated final clinical study report will then be prepared and submitted to the FDA to close out the IDE study.

Based on the interim analyses defined for the study, the maximum number of subjects allowed at any site at each interim analysis is defined in the following table.

Table 7: Maximum Subjects per Site at Each Interim Analysis

Interim Analysis Sample Size	Maximum Subjects per Site
125	25
150	30
175	35
200	40
225	45
250	50

Study subjects with symptomatic, drug-refractory paroxysmal atrial fibrillation will undergo a catheter-based ablation procedure as part of this study to eradicate the aberrant atrial rhythm. If necessary, up to two additional catheter ablation procedures within the 90-day blanking period following the initial ablation procedure may be performed.

Prior to the start of any ablation procedure, the subject's echocardiogram will be reviewed to ensure no evidence of left atrial thrombus. A routine EP study may be performed to evaluate the location, morphology, and dimensions of each pulmonary vein by venogram. Intra-cardiac echocardiography (ICE) may also be performed prior to the ablation procedure at the physician's discretion.

A subject is required to meet all the inclusion and none of the exclusion criteria to participate in the study. Enrollment occurs when a subject signs the Informed Consent Form. The subject must then meet all additional intra-procedural enrollment criteria (i.e. no intramural thrombus, etc.). If the subject does not meet all intra-procedural enrollment criteria, the subject will not be treated with the study device and will be withdrawn from the study. The screening, baseline, and withdrawal case report forms should be completed. The investigator shall report any acute procedural adverse events on the adverse event form.

These subjects who are withdrawn prior to the procedure will count against the maximum enrollment limit. However, the company requests that the maximum enrollment limit is increased accordingly to account for those who signed the Informed Consent Form but did not undergo the study procedure.

5.1 Duration of Study

Subjects will be enrolled for up to one year and have follow-up evaluations at 7 days, 30 days, 90 days, 180 days and 365 days post initial ablation procedure. All subjects will be evaluated on the day of discharge or within 48 hours (whichever comes first), at 7 days post procedure by telephone and 30 days for safety, then 90 days, 180 days, and 365 days post procedure for safety and efficacy. The total duration of the trial will be determined by the

adaptive design, and will be governed by the actual accrual rate and whether any of the pre-specified rules for early stopping are met. Expected study duration could range from 24 months to 42 months.

5.2 Primary Safety Endpoints

The primary safety endpoint is defined as the incidence of Major Complications, as defined below:

Major Complications during the procedure through 7 days:

- Death
- Stroke
- Myocardial Infarction
- Diaphragmatic paralysis
- Transient Ischemic Attack (TIA)
- Cardiac Tamponade
- Pericarditis
- Pneumothorax
- Hospitalization or Emergency Room Visit
- Vascular Access Complication
- Heart Block
- Pulmonary Edema
- Pericardial Effusion resulting in pericardiocentesis or surgical intervention
- Thromboembolism

Major Complications during the procedure through 180 days:

- Pulmonary vein stenosis
- Atrio-esophageal fistula

Major Complication definitions can be found in **Appendix L** of this protocol. All Major Complications, as reported by the clinical investigator, will be reviewed and adjudicated by the Clinical Events Committee (CEC).

All adverse events will be documented and collected once the informed consent has been signed.

In the event of a study subject death, all possible efforts will be made to obtain relevant records from the hospital or the subject's primary care physician, including death certificates, to determine the cause of death.

5.3 Primary Effectiveness Endpoint

The primary effectiveness endpoint is chronic success. Chronic success is defined to be:

- Freedom from symptomatic atrial fibrillation, atrial flutter, and atrial tachycardia episodes from days 91 - 365 after the initial ablation procedure, as documented by event recording, ECGs, and Holter monitoring.
- No use of Class I, Class II, Class III or Class IV antiarrhythmic medications during days 91 - 365 after the initial ablation procedure with the following exceptions.
    - Addition of Anti- Arrhythmic (AAD) medication which was previously ineffective for AF and does not exceed the previous historical maximum dosage (24 hour total dose).
    - Use of Atrioventricular (AV) nodal blocking agents such as beta blockers (BB) and/or calcium channel blockers (CCB) that are maintained at the current dose (does not exceed previous historical maximum dosage (24 hour total dose).
- No more than two additional ablation procedures within 90 days of the initial ablation procedure and no additional ablation procedures after day 90.
- No use of a non-study device for ablation of any atrial fibrillation target. Commercially available non-study devices may be used for atrial flutter and atrial tachycardia ablation targets.
- No ablation of an atrial fibrillation target made by removing the ablation catheter from the Artisan catheter and manually manipulating the ablation catheter.
- Pulmonary vein isolation of at least 3 out of 4 veins confirmed by pulmonary vein entrance block during the last procedure within the blanking period.
- No surgical ablation for atrial fibrillation, atrial flutter, or atrial tachycardia within 90 days of the initial ablation.
- No direct current (DC) cardioversion for atrial fibrillation, atrial flutter, or atrial tachycardia within days 91 - 365 after the initial ablation procedure.
- No catheter or surgical ablation for atrial fibrillation, atrial flutter, or atrial tachycardia within days 91 - 365 after the initial ablation procedure.

5.4 Secondary Endpoints

- **Acute Procedural Success**

  Acute procedural success is defined as the successful ablation of at least three of four pulmonary veins as shown by pulmonary vein entrance block per vein during the initial ablation procedure. A subject is considered to be an acute procedural failure if acute procedural success cannot be obtained by using the Hansen system and, as a result, manual manipulation is needed to complete the ablation procedure with the ablation catheter.

- **Chronic Safety**

  Chronic safety is defined as the incidence of Major Complications during the period from 8 – 365 days following the initial ablation procedure (excluding pulmonary vein stenosis and atrio-esophageal fistula from 8 – 180 days, which are included in the

primary safety endpoint). The incidence of pulmonary vein stenosis and atrio-esophageal fistula is included during the period from 181 – 365 days.

5.5 Additional Analyses

- Length of hospital stay,
- Total ablation time,
- Total ablation energy,
- Total fluoroscopy time,
- Total procedure time (defined as the duration of time from obtaining vascular access to sheath removal),
- Non-AF targets ablated manually,
- Ablative lesion sets in addition to those required for pulmonary vein isolation,
- Adverse events,
- Serious Adverse Events,
- Chronic success rates for subjects treated with a single procedure.

6.0 Statistical Hypotheses

6.1 Primary Safety Endpoint

The primary safety endpoint is defined as the incidence of Major Complications, including all early onset (within 7 days of the ablation procedure) Major Complications, and the incidence of esophageal injury or pulmonary vein stenosis through 180 days. The study is designed to determine if the Major Complication rate meets the pre-established target performance goal (TPG) of 16%. The null hypothesis and alternative hypothesis are:

H0: $\pi_s \geq 16\%$ vs. H1: $\pi_s < 16\%$,

where π_s is the probability of having a primary safety event. The null hypothesis is rejected when at least 95% of the posterior distribution below 16%.

6.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is chronic success as demonstrated by the freedom from symptomatic atrial arrhythmia from days 91 to 365 (as well as additional criteria defined in Section 5.3). The study is designed to determine if the effectiveness rate meets the pre-established target performance goal (TPG) of 54%. The null hypothesis and alternative hypothesis are:

H0: $\pi_E \leq 54\%$ vs. H1: $\pi_E > 54\%$,

where π_E is the probability of meeting the primary effectiveness endpoint. The null hypothesis is rejected when at least 95% of the posterior distribution is above 54%.

6.3 Secondary Safety Endpoint – Chronic Safety

The secondary safety endpoint is demonstration of the long term safety of remotely introducing and positioning ablation catheter through the Artisan Guide Catheter. The secondary safety endpoint is defined as the incidence of Major Complications from days 8 to 365.

The proportion and the one-sided 95% upper confidence level will be calculated for long term safety using the Kaplan-Meier method to account for censoring. No hypothesis test will be performed for the secondary safety endpoint.

6.4 Secondary Effectiveness Endpoint – Acute Procedural Success

The secondary effectiveness endpoint is acute success of remotely introducing and positioning of commercially available ablation catheter through the Hansen system. The secondary effectiveness endpoint is defined as the rate of acute procedure success for at least three out of four pulmonary veins as shown by pulmonary vein entrance block per vein during the initial ablation procedure. A subject is considered to be an acute failure if acute procedural success cannot be obtained by using the Hansen system and, as a result, manual manipulation was needed to complete the ablation procedure.

The rate is estimated using proportions per subject. A one-sided 95% lower confidence level will be calculated for acute success rate. No hypothesis test will be performed for this secondary effectiveness endpoint.

6.5 Justification for Sample Size

This study will use a Bayesian adaptive design. The total sample size will be no less than 125 subjects and will not exceed 250 subjects (however, the maximum may be increased to replace subjects who have been withdrawn prior to the procedure). It is estimated that 5% of the subjects enrolled will be withdrawn prior to the study procedure. Should the "true" rate for the primary safety endpoint equal 8% and the "true" primary effectiveness rate equal 72%, then the probability of study success using this adaptive design would be 98%. See **Appendix M** for details of the adaptive procedure.

6.6 Target Performance Goals

The target performance goals for the study are primarily based upon the pivotal IDE study conducted by Biosense Webster on the NaviStar® ThermoCool® device for the treatment of subjects with symptomatic paroxysmal atrial fibrillation (ClinicalTrials.Gov Identifier: NCT00116428). The results of the study were submitted to FDA in PMA Supplement P030031/S011. The inclusion and exclusion criteria and study endpoints for this study are equivalent to the NaviStar® ThermoCool® study.

The NaviStar® ThermoCool® study reported a primary safety endpoint of 11% and a 12 month primary effectiveness rate of 64%. The target performance goals are defined by incorporating a clinically nonsignificant difference to the reported safety and effectiveness ThermoCool® rates. The approach is analogous to the choice of a non-inferiority margin for a randomized non-inferiority study.

For the primary safety endpoint, a 5% margin is added to the NaviStar® ThermoCool® results, resulting in a target performance goal rate of 16%. For the primary effectiveness endpoint a 10% margin is subtracted from the ThermoCool® rate, resulting in a target performance goal of 54%.

6.7 Data Analysis

All statistical analyses will be done using the SAS software version 9.3 or later (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved), R software or StatXact (Copyright © 2010, 1989-2012, Cytel Software Corporation).

All data will be collected as detailed in the clinical trial schedule. Subject demographics, medical history, risk factors, procedure characteristics, and outcome variables will be summarized using descriptive statistics for continuous variables (e.g. mean, standard deviation) and frequency tables or proportions for discrete variables.

The "Intention to Treat" (ITT) population includes all enrolled subjects. This includes subjects who signed an informed consent form. Subjects who are not enrolled due to not meeting the intra-procedural criteria are considered to be withdrawn from the study. Subjects who have already had a 14F introducer sheath introduced who subsequently are withdrawn during the procedure prior to treatment with the study device will be monitored for any acute adverse events related to the introduction of the 14F introducer sheath. Acute safety data for these subjects will be reported as a separate cohort, since these subjects are not treated with the study device. Additional subjects may be enrolled to replace subjects who were withdrawn due to not meeting the intra-procedural enrollment criteria. The primary statistical analysis will be performed on the cohort of subjects who are enrolled, meet the intra-procedural enrollment criteria, and are treated with the study device.

The following additional endpoints will be analyzed but will not be tested for statistical significance and will be reported as proportions, or means and standard deviations.

- Length of hospital stay,
- Total ablation time,
- Total ablation energy,
- Total fluoroscopy time,
- Total procedure time,
- Non-AF targets ablated manually,
- Ablative lesion sets in addition to those required for pulmonary vein isolation,

- Adverse events,
- Serious Adverse Events,
- Chronic success rates for subjects with a single procedure.

