POLARx Cardiac Cryoablation system

Post Market Clinical Follow-up study

POLAR ICE

PY003

CLINICAL INVESTIGATION PLAN

NCT04250714

Sponsored By

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Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
A	**13 February 2020**	**C**	**N/A**	**Initial Release**	**N/A**
B	**07 May 2020**	**C**	**Multiple**	**Initial Release to the sites** (Administrative updates prior to release to sites)	**N/A**

2. Protocol Synopsis

POLARx Cardiac Cryoablation system **Post Market Clinical Follow-up study** **POLAR ICE**	
Study Objective(s)	**Primary Objective:** This is a Post Market Clinical Follow-up (PMCF) study designed to establish the continued safety and effectiveness profile of the Boston Scientific Cardiac Cryoablation System after receiving CE mark. **Secondary Objective:** The study will provide information on real-world usage of the Boston Scientific Cardiac Cryoablation System when used to perform pulmonary vein isolation (PVI) for the ablation treatment of atrial fibrillation (AF), according to the current and future guidelines and system indications for use. This may include but not limited to: repeated ablations to treat AF, concomitant or delayed adjunctive ablation strategies with other products and use of different diagnostic products to validate the results such as 3D mapping systems. Collected information and analyses will include, but not limited to, the following: • Arrhythmia characterisation at the time of enrollment: time since first AF diagnosis, number and duration of reported episodes, prior electrical cardioversions (if any); • History of prior ablations and repeated ablations during follow-up period; • Use of anti-arrhythmic drugs (AAD); • Methods used for verification of procedure success (pulmonary vein isolation): entrance/exit block, adenosine (if used), use of three-dimensional (3D) mapping.
Indication(s) for Use	Subjects enrolled in the POLAR ICE study will be clinically indicated for an ablation procedure for the treatment of atrial fibrillation according to current and future guidelines and system indications for use.
Device/System	The Boston Scientific Cardiac Cryoablation System ("Cryoablation System") consists of the following devices and components: • POLARx™ Cryoablation Catheter ("Cryoablation Catheter"); • POLARMAP™ Catheter ("Cryo Mapping Catheter"); • POLARSHEATH™ Steerable Sheath ("Cryo Steerable Sheath"); • SMARTFREEZE™ Console ("Console"); • Related Accessories.
Control Device	This study has no control device(s)

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Study Design	Prospective, non-randomized, multicenter (international), single arm study. All subjects signing the consent, undergoing the index procedure and treated with the study devices will be followed up for one year.
Planned Number of Subjects	A minimum of 200 subjects (with the possibility to expand up to maximum 400 subjects) will be included in this study. A minimum of 199 De Novo TREATMENT subjects (i.e. first treatment for AF in the left atrium) for **paroxysmal atrial fibrillation** (PAF) will be analyzed to establish the continued safety and effectiveness profile of the Cryoablation System and fulfill the PMCF requirements for the submitted labeling of the Cryoablation System. This number represents the minimum number for the primary endpoint statistical hypothesis testing. The entire study cohort will provide information on real-world usage of the Cryoablation System and will be analyzed for secondary objectives. These will include subgroup analysis in selected subjects of interest (including (but not limited to) De Novo ablation versus repeated ablations). These analyses will be non-powered but in case some of these subgroups will be poorly represented in the study, Boston Scientific may propose in the future to extend the sample size to up to 400 subjects.
Planned Number of Sites / Countries	Approximately 25 centers in Europe and Middle East will be included in the study.
Primary Safety Endpoint	Safety event free rate at 12 months post-index procedure. *Primary safety events will consist of a composite of the following procedure-related and device-related adverse events.* *Acute primary safety endpoint events, events occurring up to 7 days post-index procedure or hospital discharge, whichever is later, include:* • Death • Myocardial infarction (MI) • Persistent gastroparesis/injury to vagus nerve • Transient ischemic attack (TIA) • Stroke/Cerebrovascular accident (CVA) • Thromboembolism/Air embolism* • Cardiac tamponade/perforation • Pneumothorax • Serious vascular access complications** • Pulmonary edema/heart failure

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	• AV block not attributable to medication effect or vasovagal reaction. * Thromboembolic or /air embolic events collected in the study refer to any occlusion of blood vessel(s) that results in clinical symptoms ** Defined as prolongation of hospitalization, requirement of surgical intervention or blood transfusion *Chronic primary safety endpoint events, events occurring through 12 months post-index procedure, include:* • Atrial esophageal fistula • Pulmonary vein stenosis (≥ 70% reduction of diameter) • Symptomatic pericardial effusion • Persistent Phrenic nerve injury*** ***A non-recovered phrenic nerve injury at 12 months post-index procedure will count as a chronic primary endpoint. The study will collect information on phrenic nerve palsy observed before the end of the index procedure and, in case it occurred, will track information for potential recovery during the study visits.