6.8 **Poolability**

Investigational Site

Investigational sites will use a common protocol, the sponsor will adequately monitor the study to assure protocol compliance, and the data gathering and validation mechanisms will be the same across all study sites. The results for the primary endpoint will be stratified by clinical site. Sites with five or less subjects will be pooled together into a single pseudo site. The rates for the primary safety and primary effectiveness endpoints will be compared across sites using a Fisher's Exact test. The p-value cut off for significance will be $p=0.15$. Note that differences in results across sites due to a site/investigator effect cannot truly be assessed in a single arm study since it can be confounded with differences in demographics and baseline characteristics across sites. Hence, should the resulting p-value for the site to site comparison be less than 0.15 a comparison of demographics/baseline characteristics (including age, gender, cardiac history, CHADS score, lesion sets) across site will be made. All variables that differ across sites ($p<0.15$) will be included in a multivariate logistic regression model along with site, using the endpoint outcome as the dependent variable in order to determine if the observed site differences persist after adjustment for these characteristics.

Geographic Region

A similar analysis will be performed to compare results across the two regions, for all US sites combined and for all OUS sites combined. The study will include a maximum of seven OUS sites, and these sites may not enroll more than 50% of the total subjects enrolled in the study. The primary endpoints will be presented stratified by US versus OUS sites, and the results compared using a Fisher's Exact test. If differences in outcomes are found ($p<0.15$), then any baseline differences detected will be included in a multivariate model along with site as independent variables and the outcome variable as the dependent variable. This multivariate analysis will be performed to assess the effect of site after adjusting for potential confounders.

Ablation Catheter

A similar analysis will be performed to compare results from various ablation catheters used during the study. The primary endpoints will be presented stratified by ablation catheter type, and the results will be compared using a Fisher's Exact test. If differences in outcomes are found ($p<0.15$), then any baseline differences detected will be included in a multivariate model along with the ablation catheter as independent variables and the outcome variable as the dependent variable. This multivariate analysis will be performed to assess the effect of ablation catheter after adjusting for potential confounders.

Subject Withdrawal and Missing Data

Missing data at interim analyses and final analysis will be handled using a multiple imputation approach. Missing final outcomes for the primary efficacy and safety endpoints will be multiply imputed using a piece-wise exponential time-to-event model. Sensitivity analyses will be performed to evaluate subjects who are not compliant with the transtelephonic monitoring (TTM) requirements. See **Appendix M** for the statistical details of this model, which includes sample size

7.0 Study Procedures

7.1 Inclusion and Exclusion Criteria

Subject Inclusion and Exclusion Criteria - Subjects are required to meet all the inclusion/exclusion criteria to be eligible for participation (including intra-procedural criteria).

The following sections outline the specific inclusion and exclusion criteria for the study. Subjects who meet **all** of the general inclusion criteria and **none** of the exclusion criteria will be eligible for study participation.

Inclusion Criteria

To be eligible for enrollment in the study the following criteria must be met:

1. Subjects with paroxysmal atrial fibrillation who have had two or more spontaneously terminating episodes of atrial fibrillation that last longer than 30 seconds and shorter than 7 days, in the nine months prior to enrollment. At least one episode must be documented with ECG, transtelephonic monitoring (TTM), Holter monitor, or telemetry.
2. Failure of at least one Class I – IV anti-arrhythmic drug (AAD) for PAF as evidenced by recurrent symptomatic PAF, or intolerable side effects due to AAD. AADs are defined in **Appendix B**.
3. Signed informed consent.
4. Age 18 years or older.
5. Able and willing to comply with all pre-, post-, and follow-up testing and requirements.

Exclusion Criteria:

Subjects are **ineligible** for enrollment in the study if they meet **any** of the following criteria:

1. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
2. Previous ablation for atrial fibrillation.
3. Atrial fibrillation episodes that last less than 7 days and are terminated by cardioversion.
4. Previous valvular cardiac surgery procedure.
5. Cardiac artery bypass graft procedure within the previous 180 days.
6. Previous septal defect repair.
7. Expecting cardiac transplantation or other cardiac surgery within the next 180 days.
8. Coronary PTCA/stenting within the previous 180 days.
9. Documented left atrial thrombus on ultrasound imaging (TEE).
10. Documented history of a thrombo-embolic event within the previous 365 days.
11. Diagnosed atrial myxoma.
12. Presence of an implanted ICD.
13. Presence of permanent pacing leads.
14. Significant restrictive, constrictive, or chronic obstructive pulmonary disease or any other disease or malfunction of the lungs or respiratory system with chronic symptoms.
15. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study.
16. Women who are pregnant.

17. Acute illness or active infection at the time of index procedure documented by pain, fever, drainage, positive culture and/or leukocytosis (WBC > 11.000 mm^3) for which antibiotics have been or will be prescribed.
18. Creatinine ≥ 2.5 mg/dl (or ≥ 221 μmol/L).
19. Unstable angina.
20. Myocardial infarction within the previous 60 days.
21. Left ventricular ejection fraction less than 40%.
22. History of blood clotting or bleeding abnormalities.
23. Contraindication to anticoagulation.
24. Contraindication to computed tomography or magnetic resonance imaging procedures.
25. Life expectancy of less than 1 year.
26. Enrollment in another investigational study.
27. Uncontrolled heart failure (NYHA class III or IV heart failure).
28. Presence of an intramural thrombus, tumor, or other abnormality that precludes catheter introducing or positioning.
29. Presence of a condition that precludes vascular access.
30. Left atrial size ≥ 50mm.
31. INR greater than 3.0 within 24 hours of procedure.*
32. Use of amiodarone therapy within the 3 months prior to the ablation procedure

If subject's INR is minimally >3.0 within 24 hours pre-procedure, another INR may be done on day of procedure, if INR results < 3.0, subject may be enrolled.

7.2 Assignment of Subject Identification Number

All subjects screened and enrolled in the study will be assigned a subject ID number. The format is alpha numeric and three parts. The first part represents the three character site identifier (assigned by Hansen Medical) consisting of two digits followed by the letter "A", i.e., 01A, 02A, etc. The second part is numeric (three digits), assigned sequentially beginning with 001 for the first subject. The third part consists of the subject's initials. Thus, the first subject, Mickey Sue Mouse at site 01 will be assigned 01A-001-MSM; the next subject, Donald Duck (no middle name), will be assigned an identification number of 01A-002-D-D, etc. Per regulations, we cannot collect subject initials for all of the OUS sites participating in this study, therefore we will use "OUS" for all OUS subject initials. The subject initials for OUS sites will be: site identifier (assigned by Hansen Medical) – identifying sequential number- OUS.

7.3 Baseline, Pre-Procedure, Procedure, Pre-Discharge and Follow-up

The definition of study time points and schedule of study assessments to take place during the study are outlined in Table 8 and Table 9below. The events and assessments that are to

take place at each study time point are described in detail below. Standard of care for events and assessments may vary from site to site.

7.3.1 Screening/Baseline Evaluation – within 30 days of enrollment

The following baseline data must be collected from all subjects prior to enrollment in the study. Subjects will be screened for eligibility by the investigator or designee. Subjects who meet the eligibility criteria for participation will be required to read and sign an Informed Consent Form prior to baseline evaluation. A medical history inclusive of medications will be taken and a physical examination will be performed to assess overall physical status.

Test results that are within the timeframes specified below may be used even though the actual test was done prior to the subject's informed consent. This may be done only for standard of care tests with the intent to minimize stress and discomfort to the subject and reduce costs. Required screening evaluations include the following.

The following evaluations will be conducted at the baseline visit:

- Inclusion/Exclusion criteria assessment,
- Informed consent,
- Demographics,
- Medical history,
- Medication history: Antiarrhythmics (2 years); Anti-platelets & Anticoagulation (3 months),
- Physical examination,
    - Vital signs,
    - New York Heart Association (NYHA) Class (see **Appendix E**),
- Laboratory evaluations,
    - CBC,
    - INR (only if subject previously on anticoagulation therapy),
    - Serum Creatinine,
    - Blood Urea Nitrogen (BUN),
    - Pregnancy test (women of child bearing potential) – ***within 7 days of procedure,***
        - If a subject become pregnant during this study, she must notify the site staff
- TTE to assess cardiac structure, function, LA size and EF **(*within 3 months prior to procedure),***
- *CT or MR **(within 3 months prior to procedure)*** to evaluate pulmonary vein and left atrial morphology and dimensions.

Note: If a CT or MR is performed at baseline, the same imaging specifications performed at baseline must be performed at the follow-up visit for 180 and 365 day.

7.3.2 Pre-Procedure Evaluation – Within 24 hours of procedure

Within 24 hours prior to the initial ablation the following will be done:

- Blood will be drawn to measure for INR value*,
- 12-lead electrocardiogram (ECG) performed to check for cardiac rhythm and indication of myocardial ischemia,
- TEE/ICE should be performed to assess for possible atrial thrombus 24 hours prior to procedure or the day of the procedure. Also to establish that thrombus, cardiac structure, function, LA size and EF meet protocol criteria.

**If subject's INR is minimally >3.0 within 24 hours pre-procedure, another INR may be done on day of procedure, if INR results < 3.0, subject may be enrolled.*

Table 8: Definition of Study Time Points

Interval	Time Point and Window (if applicable)
Screening/Baseline	Within 30 days except for pregnancy test (within 7 days), from initial ablation
Pre-procedure	Within 24 hours prior to the initial ablation.
Enrollment	Subject is considered to be enrolled once they sign the Informed Consent Form.
Discharge	0 – 48 hours or prior to discharge; whichever comes first.
7-Day Follow-up	7 days ± 3 days.
30-Day Follow-up	30 days ± 14 days post initial ablation procedure.
90-Day Follow-up	90 days ± 14 days post initial ablation procedure.
180- Day Follow-up	180 days (6 months) ± 30 days post initial ablation procedure.
365- Day Follow-up	365 days ± 30 days post initial ablation procedure.

7.3.3 Study Procedure

Pulmonary vein (PV) isolation is the required ablation procedure. Additional optional ablation procedures are allowed based on clinical findings after the PV isolation is completed. Any non-PV foci identified in the left atrium (LA) and/or right atrium (RA) that trigger AF should be ablated. Isolation of the superior vena cava (SVC) should be performed if AF triggers are identified inside the SVC. Atrial linear lesions are allowed only if any arrhythmia is induced post PV isolation.

- In the US, several catheters are approved for the treatment of various cardiac arrhythmias. Only commercially available catheters that meet the specifications defined in this protocol may be used in this study. The subjects will be prepared, hemostatic introducers will be inserted, and anesthesia will be delivered per the standard protocol for the electrophysiology (EP) lab. A 30cm 14F femoral introducer sheath is recommended for introducing of the Artisan catheter.
- A single or double trans-septal puncture will be completed per standard EP lab protocol to access the left atrium.
- Systematic anticoagulation with heparin shall be administered per standard EP lab protocol with a recommended activated clotting time (ACT) of 300-400 seconds checked every 30 minutes.
- Evaluation of the location, morphology, and dimensions of each pulmonary vein by venogram or ultrasound may be performed at the discretion of the investigator. To evaluate the presence of intracardiac thrombus, TEE should be performed 24 hours prior to the procedure or the day of the procedure.
- Diagnostic catheters, such as coronary sinus and circular mapping catheters may be appropriately placed during the procedure at the discretion of the investigator.
- A routine EP study may be performed at the discretion of the investigator.
- Precautionary measures such as phrenic nerve pacing may be performed at investigator discretion prior to ablation.
- An esophageal temperature probe shall be placed to monitor esophageal temperature when ablating of the posterior left atrial wall.
- If the subject is in atrial fibrillation, cardioversion may be performed at the discretion of the investigator.
- A baseline structural echocardiogram (trans-thoracic, trans-esophageal, intra cardiac or IVUS) will be performed just prior to the introduction of the ablation catheter and a start time will be noted for the ablation portion of the procedure.
- If subject meets any of the intra-operative exclusion criteria, withdraw the subject from the study. The screening, baseline, and withdrawal case report forms should be completed. Any acute procedural adverse events shall be reported on the adverse event form.

- The ablation catheter shall be inserted into the Artisan catheter. If the ablation catheter does not fit smoothly through the Artisan catheter, the poorly fitting catheter should not be used and should be replaced with another catheter.
- Ablation of the cavotricuspid isthmus may be performed only in subjects with a history of typical atrial flutter or inducible cavotricuspid isthmus dependent atrial flutter.
- SVC isolation shall be performed if AF triggering potentials are noted in the SVC.
- The ablation catheter will be remotely manipulated to map and ablate within the atria.
    - The ablation catheter shall be placed within the Artisan catheter and manually introduced into the subject under fluoroscopic guidance.
    - A CARTO or EnSite Velocity three-dimensional electroanatomic mapping system shall be used to map the anatomical locations of pulmonary veins and ablative lesions.
    - A circumferential anatomical approach shall be used to electrically isolate the pulmonary veins.

      Recommended Ablation Parameters:

      Place ablative lesions 1-2 cm outside of the pulmonary veins in order to minimize the risk of pulmonary vein stenosis. Target Sensei® IntelliSense readings of 10-20g, with a maximum of 40g, during lesion creation.

      RF power should typically be set to 20-25W with a nominal maximum power of 30W. Starting at 20-25W in an anatomical region, RF power may be increased after 15 seconds in 5W increments to achieve a transmural lesion as shown by local atrial electrogram attenuation or splitting. Ablation duration at a single anatomical lesion location is recommended to be limited to 30 seconds. If the ablation output time for the RF generator is set for longer than 30 seconds, the ablation catheter should be moved so that the ablation duration in a particular location doesn't exceed 30 seconds.

      When ablating on the posterior left atrial wall, power should be reduced to mitigate the occurrence of an atrio-esophageal fistula. RF power should typically be set to 15-20W, and should not exceed 20W. Esophageal temperature should be monitored and energy delivery should be terminated if the esophageal temperature reaches or exceeds 41°C, as measured from the esophageal temperature probe.

      Remember that stable contact between the catheter tip and the tissue increases the efficiency of RF power transfer to the tissue.

      For power levels up to 30W, a flow rate of 17 ml/min should be used (refer to the catheter Instructions for Use for specific recommendations for flow rate). If the temperature increases to greater than 50°C or the impedance rises 20Ω or more, the RF application should be terminated

immediately, the ablation catheter should be removed and the coagulum removed (if present), and irrigation flow confirmed before the catheter is used again.

- Verification of electrical PV isolation: A circular or basket catheter shall be used for verification of PV isolation by demonstrating entrance block for each pulmonary vein. Confirmation of PV isolation in at least 3 of 4 pulmonary veins must be achieved to meet the criteria for acute procedural success.

- A second structural cardiac echocardiogram (trans-thoracic, trans-esophageal, intra cardiac or IVUS) will be performed five minutes after the ablation catheter is removed from the subject to assess for the presence of a pericardial effusion. The time of this evaluation will be documented.
- Refer to the Hansen Medical Artisan IFUs and the ablation catheter IFU for more catheter use information.
  - It should be recorded in case report forms if it is not possible to safely complete treatment of a pulmonary vein due to proximity of the phrenic nerve or esophagus.
  - Additional optional ablation lesions shall be noted (for example: mitral isthmus, cavo-tricuspid isthmus, or non-pulmonary vein foci).
  - For every RF energy application, the following ablation information will be collected: force, power, impedance value, temperature, irrigation flow rate, and ablation duration. Refer to the case report forms for specific items.

Post-Procedural Care:

- Subjects will be monitored in the recovery room until stable per the investigative site's standard post-treatment procedures.
- Low molecular weight or intravenous heparin should be used as a bridge to resumption of systemic anticoagulation following catheter ablation and sheath removal. All subjects should be on anticoagulation therapy for at least two months following the procedure. Decisions regarding the use of anticoagulation therapy for longer than two months following procedure should be based on the subject's risk factors for stroke and not the presence or type of AF. A $CHADS_2$ score will be used to determine the risk of stroke for the subjects and their need for anticoagulation therapy. Discontinuation of anticoagulation therapy beyond two months post ablation is not recommended in subjects who have a congestive heart failure, history of high blood pressure, age (75 years), diabetes, prior stroke or transient ischemic attack $CHADS_2$ score of ≥ 2. Either aspirin or warfarin is appropriate for subjects with a $CHADS_2$ score of 1. Refer to **Appendix N** for the $CHADS_2$ score.

  This anticoagulation strategy is based on the 2012 HRS Consensus Task Force recommendations, as listed on Table 4, Page 24 of the referenced HRS document.
- Each subject may be treated again using the Hansen System up to two more times during the blanking period.

- Any follow-up ablation procedure conducted within the study timeline for each patient, will need to be documented. The repeat ablation procedural date(s) and if the procedure was conducted manually or robotically will be the data points collected in the study database.

- Proton pump inhibitors should be administered for 4 weeks post ablation.

7.3.4 Antiarrhythmic Drug (AAD) Therapy

If the subject is being maintained on beta blocking agents, calcium channel blockers or digitalis for a condition other than for AAD purposes, this medication shall be maintained throughout the duration of the subject's involvement in this investigation unless deemed unnecessary or detrimental to the subject by the treating physician.

- Procedure through 90 days (blanking period)

  After the ablation procedure, subjects may be placed on AAD therapy:

  - As prophylaxis for early AF recurrence
  - For treatment of left atrial flutter

  A new medication or a previously prescribed medication may be used.

  It is recommended to withdraw AAD therapy 4-6 week post procedure to evaluate the subject's arrhythmia status.

  - If symptomatic AF recurs following removal of AAD therapy during the blanking period, subjects may be offered an additional ablation procedure and/or placed on long term AAD therapy at the discretion of the investigator with a previously ineffective, but tolerated AAD dose.
  - Class I, Class II, Class III and Class IV drugs may be used except amiodarone
  - It is recommended that subjects be started on long term AAD therapy no later than 1-2 weeks prior to the end of the blanking period to ensure that adequate dosing is achieved.

- 91 - 365 days (after the blanking period)
  - Subjects may continue or start a previously used AAD medication up to the maximum historical dose 2 years prior to the procedure

As a component of the primary effectiveness endpoint, success with respect to AAD therapy is defined as:

- Freedom from AAD therapy from 90-365 days (after the blanking period)
- Use of previously used AAD medication from 90-365 days which does not exceed the maximum historical dose 2 years prior to the procedure

An AAD failure is defined as:

- Use of previously used AAD medication from 90-365 days (after the blanking period) which exceeds the maximum historical dose 2 years prior to the procedure
- New AAD therapy (not previously taken prior to procedure or during the blanking period) started after the blanking period

This antiarrhythmic treatment strategy is based on the NaviStar® ThermoCool® IDE study. The strategy acknowledges that it is common practice to reinitiate antiarrhythmic drug therapy to attempt to control the AF.

7.3.5 Pre-Discharge Evaluation

Subjects will be evaluated for any change in antiarrhythmic, anti-platelet or anticoagulation medication from baseline medication, Major Complications (MC) and adverse events (AE) **before hospital discharge or within 48 hours, whichever comes first.** The following evaluations will be performed at this pre-discharge visit:

- Record any changes in baseline anticoagulants, anti-platelets, or anti-arrhythmic medications,
- Major Complications,
- Adverse events,
- CBC,
- BUN/CR,
- 12-lead ECG,
- Physical examination, including pulse rate, respiration rate, and blood pressure.

7.3.6 Follow-up Evaluation

7 days (± 3 days) post procedure

A scripted phone call will be made to the subject to assess for Major Complications, concomitant medications (antiarrhythmic, anti-platelet, anticoagulation, or proton pump inhibitor) and adverse events since discharge from the hospital.

30 days (± 14 days) post procedure

Subjects will be asked to return for a follow-up visit at 30 ± 14 days. At this follow-up visit, subjects will undergo an evaluation for changes in medications (antiarrhythmic, anti-platelet or anticoagulation), Major Complications and adverse events. The following evaluations will be performed at this follow-up visit:

- Physical examination including, pulse rate, respiration rate, and blood pressure,

- NYHA classification,
- Concomitant medications (antiarrhythmic, anti-platelet, anticoagulation, or proton pump inhibitor),
- 12-lead ECG,
- Major Complications,
- Adverse events.

90 days (± 14 days) post procedure

Subjects will be asked to return for a follow-up visit at 90 days (± 14 days). At this follow-up visit, subjects will undergo an evaluation for changes in medications (antiarrhythmic, anti-platelet or anticoagulation), Major Complications and adverse events. The following evaluations will be performed at this follow-up visit:

- Physical examination,
- NYHA classification,
- Concomitant medications (antiarrhythmic, anti-platelet or anti-coagulation),
- 12-lead ECG,
- Event recorder issued to subject at this visit to be in effect through day 365 (1 year) to document symptomatic recurrence of AF. Asymptomatic trans-telephonic monitoring (TTM) is required weekly for the first 8 weeks and for any symptomatic episodes. After 8 weeks, asymptomatic transtelephonic monitoring is required once per month and with symptomatic episodes throughout the end of the study.
- Major Complications,
- Adverse events,
- Discontinuation of AAD.

180 days (± 30 days) post procedure

Subjects will be asked to return for a follow-up visit at 180 days (± 30 days). At this follow-up visit, subjects will undergo an evaluation for changes in medications (antiarrhythmic, anti-platelet or anticoagulation), Major Complications and adverse events. This visit will specifically evaluate the presence of esophageal injury or pulmonary vein stenosis.

The following evaluations will be performed at this follow-up visit:

- Physical examination,
- NYHA classification,

- Concomitant medications (antiarrhythmic, anti-platelet or anticoagulation),
- 12-lead ECG,
- 24 hour Holter monitor,
- Cardiac CT or MR*,
- Major Complications,
- Adverse events.

Note: The safety CT/MR imaging must have the same Imaging parameters as the Baseline. For example, if a CT performed at baseline, a CT must be performed at this visit with the same imaging specifications.

365 days (± 30 days) post procedure

Subjects will be asked to return for a follow-up visit at 365 (± 30 days). At this follow-up visit, subjects will undergo an evaluation for changes in medications (anti-arrhythmic, anti-platelet or anticoagulation), Major Complications and adverse events. The following evaluations will be performed at this follow-up visit:

- Physical examination,
- NYHA classification,
- Concomitant medications (antiarrhythmic, anti-platelet or anticoagulation),
- 12-lead ECG,
- 24 hour Holter monitor,
- Major Complications,
- Adverse events,
- Cardiac CT or MR: *only required in subjects showing more than 50% narrowing of a pulmonary vein at the 180 day cardiac CT or MR imaging. The imaging modality and parameters must be the same as the initial baseline imaging.*
- Study Exit.

If at any time during the follow-up period a subject shows potential signs of pulmonary vein stenosis or atrio-esophageal fistula, the standard of care should be followed inclusive of the appropriate imaging for diagnosis. All reports of imaging done outside of the protocol required follow-up are to be forwarded to the Sponsor.

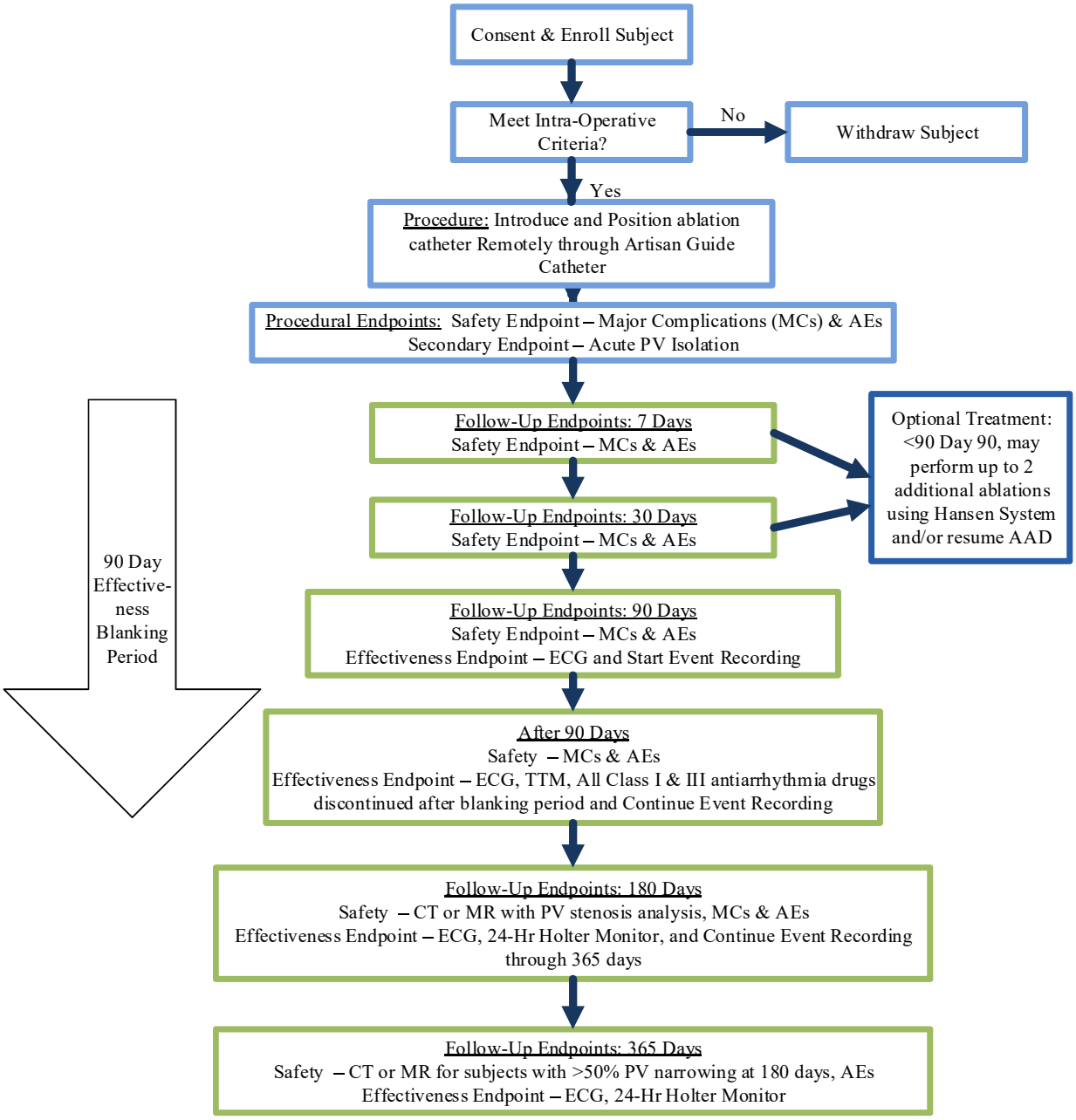
Table 9: Schedule of Study Assessments

	Screening/ Baseline (testing within 30 d)	Pre-Procedure (within 24 hrs.)	Procedure	Pre-Discharge	7-Day Follow-up (± 3d)	30 Day Follow-up (± 14d)	90 Day Follow-up (±14d)	180 Day Follow-up (± 30d)	365 Day Follow-up (± 30d)
Informed Consent	X								
Demographics and Medical History	X								
Physical Exam/Vital Signs	X			X		X	X	X	X
Medication History[1]	X			X	X	X[1]	X	X	X
Cardiac CT/MR*	X[8]							X	X[11]
12 lead ECG		X	X[9]	X		X	X	X	X
NYHA Class	X					X	X	X	X
TEE/ICE		X[5]							
TTE	X[10]		X [6]						
Esophageal temperature monitoring			X						
24 hr. Holter Monitor								X	X
Event Recorder (3 thru 12 months)							X[7]	X	X
CBC	X			X					
BUN/Creatinine	X			X		X[4]			
INR[2]	X	X							
Pregnancy Test (within 7 days)		X[3]							
Adverse Events			X	X	X	X	X	X	X
Device Performance			X						
Proton Pump Inhibitor Administration				X	X	discontinue			

1. Antiarrhythmic Anti-platelet, Anticoagulation
2. Only if subject on anticoagulation therapy
3. Within 7 days of Procedure. Applicable to female of childbearing potential.
4. Applicable only to subject in chronic renal failure or who had an elevated creatinine during index hospitalization.
5. Within 24 hours of procedure, or at the onset of the procedure for both structural and thrombus evaluation.
6. TTE, TEE, ICE or IVUS required prior to ablation catheter insertion and 5 minutes after ablation catheter removal.
7. Each subject is to be given an event recorder at the 90 day visit. Subjects should continue to use event recorder as instructed thru the 365 day f/u visit.
8. Within 3 months of initial ablation procedure
9. Done at end of procedure prior to leaving EP lab.
10. Within 3 months prior to procedure
11. Subjects showing pulmonary vein (PV) narrowing of more than 50% at 180 day f/u visit shall have a cardiac CT or MR scan to evaluate for PV stenosis at 365 days.

*Note: If a CT or MR is performed at baseline, the same imaging specifications must be used at the follow-up visit for 180 and 365 days.

Figure 5: Study Algorithm for Subject Participation



7.4 Missed Follow-up Visits

If a subject refuses to return for any follow-up visit, the investigator or research personnel will attempt to obtain at least vital status and whether or not the subject has experienced episodes of AF. A Protocol Deviation eCRF will be completed for each missed visit. The investigator will remain responsible for subject follow-up and data integrity. A subject may be exited from the study if he/she has missed two consecutive follow-up appointments. However, 3 documented attempts by investigator and study staff must be made prior to subject withdrawal. An escalation of the follow-up attempts should be used at the site's discretion. Escalation includes telephone calls, certified letters, email notification, and calls to family members.

7.5 Subject Withdrawal or Lost to Follow-up

A subject may voluntarily withdraw from the study at any time. The investigator and research staff should encourage all subjects to return for the Protocol required follow-up visits. If a subject refuses study follow-up, he/she should be encouraged to be followed by a physician per the standard of care and the investigation site should attempt to collect vital status and study related adverse events.

The investigator may also withdraw the subject's participation in the study.

A subject will be considered lost to follow-up and terminated from the study by the Sponsor once the subject has missed two consecutive follow-up appointments and three documented attempts have been made by the investigator to contact the subject or subject's relatives to schedule each appointment. One of the three documented attempts must include a certified letter. The Investigator must complete the appropriate eCRF documenting the subject's termination from the clinical study.

7.6 Bias Control Measures - Core Laboratory Data Analysis

7.6.1 Cardiac CT/MR

A cardiac core laboratory will be utilized to allow for the objective evaluation of pre- and post-procedure CT/MR imaging. Evaluations of these images will be performed by the core lab's technical personnel trained in the evaluation of the images to detect the presence or absence of pulmonary vein stenosis per the core lab protocol. The core lab will provide an imaging protocol for each type of imaging test listed in the protocol. Uniformity of these tests maximizes the accuracy of the comparison between the pre- and post-procedure results of each subject and comparison of test results between sites. A baseline cardiac CT/MR (performed within 3 months of the study procedure) must be completed for each study subject and submitted to the cardiac core laboratory for comparison to the study-required CT/MR image/s.

7.6.2 Holter Monitoring and Event Recording

A core laboratory will be used to evaluate the events obtained from the 24-hour Holter monitors and ECG data at the 6 and 12 month follow-up visits for recurrence of an atrial arrhythmia (atrial fibrillation, atrial flutter or atrial tachycardia) episode. Initial

evaluations will be done by a technical person trained in the evaluation for these tests and the initial evaluations will be affirmed by a physician.

In addition to the clinical sites following the study subjects, the core lab also will track the subjects to ensure that each subject remains active in the use of their event monitor. Subjects will be provided a TTM monitor at the 90-day visit. The core lab will create and provide copies of the required TTM schedules for subjects to transmit their weekly and monthly transmissions in accordance with the protocol requirements. Subjects are required to submit asymptomatic readings weekly for 8 weeks following the blanking period, then once a month on a monthly basis for the remainder of the study. Study subjects also will be instructed to use the event monitor at any time following their 90 day through day 365 follow up visit for any recurrence of their symptoms. The core lab will accept subject transmission 24 hours a day and 7 days per week. If a study subject misses their scheduled transmission, the core lab will contact the site until the subject is reached and a transmission has been received.

Study subjects will be considered compliant with the use of the TTM device if they transmit within ±3 days of their scheduled transmission date and achieve at least 80% of their scheduled transmissions. If the TTM compliance rate is less than 80%, it will be considered as a major protocol deviation.

7.7 Clinical Events Committee

A committee of physicians, with a specialty related to the study procedure and not associated with Hansen Medical will be selected as the Clinical Events Committee (CEC) for this trial. Responsibilities of the CEC are listed below:

- The approval of specific criteria used to define and categorize clinical events and clinical endpoints in the study in conjunction with the Sponsor.
- Reviewing and adjudicating all investigator-indicated device-related adverse events and all adverse events that have the potential to be Major Complications, including the occurrence of early onset events 7 days post ablation procedure) and the incidence of esophageal injury and pulmonary vein stenosis through 180 days.
- Review and adjudicate the following potential Major Complications (Section 7.8.3) that occur within 7 days of the ablation procedure, including:

  - Death,
  - Stroke,
  - Myocardial infarction,
  - Diaphragmatic paralysis,
  - Transient ischemic attack (TIA),
  - Cardiac tamponade,
  - Pericarditis,
  - Pneumothorax,
  - Hospitalization or emergency room visit,

- Vascular access complications,
- Heart block,
- Pulmonary edema,
- Pericardial effusion resulting in pericardiocentesis or surgical intervention,
- Thromboembolism.

- Review and adjudicate the occurrence of pulmonary vein stenosis or atrio-esophageal fistula through day 180.
- Review and adjudicate adverse events reported as possibly/probably device-related.
- Re-adjudicate events in question or when data subsequently changes or new data become available.
- See **Appendix L** for a definition of all Major Complications.

7.8 Adverse Events

Adverse events (AEs) are defined as any unfavorable and unintended sign, symptom, or disease possibly associated with the study procedure, study device or required study testing. This does not imply that there is a relationship between the adverse event and the device under investigation. All AEs will be recorded onto the Electronic Data Capture (EDC) case report form for visits (post procedure) documented in the permanent medical record. The investigator is ultimately responsible for reporting AEs to the Sponsor. The investigator will evaluate the AE in detail, including the date of onset, description, severity, duration, outcome, and causality as specified in this section.

Intensity or Severity of an Adverse Event:

The intensity or severity of each AE must be assessed according to the following classification:

Table 10: Adverse Event Severity

Mild	An event that results in minimal transient impairment of a body function or damage to a body structure, and/or does not require intervention other than monitoring.
Moderate	An event which results in moderate transient impairment of a body function or damage to a body structure, or which requires intervention, such as the administration of medication or cardioversion, to prevent permanent impairment of body function or damage to body structure.
Severe	An event which is life threatening, which results in a permanent impairment of a body function or damage to a body structure, or which requires significant intervention, such as the major surgery, to prevent permanent impairment of body function or damage to body structure.

Outcome:

The outcome of each AE must be assessed according to the following classification:

Table 11: Adverse Event Outcome

Resolved	Subject fully recovered with no observable residual effects.
Improved	Subject's condition improved, but residual effects remain.
Unchanged	AE is ongoing.
Worsened	Subject's overall condition worsened.
Death	Subject died as a result of the AE (whether or not the AE is related to the investigational device or procedure).

Causality:

The causality of each AE must be assessed according to the following classification:

Table 12: Adverse Event Causality

Device –related	The investigational device directly caused or contributed to the AE.
Possibly device related	The investigational device may have caused or contributed to the AE.
Procedure related	The event is directly associated by timing and/or is pathophysiologic with standard electrophysiology or ablation procedure described in this protocol.
Possibly procedure related	The event may be associated by timing and/or is pathophysiologic with standard electrophysiology or ablation procedure described in this protocol.
Not related	The event is not associated with the investigational device or the procedure described in this protocol.

7.8.1 Anticipated Adverse Events

Procedure and device-related complications that may be anticipated in subjects undergoing electrophysiology ablation treatment are listed in Section 8.1.under the risk management section. These pre-defined complications are considered anticipated AEs.

Additionally, adverse events that are inherent to an interventional procedure and expected to occur in most subjects for a projected duration according to the opinion of the investigator may be considered unavoidable. Such events include, but are not limited to, those listed in Table 13. ***Such adverse events that are considered expected and unavoidable to the study (ablation) procedure should not be reported during the study.***

Table 13: DO NOT REPORT: Adverse events related to the initial ablation

Description of the Event	Time Frame from the Index Procedure
Anesthesia-related nausea and/or vomiting.	Resolved within 48 hours with or without antiemetics.
Headache related to NPO status.	Resolved within 24 hours with or without pain medication.
Back pain related to laying on table.	Resolved within 48 hours with or without pain medication.
Pain at access site.	Resolved within 72 hours with or without pain medication.
Sleep problems or insomnia.	Resolved within 72 hours with or without sleeping medication.
Mild to moderate bruising or ecchymosis at access site.	Resolved within 7 days post procedure.
Vaso-Vagal reaction with access site introducer sheath removal.	Reversed with fluid bolus and/or atropine administration.
Self-limiting pericarditis attributable to the ablation procedure defined as pleuritic chest discomfort with or without pericardial rub and ECG changes which did not require prolonged hospitalization.	Physician discretion
Nodal dysfunction rhythms (sick sinus syndrome, sinus bradycardia, sinus arrest or AV blocks) that resulted in symptomatic bradycardia, unrelated to the ablation procedure or pre-existing disease states, treated with pacemaker implantation	N/A
Recurrent AF is not considered an AE. If recurrent AF triggers an event considered to be an AE (hospitalization >24hrs, stroke, etc.) then that event will be documented on the AE case report form.	N/A

7.8.2 Serious Adverse Events (SAEs):

A Serious Adverse Event is any untoward medical occurrence that:

1. Results in death,
2. Is life-threatening,
3. Requires hospitalization or prolongation of existing hospitalization *,
4. Results in persistent or significant disability/incapacity,
5. Requires medical or surgical intervention to prevent serious outcome.

An observational, overnight hospital admission < 24 hours in duration does not qualify as a SAE.

All serious adverse events must be reported by eCRF (entering the information into the study electronic database) by the investigator or their designee within 24 hours of receiving the report. The investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn

consent, or the adverse event is otherwise explained. Investigators also are required to inform their IRB/EC of serious adverse events (as outlined in their IRB/EC procedures) and in accordance with FDA and local regulatory requirements. All related medical records will be required for submission to Hansen Medical for serious adverse events reported.

Any death or atrio-esophageal fistula shall be reported to the FDA by Hansen Medical no later than 10 working days from Hansen Medical's original receipt of the information.

The Hansen Medical contact for questions is:

Tammy Drew
Project Lead, Senior Clinical Research Associate
Telephone: 650-404-2765
E-mail: tammy_drew@hansenmedical.com

7.8.3 Major Complications

Major Complications are adverse events which may occur in conjunction with or following atrial ablation that are included in the primary safety endpoint for this study. The list and definitions for adverse events that are considered Major Complications are outlined in **Appendix L**.

Should a Major Complication occur, the investigator is required to report by eCRF all available information regarding the Major Complication to the Sponsor promptly upon learning of the event. Additional time may be required in order to obtain the background details related to a Major Complication; however, the report of its occurrence should be made to the Sponsor once the investigator first learns of the event. All related medical records will be required for submission to Hansen Medical for Major Complications that are reported.

All potential Major Complications reported will be reviewed and adjudicated by the CEC. Major Complications will be classified as either a Primary Safety Endpoint or a Chronic Safety Event depending on the event occurrence following the ablation procedure, (Refer to definitions in Sections 5.2 and 5.4).

7.8.4 Unanticipated Adverse Device Effects

An unanticipated adverse device effect (UADE) is defined as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity, or degree of incidence in the investigational plan 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 subjects" (21 CFR Part 812.39).

The investigator must notify the Sponsor and IRB/EC of any UADE occurring during the clinical study no later than 10 working days after the investigator learns of the event. All UADEs must be documented by the investigator including the date of onset, a complete description of the event, possible reason(s) for the event, severity, duration, actions taken and outcome. Copies of all supporting documents should be sent to Hansen Medical.

Any UADEs that occur during the course of the Study will be reported to the participating investigators and their IRBs/ECs. A report from the Sponsor will be submitted to the FDA no later than 10 working days after being notified by the investigator.

7.9 Mechanical Failures or Malfunction

If study device failures or malfunctions occur, contact Hansen Customer Service at 1-866-426-0804, and refer to the Return Material Authorization (RMA) process in **Appendix J**.

Examples of possible device malfunctions include:

- Packaging is defective,
- Device physically deforms or breaks, even if caused by user error,
- Device fails to perform as intended.

7.10 Medical Device Vigilance reporting (EU sites)

For European investigational sites, the Medical Device Vigilance System will be used to report incidents to the appropriate regulatory agencies.

7.11 Data and Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) is comprised of an independent group of experts serving in an individual capacity to provide their expertise and recommendations to Hansen Medical concerning the conduct of the study. The board is composed of members including a biostatistician and physicians from one or more of the following disciplines: cardiology, neurology, and/or cardiac electrophysiology. This board will assemble to review the results of each interim analysis or on an urgent basis (as needed) to review all CEC-adjudicated Major Complications and device-related adverse events. The board has the responsibility to advise the Sponsor about the appropriateness of continuing, or terminating the study based on the findings of their review. The board will generate reports to support their findings.

7.12 Data Collection and Evaluation

Data gathered during the course of the study will be documented through electronic data capture (EDC). Missing, incomplete or inconsistent data will be requested from the investigation site personnel and appropriate corrections will be made. An audit trail will identify all changes and corrections to the electronic data. Training on the use of the EDC system along with instructions for completion of the EDC eCRFs will be provided to the study site personnel by Hansen Medical or its designee.

7.13 Source Documentation

Regulations require that an investigator maintain information in the study subject's medical record to corroborate data collected on the eCRF. To comply with these regulatory requirements, all medical records pertaining to each subject's participation in the study should be maintained and made available as required by Hansen Medical and/or its designee as well as regulatory inspectors. Access to original medical records must be provided. Complete medical (clinical and hospital) records include but are not limited to the following documentation.

- Medical history/physical condition of the subject before involvement in the study, date and reports on study required testing sufficient to verify clinical protocol entry criteria.
- Description of device usage during study procedure (procedural logs, drugs administered during the procedure, device identification information and disposition, date, time, imaging results and clinical findings, study specific worksheets etc.).
- Signed notes in the subject's medical record on the enrollment day that identify and include: the subject's date of enrollment, procedure date, the study sponsor (Hansen Medical), site name, the subject's assigned study identification number, and documentation and confirmation that the appropriate informed consent was obtained from the subject.
- Dated and signed notes for each subject's study-required visit.
- Lab test results.
- All ECG, Ultrasound, CT, MR and any other imaging reports, etc.
- Dated printouts or reports of special assessments (ECG report, imaging report, laboratory results etc.).
- Adverse event reporting and follow-up of the adverse event. Information in the medical record should include at a minimum the following: event description, severity, seriousness, onset date, date site became aware of event, duration, relation to study device, treatment, and outcome of the adverse event.
- Study subject's condition upon completion of or withdrawal from the study. This includes number and type of attempts to ensure subject compliance to study-required visits.

Source Documentation must be available at all times for inspection by the study monitors and regulatory inspectors.

7.14 Protocol Deviations/Violations

A protocol deviation occurs when a clinical investigator and/or study site personnel do not conduct the study according to the clinical investigational plan (protocol). All deviations must be recorded on the eCRF: Protocol Deviation**.** United States regulations (21 CFR 812.140) require that investigators maintain accurate, complete, and current records relating to the clinical study. This includes documents showing the dates and reasons for each deviation from the clinical investigational plan. Depending upon the nature of the protocol deviation, expedited reporting and prior approval from Hansen Medical may be

required. All deviations will be summarized and submitted in IDE progress reports, annual reports, and the final study report to the FDA.

If Hansen Medical finds that an investigator is not complying with the executed study agreements, the investigational plan, the FDA regulations, or the requirements of the reviewing IRB, prompt action will be taken to secure compliance. In addition, the participation of the investigator may be terminated (21 CFR 812.46). Additional information is provided in Section 13.4 – Study Termination.

7.14.1 Deviations with Expedited Reporting Requirements

For the following types of protocol deviations (per 21 CFR 812.150), an investigator is required to notify Hansen Medical and the IRB within 5 business days of the deviation.

- Emergency Deviation from the Investigational Plan (a deviation to protect the life or physical well-being of a subject in an emergency).
- Failure to Obtain Informed Consent from the subject.
- Failure to apply any of the inclusion and exclusion criteria for subject enrollment into the study.

Notification to Hansen Medical and/or the IRB should be documented and maintained in the clinical study file at the site and at Hansen Medical.

7.14.2 Deviations Requiring Prior Approval

An investigator is required to obtain prior approval from clinical study management at Hansen Medical and the IRB before initiating deviations from the Investigational Plan that affect the scientific soundness of the plan, or the rights, safety, and welfare of the subjects (non-emergent situation). However, prior approval is not required in situations where unforeseen circumstances are beyond the investigator's control, e.g., subject did not attend scheduled follow-up visit, laboratory test was performed incorrectly, and test equipment did not operate properly.

7.14.3 Non-Urgent Deviations

Protocol deviations which do not have the urgency associated with expedited notification or prior Hansen Medical/ IRB approval (as discussed in the above paragraphs) will be reported upon discovery, such as during completion of eCRFs or a monitoring visit.

8.0 Risk Analysis

8.1 Potential Risks

The primary risks associated with use as proposed in this study are not necessarily associated with the Hansen System, but are inherent in performing any interventional electrophysiological or ablation procedure. These risks include major adverse cardiac events (MACE), venous perforation and dissection, cardiac tissue damage, and cardiac wall perforation with accompanying clinically significant hemo-pericardium and/or

cardiac tamponade requiring further intervention. When used on the left side of the heart, additional risks include distal emboli leading to myocardial infarction and/or stroke, pulmonary vein (PV) stenosis, esophageal injury/atrio-esophageal fistula and phrenic nerve injury. The MACE rates associated with the use of the Hansen System are not anticipated to be greater than those associated with manual positioning of intra-cardiac ablation catheters.

2012 HRS Consensus Task Force identifies the general risks with atrial mapping and ablation procedures (Table 6, Page 41 of the referenced HRS document) include but are not limited to:

Systemic

- Allergic reactions
- Drug reactions
- Death
- Fever
- Infection/sepsis
- Low blood pressure
- Ischemia/infarction of tissue/organ

Cardio-Pulmonary

- Angina/coronary ischemia
- Arrhythmias
- Atrial/septal defect requiring repair
- Bradycardia or other conduction disturbances
- Cardiac arrest
- Cardiac effusion
- Congestive heart failure
- Damage to the heart valves and/or supporting structures
- Dyspnea
- Endocarditis
- Hemoptysis
- Myocardial infarction
- Need for a permanent pacemaker
- Perforation of the cardiac muscle
- Pericarditis

- Pulmonary edema
- Pulmonary embolism
- Pulmonary hypertension
- Pleurisy
- Pulmonary vein stenosis
- Pulmonary vein obstruction
- Respiratory arrest
- Tamponade
- Ventricular fibrillation

Vascular

- Aneurysm
- Arteriovenous fistula
- Blood clots in peripheral arteries and/or veins
- Pain and tenderness at access site
- Perforation or rupture of a blood vessel
- Pseudoaneurysm
- Temporary or total occlusion of the blood vessel
- Thrombophlebitis
- Thromboembolic episodes
- Vascular access complications requiring intervention (e.g. bleeding and/or hematoma, vessel dissection, pseudoaneurysm, retroperitoneal hemorrhage, and infection)
- Vessel spasm

Neurological

- Silent cerebral embolism
- Stroke or other neurological complication (e.g., paralysis, paraplegia or aphasia)
- Transient ischemic attacks (TIAs)
- Changes in mental status
- Femoral neuropathy
- Nerve injury/peripheral neuropathy
- Vagal nerve injury

Other

- Esophageal injury, e.g. Atrio-esophageal fistula

- Bleeding from anticoagulant medications
- Gastric motility/pyloric spasm
- Headache
- Heparin induced thrombocytopenia (HIT)
- Permanent or temporary nerve damage to the heart or diaphragm
- Renal failure/insufficiency, transient or chronic
- Surgery required for treatment of an adverse event
- Increased exposure to radiation

Subjects will be offered sedation throughout the procedure. General risks of sedation include but are not limited to:

- Allergic reaction
- Aspiration
- Cardiac arrest
- Death
- Low/high blood pressure
- Nausea and/or vomiting
- Respiratory difficulties
- Headache

Clinical evaluation of the Hansen System in humans is justified because the risks are reasonable in relation to the expected benefits of device use.

Other risks potentially associated with the Artisan Extend Catheter include:

- Prolongation of the procedure
- General vessel damage
- Damage to vessels adjacent to the vessels used for advancing the system

8.2 Minimization of Risks

Efforts will be made throughout the course of this investigation to minimize these risks to subjects choosing to participate. The following general efforts will be made to minimize these risks:

- Clearly defining the subject inclusion/exclusion criteria that ensure only appropriate subjects are enrolled.
- Clear conduct and documentation of the subject consent process by the investigator or the delegated authority at the site.
- Ensuring that the treatment and follow-up of subjects are consistent with current medical practices.

- Selecting investigators who are experienced in EP and ablation procedures.
- Training to the study protocol.
- Specific investigator eligibility criteria to participate in study (see Section 9.1).
- Frequent monitoring visits to investigational sites and status reports to the principal investigator and study administration personnel.

Additionally, every subject participating in this study will undergo the following to determine their anatomical suitability for the study procedure:

- Cardiac CT or MR
- ECG
- TTE and/or TEE
- Intra-procedural echocardiogram

Post procedure, subjects will be closely monitored in order to ensure for early detection & intervention for any observed adverse events.

8.3 Potential Benefits

Although there is no guarantee of benefit, the Hansen System may offer the following benefits to the delivery of the ablation catheter with the intent to isolate and treat the pulmonary veins

- Effective single treatment success rate,
- Reduced procedure time,
- Reduced exposure time to ionizing radiation for the subject and physician.

9.0 Selection of Clinical Investigators

9.1 Clinical Investigator Requirements

Investigators selected will be responsible for fulfilling the clinical study requirements specified in this investigational plan. The study center must have the necessary resources to comply with the requirements. The following criteria will be used to select investigators for participation in the clinical study:

- Investigator is qualified by training and expertise in EP and ablation procedures.
- Investigator and sub-investigators must have previous experience using the Hansen System. Hansen Medical must give approval for each physician, individually, to treat subjects. This will be based on prior experience and training. Principal investigators shall attest to having performed at least 100 manual ablation procedures. In addition, physicians must have completed at least 20 Hansen remote procedures in the past 12 months to be qualified to be part of the study. Physicians may be asked to cease study participation if they consistently fail to enroll 2 study subjects per month.

- Investigational sites must have an established Institutional Review Board (IRB) or identified contract IRB. IRBs must operate and function in conformance with 21 CFR Part 56.
- Investigational sites must possess adequate research personnel to manage the administration of the study at the investigative site and to collect the data for sponsor submission.
- Investigator and clinical research staff have experience with US IDE studies and have the time to conduct the study in accordance with the investigational plan.
- Agreement to comply with the investigational plan and regulatory requirements.
- Adequate volume of potential subjects who meet the eligibility criteria.
- The number of simultaneous competing clinical studies should be such that the study investigator commits to enrolling a minimum of 2 subjects per month into the Hansen study.
- Investigators are expected to enroll at least 2 subjects per month within the first 3 months after receipt of a Sponsor site activation letter.
- Appropriate facilities, resources, and equipment to conduct the study.
- Commitment by investigational personnel (investigator and study personnel) to undergo required study training.
- Commitment and able to complete study initiation activities in a timely manner (2-4 months).

All investigators will sign the appropriate study-related agreements (Investigator/Sub-Investigator Agreement, Clinical Research agreement) before study initiation.

9.1.1 Training of Clinical Investigators

All principal investigators have completed Hansen Medical Level II training and records are on file at Hansen Medical in the Training department.

9.1.1.1 Protocol Training

The training of appropriate clinical site personnel will be the responsibility of Hansen Medical or its designee. To ensure uniform data collection and protocol compliance, a formal educational session to study personnel will include: review of the protocol, review of inclusion and exclusion criteria, instructions on procedural data collection and submission, and regulatory requirements.

9.2 Subject Population

The study population considered eligible for this study includes adult subjects diagnosed with symptomatic paroxysmal atrial fibrillation refractory to medical treatment, suitable for treatment with a commercially available ablation catheter, who meet the inclusion criteria and do not meet any of the exclusion criteria and are willing to comply with all protocol required testing and follow-up. All subjects who are considered eligible for pulmonary vein ablation will be consecutively screened for inclusion into this study.

A Subject Screening Log will be maintained at each center to document select information about the subjects screened for enrollment. This log will document which subjects met the eligibility criteria and which subjects did not. For those that did not meet the eligibility criteria, the reasons for non-enrollment will be documented. Should a study eligible subject refuse consent, reason for refusal should be noted on the screening log, as well. The Screening Log will be evaluated and discussed at each monitoring visit.

9.3 Subject Enrollment

Initiation of enrollment into the clinical study will begin following FDA supplemental IDE approval, investigative site Institutional Review Board (IRB), Ethics Committee (EC) approval and collection of all required regulatory documents by Hansen Medical. A site should be in receipt of a site activation letter from the sponsor in order to initiate enrollment into the study. Subject eligibility will initially be determined by the investigator based on the inclusion/exclusion criteria. All subjects must be considered candidates for pulmonary vein isolation via a catheter ablation procedure. The investigator will inform the subject of his/her eligibility and discuss the clinical study with the subject including the risks, benefits and required follow-up procedures before obtaining informed consent (see **Appendix C** for Informed Consent template). Informed consent and The Health Insurance Portability and Accountability Act (HIPAA) documents must be obtained prior to accessing any study related subject information or performing any baseline study-specific procedures. The informed consent process must be documented in writing in the subject's medical record.

10.0 Investigator Responsibilities

10.1 Essential Documents for Study Start

Investigators are required to provide Hansen Medical the following information prior to subject enrollment at the clinical site:

- Executed Non-Disclosure agreement.
- Copy of Principal Investigators' curriculum vitae, signed & dated within 2 years. Signed and dated sub-investigators' curriculum vitae must be collected prior to their participation in the study.
- Copy of current Principal Investigator's license. Sub-investigator's licenses must be collected prior to their participation in the study.
- Executed Clinical Study Agreement. Signed Sub-Investigator Agreements must be collected prior to their participation in the study.
- Executed Site contract inclusive of budget agreement.
- Financial disclosure for Principal Investigator. Sub-Investigator financial disclosures must be collected prior to their participation in the study.
- IRB membership list or General assurance number.
- Laboratory certification and normal ranges for the determinations described by the protocol.

- Copy of the IRB approval letter and IRB-approved informed consent document.
- Training Records, as applicable (investigational plan, data collection) for all site personnel currently involved in study activities.
- Completed Delegation of Authority (DOA) log listing all personnel currently involved in this study. The DOA is a living document and should be updated as study personnel are added to or leave the study.
- Investigator signed Protocol Acknowledgement Form.

10.2 Specific Investigator Responsibilities

10.2.1 Subject Informed Consent

Each potential subject that meets the inclusion/exclusion criteria for this clinical study will be informed of the requirements for participating in the clinical study. Subjects will be provided with a copy of the Informed Consent Form and an opportunity to discuss any questions with the Investigator or trained designee. Subjects will be informed that their medical records will be subject to review by the Sponsor, its designees and the FDA, and will be asked to sign an Authorization for the Use and Disclosure of Protected Health Information.

Subjects will be informed that they may refuse to participate in this clinical study without loss of benefits to which they are otherwise entitled, and that if they choose to participate, they may withdraw at any time without prejudice to future care. Once a subject agrees to the study requirements, the Informed Consent Form and Authorization for the Use and Disclosure of Protected Health Information (Sample HIPAA Consent found **Appendix D**) must be signed and dated by the subject or legal representative and the Investigator (or designee). The original signed Informed Consent Form for each subject will be retained by the investigative site and is subject to review by the FDA and the Sponsor. A copy of the Sponsor's Informed Consent Form template is provided in **Appendix C.**

10.3 Compliance

The investigator is ultimately responsible for all aspects of this study pertaining to study activities at the investigation site. The investigator agrees to supervise and direct the performance of the study and specifically (but not limited too) be responsible for the following throughout participation in the clinical study:

- Ensure the clinical study is conducted according to the Investigator Agreement, the study protocol, all conditions of the FDA and IRB/EC approvals, and applicable FDA and any other local regulations.
- Ensure the clinical personnel at the investigation site assigned to the clinical study have participated in training on the clinical protocol, case report forms, and study device and data collection requirements.
- When delegating study tasks, the investigator is responsible for providing adequate supervision of those to whom tasks are delegated. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study. The investigator should ensure that

any individual to whom a task is delegated is qualified by education, training, and experience (and state licensure where relevant) to perform the delegated task.

- Identify a Study Coordinator for the site. Working with and under the authority of the investigator, the study coordinator assures that all study requirements are fulfilled, and is the contact person at the site for all aspects of study administration.
- Protect the rights, safety, and welfare of subjects under his/her care.
- Track device usage in subjects.
- Report all adverse events to the Sponsor and IRB/EC as specified in this investigational plan and additionally as required by site's IRB/EC.
- Ensure that informed consent is properly obtained and the process documented in writing in the subject's medical record.

10.4 Device Accountability

The Sensei® X Robotic Catheter Systems and the family of Artisan guide catheters for this study will be labeled with the current, 510(k) cleared indication. Separate investigational device IFUs describing use specific for the clinical trial are provided with the protocol and include the statement "CAUTION-Investigational Device. Limited by Federal (or United States) Law to Investigational Use." See **Appendix I** for copies of the investigational device Sensei® X, Artisan and Artisan Extend Guide Catheter IFUs. A device tracking log and completion instructions will be provided to the Investigational Site personnel for the purpose of device tracking. Device tracking logs will be reviewed at the site on a regular basis by study monitors.

With the exception of devices requiring investigation for performance-related issues, single-use (disposable) items will not be retained.

In order to return a device to Hansen Medical (e.g., for evaluation of a performance issue), call Customer Service @ 1-866-426-0804 and follow the flow sheet in **Appendix J**.

10.5 Investigator Reports

The investigator is responsible for the preparation, review, signature, and submission of the reports listed below. These are subject to FDA inspection.

Table 14: Investigator Reporting Requirements

REPORT	SUBMIT TO	DESCRIPTION
Unanticipated Adverse Device Effect (UADE)	SPONSOR and IRB/EC	The investigator must submit to the Sponsor and reviewing IRB a report of any UADE as soon as possible but not more than 10 working days after the investigator first learns of the effect.
Withdrawal of IRB Approval	SPONSOR	The investigator must report a withdrawal of the reviewing IRB approval within 5 working days.
Progress Report	SPONSOR and IRB/EC	The investigator must submit this report at regular intervals, but not less than once per year.
Deviation from Protocol in Emergency Situation (if it was made to protect the life or physical well-being of a subject)	SPONSOR and IRB/EC	Deviation must be reported within 5 working days.
Deviation from Protocol Other	SPONSOR and IRB/EC	If the deviation may affect the scientific soundness of the plan or the rights, safety, and welfare of the subject (and is not an emergency), the deviation must be approved by SPONSOR, the reviewing IRB, and FDA prior to implementation. If the deviation does not affect these issues (study soundness, rights, safety, etc.), then only SPONSOR must approve the deviation prior to implementation.
Final Report	SPONSOR and IRB/EC	This report must be submitted within 3 months after the termination or completion of the study.
All Case Report Forms	SPONSOR and IRB/EC (if requested)	Please refer to guidelines in Table 16.

Note: reporting must be followed as required by national laws

11.0 Institutional Review Board/ Ethics Committee

It is the responsibility of the investigator to obtain approval of the protocol, subsequent protocol amendments, and informed consent from the IRB/EC at the study site prior to commencement of the study and enrollment of the first subject at a given site. All correspondence with the IRB/EC should be retained in the study regulatory binder. Copies of IRB approvals should be forwarded to Hansen Medical. All adverse events and protocol deviations must be reported and study reports submitted per IRB/EC requirements, with copies also forwarded to Hansen Medical.

12.0 Sponsor and Monitor Responsibilities

12.1 Sponsor

The Sponsor will be responsible for ensuring the investigators have the necessary skills, training and information to properly conduct the clinical study. The Sponsor will ensure proper monitoring of the clinical study, ensure IRB/EC approval is obtained and provide information to the investigators, the reviewing IRBs/EC and FDA concerning the progress and new information

about the clinical study. The Sponsor will conduct the clinical study in accordance with applicable ISO, ICH and FDA regulations. The Sponsor of this study is:

Hansen Medical, Inc.
800 East Middlefield Rd.
Mountain View, CA 94043
Telephone: 650-404-5800
Facsimile: 650-404-2793

12.2 Sponsor Reports

Hansen Medical is responsible for the preparation of, the accuracy of the data contained in, the review of and the submission of the reports listed below. These reports also are subject to FDA inspection and the retention requirements described for sponsor records.

Table 15: Sponsor Reporting Requirements

REPORT	SUBMIT TO	DESCRIPTION
Unanticipated Adverse Device Effect (UADE)	FDA, IRB/EC, Investigators	SPONSOR will report UADE evaluation within 10 working days after receiving notice of the effect.
Withdrawal of IRB/EC Approval	FDA, IRB/EC, Investigators	Notification will be made within 5 working days after receipt of approval withdrawal.
Withdrawal of FDA Approval	IRB/EC and Investigators	Notification will be made within 5 working days after receipt of the withdrawal of approval.
Current Investigator List	FDA	SPONSOR will provide an updated investigator list as required by 21 CFR 812.150(b) (4).
Progress Report	FDA, IRB/ECs, Investigators	An annual progress report will be submitted.
Recall and Device Disposition	FDA, IRB/ECs, Investigators	Notification will be made within 30 working days after the request is made, and will include the reasons for any request that an investigator return, repair or otherwise dispose of any devices.
Final Report	FDA, IRB/ECs, Investigators	SPONSOR will notify FDA within 30 working days of the completion or termination of the study. A final report will be submitted within 6 months after completion or termination.

12.3 Study Management and Monitoring

The Clinical Project Manager is qualified by training and experience to oversee the progress of the study and will ensure that the investigators and their staffs understand and adhere to both the regulatory requirements and the study protocol. The Clinical Project Manager will assist in resolution of any problems that may arise during the study. The Sponsor may work with a CRO to assist in investigative site monitoring for this study. The CRO will be directly supervised and coordinated by the Clinical Project Manager.

The Project Lead for this study is:

Tammy Drew
Hansen Medical, Inc.
800 East Middlefield Rd.
Mountain View, CA 94043
Telephone: 650-404-2765
Facsimile: 650-404-2793
E-mail: Tammy_Drew@hansenmedical.com

The Sponsor or designee will monitor all data submitted during the clinical study using their standard operating procedures for the monitoring process.

12.4 Monitoring Procedures

The monitoring procedures for this clinical study will include a pre-investigation site visit, review of completed data forms and other study documents, and periodic on-site monitoring. One hundred percent (100%) monitoring will be done for this study. A final monitoring visit will also be conducted. The study monitor(s) will assist with communication between the investigator and Hansen Medical.

12.4.1 Pre-Investigation Site Visit

Sites will be qualified to assure they have adequate EP and ablation experience, adequate time, subject population, facilities, staff support, commitment to the clinical study, etc.

In addition, an initiation visit will be conducted to assure that each investigator and investigation site staff understands the protocol and the investigator's obligations. Topics to be discussed will include:

- FDA regulations pertaining to the clinical study, including obligations of investigators and inspection procedures by FDA and the Sponsor.
- IRB/EC approval, continuing annual review and approval, and documentation to be provided.
- Training of investigators and coordinators and other study personnel to ensure site understanding of responsibilities and FDA regulations pertaining to the clinical study and the protocol.
- Informed consent requirements for each subject participating in the clinical study. Written informed consent must be obtained using the Informed Consent Form approved by the reviewing IRB/EC and Sponsor. Documentation of the Informed Consent process must be in each subject's chart.
- Record keeping requirements including required source documentation and device accountability.
- Completion and timely submission of eCRFs.
- Administrative, AEs, UADEs, and other reports and time frames.

Written site qualification and initiation visit reports will be filed with Hansen Medical. The monitor will document the resolution of any concerns and the completion of any appropriate follow-up activities resulting from the visit.

12.4.2 Periodic Site Visits

Periodic on-site monitoring visits will be made to ensure adherence to all applicable regulations, including:

- The investigator's adherence to the investigational plan,
- Appropriate informed consent practices,
- The accurate completion of all required case report forms,
- The accurate completion of all queries,
- The complete and accurate reporting of all adverse events,
- The maintenance of current IRB/EC approval and submission of required study progress reports to the IRB/EC,
- The maintenance of records and reports,
- The resolution of any study management issues.

The study monitor(s) will be responsible to complete a review of source documents for accuracy, completeness, and legibility. At a minimum, it is recommended that corresponding eCRFs be completed in EDC and ready for monitoring according to the time frames below.

Table 16: eCRF Completion

eCRF	Recommended Completion Time
Enrollment Form	Within 24 Hours
Index Procedure Forms (baseline through discharge)	Within 14 Days
7 day Phone Call	Within 7 Days
30, 90, 180 & 365 Day eCRFs	Within 14 Days
Serious Adverse Event Form	Fax Within 24 Hours
Device Performance Form, if a failure mode noted	Within 24 Hours
Study Exit Form due to AE or Lost to F/U	Within 72 Hours
Other Forms (Protocol Deviation, AE Narrative Summary, etc.)	Within 14 Days
Event Recorder	Within 14 Days
Holter Monitor	Within 14 Days

12.4.3 Clinical Monitor Reports

Site monitoring visits will be documented in a written monitoring report, prepared by the Sponsor's Clinical Monitor(s), or Sponsor's designee. Monitoring reports will include the progress of the study and identification of any follow-up activities or concerns from review of the subject records, study management documents, and informed consent forms. Resolution of concerns and completion of assigned tasks will also be documented in the monitoring report. A summary of the report will be given to the investigator in the form of a follow-up visit letter.

12.4.4 Final Monitoring Review and Study Closeout

A close-out or final visit will be conducted at each site. Any ongoing responsibilities will be discussed with the investigator and the investigation site personnel. A final monitoring report will be completed. A study closure letter will be sent to the investigator indicating the status of the study. It is the responsibility of the investigator to inform the Institution's IRB/EC in writing with the submission of the closure letter.

13.0 Ethical Considerations

13.1 Human Subjects Protection

The study will be performed in accordance with the relevant parts of the ICH Guidelines for GCP, 21 CFR 812, 50 and 56, and the Declaration of Helsinki.

Sponsor and Investigator will comply with applicable sections of ISO 14155:2011 and any regional or national regulations, as appropriate.

Investigator will not begin the clinical investigation until Investigator obtains the required written approval or favorable opinion from the IRB/ EC or regulatory authority, if appropriate.

Investigator will follow any additional requirements imposed by the IRB/EC or regulatory authority, if appropriate.

Sponsor will provide insurance for subjects, if required by national regulations.

13.2 Emergency Actions

Hansen Medical accepts the right of the investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well-being of a study subject. The investigator must give notice of any emergency deviations and justification for the deviation to the study personnel responsible at Hansen Medical and the IRB/ EC as quickly as possible after the episode, in any event no later than 5 working days after the emergency**.**

13.3 Amending the Protocol

This protocol is to be followed exactly. If needed, Hansen Medical must write amendments in order to alter the protocol. If any changes are required that affect the rights, safety, or welfare of the subjects or the scientific soundness of the study plan, they will be submitted to FDA as an

amendment or supplement to the IDE. Upon approval by the FDA, submission to each IRB/EC will occur.

No amendment to the protocol can be implemented before achieving all regulatory approvals, as per country specific regulations.

13.4 Study Termination

Hansen Medical, the US FDA and/or the European EC have the right to terminate this study at any time and remove all study materials from the site. A study may be terminated for any of the following reasons:

- Unsatisfactory rate of subject enrollment or compliance to eligibility criteria.
- Repeated noncompliance with the investigational plan.
- Inaccurate, incomplete, and/or untimely submission of data.
- The rate or severity of adverse events in the Hansen study or other similar studies indicates a potential health hazard to the subjects caused by the device.

14.0 Publication Policy

Sponsor will limit its review to a determination of whether Confidential Information is disclosed and shall not attempt to censor or in any way interfere with presentation or conclusions beyond the extent necessary to protect Confidential Information, to allow Sponsor to protect its rights in patentable or copyrightable material, and to check for technical correctness of Sponsor information. When reasonably requested by Sponsor, Institution and Principal Investigator will delay publication up to an additional 60 days to allow Sponsor to protect its rights in patentable or copyrightable material.

15.0 Study Definitions

AF Episode: An episode of AF 30 seconds or longer in duration on Holter or Trans-telephonic Monitoring (TTM), or 10 seconds in duration on 12-lead ECG.

Atrial Tachyarrhythmia Episode: An episode of atrial tachycardia, tachyarrhythmia (atrial fibrillation, atrial flutter or atrial) 30 seconds or longer in duration on Holter or Trans-telephonic Monitoring (TTM), or 10 seconds in duration on 12-lead ECG.

Blanking period: 90 day period between the index ablation procedure and the continuation of the 12 month follow-up period. If a subject is symptomatic during the 90 day blanking period, he/she may be placed on a previously ineffective Anti arrhythmic Drug (AAD). If a subject remains symptomatic, the AAD dose may be increased, a new AAD added, or the subject may be treated again using the Hansen System up to two more times before day 90. At the 90 day visit, subject will need to discontinue any class I, class II, class III and class IV AADs or maintain AAD's that were ineffective at baseline, at a dosage level less than or equal to the maximum baseline dosage. Calcium channel and beta blocker medications may continue for uses other than an antiarrhythmic drug.

Bleeding: A Major Complication of AF ablation if it requires and/or is treated with transfusion or results in a 20% or greater fall in HCT.

Discontinued Subjects: Subjects in whom the ablation catheter was inserted but did not undergo ablation or attempted ablation (no RF energy applied). Subjects are considered 'discontinued' if ablation was not possible due to non-study equipment failure or if their arrhythmia was determined to be a non-study arrhythmia (e.g. atrial flutter). These subjects will be followed for 7 days for safety endpoint evaluation.

Enrollment: Subject is considered to be enrolled once they have signed the informed consent form.

Paroxysmal AF: An atrial fibrillation where a subject has two or more spontaneously terminating episodes of atrial fibrillation that last longer than 30 seconds and shorter than seven days.

Screening Failure: Subject is excluded from enrollment from the study if they do not meet 1 or more of the pre-operative inclusion/exclusion criteria.

Symptomatic AF: Symptoms of AF that were experienced by the subject, made them seek medical attention, and were concurrent with a documented episode by ECG, event monitor and/or Holter monitoring. Symptoms may have included palpitations, irregular, rapid or slow pulse, dizziness, weakness, chest discomfort and breathlessness.

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Appendix A Adverse Event Definitions

In addition to the definitions of Major Complications provided in **Appendix L** of the protocol, the following definitions apply to expected adverse events that may occur and must be reported throughout this clinical study. Events reported should represent a new onset or increase in the severity of the condition from the time of enrollment (the subject is considered to be enrolled at the time of the procedure).

A. SYSTEMIC COMPLICATIONS	DEFINITION
Allergic reaction (to contrast, drugs, anesthesia)	Allergy symptoms include but are not limited to: eye or skin redness, hives, rash, eye or skin itch, swelling, difficult breathing, respiratory arrest, sudden death.
Fever	Oral temperature > 101°F
Infection	The invasion of the body by pathogenic microorganisms and their multiplication which can lead to tissues damage and disease requiring treatment, e.g. endocarditis, pericarditis, sepsis.
Sepsis	Systemic infection with confirmed positive blood cultures.
Low Blood Pressure	Any blood pressure that is below the normal expected for an individual and has accompanying symptoms of hypo-perfusion (confusion, light-headedness, dizziness, syncope, etc.)
Ischemia/infarction of tissue/organ	Decrease blood supply to body tissue due to obstruction of blood flow.
Other Systemic Complications	Any new or exacerbated significant systemic complication that causes clinically relevant changes in the subject's health for which medical attention is required.

B. CARDIO-PULMONARY	DEFINITION
Angina/coronary ischemia	Chest, neck, arm, back, or other pain related to decreased coronary blood flow.
Arrhythmias	The development of a new atrial and/or ventricular arrhythmia or significant increase in the severity of a preexisting arrhythmia, that requires intervention or results in the signs and symptoms of vital organ hypoperfusion, such as dizziness, lightheadedness, or syncope, or any episode of cardiac arrest.
Atrial/Septal defect requiring repair	Defined as a significant residual atrial septal opening. Reported as clinically significant if intervention is performed for the primary purpose of repairing the ASD. If cardiac surgery is indicated for reasons other than residual ASD and the ASD is repaired at the same time, this does not meet the definition of clinically significant ASD.
Cardiac Arrest	Sudden cessation of heartbeat and cardiac function, resulting in the loss of effective circulation.
Congestive Heart Failure	Failure of the heart to pump blood with normal efficiency. Development of an acute episode of or exacerbation of existing low cardiac output or fluid overload accompanied by peripheral and/or pulmonary edema.
Endocarditis	Inflammation of the endocardium. Left untreated can cause systemic emboli and cardiac valve dysfunction.
Damage to heart valves and / or supporting structures	Defined as damage to a heart valve or supporting structure which requires intervention as a result of damage.
Dyspnea	New onset or increasing episodes of shortness of breath.

B. CARDIO-PULMONARY	DEFINITION
1st and 2nd degree heart block not requiring treatment	New onset 1st or 2nd degree heart block not requiring treatment.
Hemoptysis	Coughing up blood.
Need for a permanent pacemaker	Bradycardia rhythm that becomes chronic (lasting more than a few days), results in intolerable symptoms or is believed to be irreversible requiring implantation of a permanent pacemaker.
Perforation of cardiac muscle	Perforation of the heart muscle requiring additional treatment (including efforts to seal the perforation or pericardial drainage), or resulting in significant pericardial effusion, tamponade, myocardial infarction, or death.
Pulmonary Hypertension	Increased pressure in the pulmonary vessels eventually leading to heart failure. Symptoms can include chest pain (frontal), dyspnea with activity, lightheadedness with activity, dizziness, fatigue, weakness.
Pulmonary vein obstruction	An obstruction in the pulmonary vein that can decrease blood flow to the atria.
Pleurisy	Pleurisy is an inflammation of the pleura often causing symptom of stabbing pain in the chest aggravated by breathing, chest tenderness, cough, and shortness of breath. Often associated with a pericardial rub heard on auscultation.
Respiratory Arrest	Sudden complete cessation of respiratory movement.
Ventricular fibrillation	An abnormally rapid heart rhythm that originates from a ventricle where the ventricles beat rapidly in a chaotic, purposeless fashion not allowing the heart to pump blood effectively to the body.
Other Cardio-Pulmonary Complications	Any new or exacerbated significant cardiac or pulmonary complication that causes clinically relevant changes in the subject's health for which medical attention is required.

C. VASCULAR COMPLICATIONS	DEFINITION
Air Embolism	Obstruction of the circulation by air that has gained entrance to a blood vessel(s).
Aneurysm	Localized widening (dilatation) of an artery, vein, or the heart. At the area of an aneurysm, there is typically a bulge and the wall is weakened and may rupture.
Atrio-venous fistula	Formation of an abnormal connection between the lumens of an artery and a vein as documented by CT, ultrasound, angiography, or direct observation.
Access site discomfort	Pain and/or tenderness at the access site.
Bleeding	Bleeding requiring observation resulting in prolonged hospitalization and/or transfusion and/or treatment other than applying pressure & bandage.
Hematoma	A mass of usually clotted blood that forms in tissue, organ or body space as a result of leakage from a blood vessel that requires additional treatment beyond applying pressure.
Retroperitoneal hemorrhage	Bleeding into the retroperitoneal space. RPH is often associated with femoral artery sheath placement superior to the inferior epigastric artery resulting in vessel perforation.
Perforation or rupture of a blood vessel	Defined as perforation in an access vessel wall or the aorta confirmed by extravasations of contrast under fluoroscopy.

C. VASCULAR COMPLICATIONS	DEFINITION
Pseudoaneurysm	Enlargement of the aorta, iliac, or femoral arteries, which contain some or all of the medial layer, the adventitia, and periaortic tissue most commonly associated with previous aortic operative procedures, trauma, and/or infection. Pseudoaneurysms typically present as a well-defined collection of blood outside the vessel wall from contained rupture.
Temporary or total occlusion of an artery	Vessel lumen narrowing or obstruction by atherosclerotic plaque, thrombus, or embolism causing a decrease or occlusion of blood supply to the extremities.
Thrombophlebitis	Inflammation of a vein that occurs when a blood clot forms.
Vessel Spasm	A sudden constriction of a vessel limiting blood flow downstream.
Other Access site complications	Any new or exacerbated significant vascular complication that causes clinically relevant changes in the subject's health for which medical attention is required.

D. NEUROLOGIC COMPLICATIONS	DEFINITION
Change in Mental Status	A delirium or acute confusional state associated with a disturbance in cognition, mood, attention, arousal, and self-awareness, as evidenced on clinical assessment, which arises acutely, either without prior intellectual impairment or superimposed on chronic intellectual impairment.
Femoral Neuropathy	Pain and numbness in the anterior thigh associated with quadriceps muscle weakness and decreased patellar reflex lasting > 1 month after treatment.
Nerve Injury/Peripheral Neuropathy	Direct damage to nerves surrounding the access site, operative field, and the resultant signs and/or symptoms of such damage.
Other neurologic complications	Any new or exacerbated significant neurologic complication that causes clinically relevant changes in the subject's health for which medical attention is required.

E. OTHER COMPLICATIONS	DEFINITION
Headache	Headache lasting >24 hours and/or not relieved by pain medication.
Heparin induced thrombocytopenia (HIT)	Development of thrombocytopenia (low platelet counts) due to the administration of Heparin. It predisposes to thrombosis, the formation of abnormal blood clots inside a blood vessel.
Renal Insufficiency	Slowly progressive failure of renal function resulting from some disease, e.g., diabetes, cancer, hypertension, glomerulonephritis, that causes gradual destruction of the kidneys, or if creatinine levels are available, an increase of > 25% above the pre-procedure creatinine level.
Renal failure	Defined as a new need for dialysis or a creatinine increasing to 3.5 mg/dL or greater. Not included as Renal Failure is any Renal Dysfunction defined as an increase of creatinine over 1.0 mg/dL over the baseline.
Surgery required for treatment of an Adverse Event	Emergent or Urgent surgery required to treat an adverse event.
Increased exposure to radiation	Radiation exposure resulting in symptoms consistent with overexposure to radiation.
Other possible adverse effects	Any new or exacerbated significant complication that causes clinically relevant changes in the subject's health for which medical attention is required.

Appendix B Classes of Anti-Arrhythmic Drugs (Vaughn-Williams Classification)

CLASS IA – Sodium channel block (intermediate association/ disassociation)
Uses: APB and VPB suppression, SVT and VT suppression, AF or atrial flutter, and Ventricular Fibrillation suppression
Disopyramide
Procainamide
Quinidine

CLASS 1B – Sodium channel block (fast association/ disassociation)
Uses: Suppression of ventricular tachycardia and atrial fibrillation
Lidocaine
Mexiletine
Phenytoin
Tocainide

CLASS IC
Uses: APB and VPB suppression, SVT and VT suppression, AF or atrial flutter, and ventricular fibrillation suppression
Flecainide
Propafenone
Moricizine

CLASS II - β-Blockers
Uses: Supraventricular tachyarrhythmias (APB, ST, SVT, AF, atrial flutter) and ventricular arrhythmias (often in a suppressive role)
Atenolol
Carvedilol
Acebutolol
Betaxolol
Bisoprolol
Esmolol
Metoprolol
Nadolol
Propranolol
Timolol

CLASS III – Potassium channel blocker
Uses: Any tachyarrhythmia except Torsades' de Pointes ventricular tachycardia
Amiodarone
Azimilide
Bretylium
Dofetilide
Dronedarone
E-4031
Ibutilide
Sotalol

CLASS IV - Calcium channel blockers
Uses: Termination of SVT and slowing of rapid AF or atrial flutter
Diltiazem
Verapamil

Class V
Uses: Suppression of SVT, especially in Heart Failure with AF, contraindicated in ventricular arryhythmias. Magnesium Sulfate used in Torsades' de Pointes
Adenosine
Digoxin
Magnesium Sulfate