Primary Effectiveness Endpoint	Failure free rate at 12 months post-index procedure.
	Failure defined as:
	• Failure to achieve acute procedural success* in the index procedure;
	• More than one repeat procedure during the blanking period (within 90 days post-index procedure);
	• Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia event (≥ 30 seconds in duration or from a 10 second 12-lead ECG) between days 91 and days 365 post-index procedure **;
	• Any of the following interventions for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between days 91 and days 365 post-index procedure:
	  • Repeat procedure;
	  • Electrical and/or pharmacological cardioversion for AF/AFL/AT;
	  • Prescribed a higher dose of any AAD*** documented at baseline or a new AAD*** not documented at baseline.
	
	* Acute procedural success is defined as isolation of the all pulmonary veins or anatomical equivalents achieved with the Cryoablation Catheter at the end of the index procedure and as demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion).

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	** Subjects will be monitored for recurrences of the arrhythmias by means of clinical visits, ECG and 24-hour Holter monitoring. Recurrences documented with other devices only (eg. ILR, PM, ICD, CRT) will not be counted as primary effectiveness endpoint events *** AADs for endpoint will consist of all Class I/III and any Class II/IV medications taken for control of AF/AT/AFL recurrence
Secondary Effectiveness Endpoint	Documentation and rate of acute procedural success, defined as pulmonary vein isolation achieved with the Cryoablation System. Electrical isolation of a PV is demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion). Information on isolation method used per site standard of care will be collected with a minimum by entrance block in all PVs or anatomical equivalents. Additional data, if available, will be collected on Exit Block or Conduction Block verification using 3D mapping.
Additional Endpoints	Additional endpoints and analyses include, but are not limited to: • Procedure times: LA dwell time*, total ablation time, number of cryo applications per vein, time to thaw, total fluoroscopy time and total procedure time; • Time-To-Isolation per ablation application, if available; • Freedom from recurrence of individual types of atrial arrhythmias (AF, AFL, AT) between days 91 and days 365 post-index procedure; • Analysis of ablation techniques (i.e. segmental approach to left common trunk, additional linear ablations, etc.); • Analysis of different anaesthesia techniques (General anaesthesia with or without intubation versus sedation); • Freedom from recurrence in subjects with non-common anatomical configurations of PV (e.g. left common trunk); • Freedom from primary effectiveness failure evaluated in subgroups of subjects (termination of AAD versus continuation of AAD after blanking period); • For the subgroup of subjects undergoing 3D mapping with the Boston Scientific mapping Rhythmia system and performing a post-procedural map, map information will be collected to determine lesion locations;

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	• For subjects that will undergo repeat ablation during the course of the clinical follow-up, anatomical location of ablations gaps will be assessed. * LA dwell time is defined as time from the Cryoablation Catheter introduced in the left atrium (LA) to the last time of Cryoablation Catheter exiting the LA. Additional ancillary analyses on specific subgroup of subjects, may be presented. These analyses will include but not limited to the following: • Age (<60 versus ≥ 60 years); • Gender (Male versus Female); • Monitoring (Subjects with data from continuous ECG recording systems (eg. ILR, PM, ICD, CRT) versus those without).
Method of Assigning subjects to Treatment	Any subject who signs the consent form will be considered enrolled in the study. Any subject that signs the consent form, has the study device inserted into the body and undergoes protocol specific treatment for the intended disease (cryoablation) will be assigned to the TREATMENT group. The 12 Month follow-up data from minimum 199 De Novo TREATMENT subjects with paroxysmal atrial fibrillation will serve as PMCF data and an interim report will be generated once the follow-ups are completed.
Follow-up Schedule	Visits schedule: pre-discharge, 3 months (blanking period), 6 months and 12 months.
Study Duration	Enrollment is expected to be completed in approximately 12 months; therefore, the total study duration is estimated to be approximately 24 months.
Participant Duration	The study duration for each subject is expected to be approximately 12 months.
Inclusion Criteria	1. Subjects indicated for the treatment of AF with the cryoablation system according to current and future Guidelines and system indications for use;

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	2. Subjects who are willing and capable of providing informed consent; 3. Subjects who are willing and capable of participating in all testing associated with this clinical study at an approved clinical investigational center; 4. Subjects whose age is 18 years or above, or who are of legal age to give informed consent specific to state and national law.
Exclusion Criteria	1. Any known contraindication to an AF ablation or anticoagulation, including those listed in the instructions for use; 2. Subjects with indication for treatment of AF that is not according to current and future Guidelines and system indications for use; 3. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause; 4. Known or pre-existing severe Pulmonary Vein Stenosis; 5. Evidence of myxoma, LA thrombus or intracardiac mural thrombus; 6. Previous cardiac surgery (e.g. ventriculotomy or atriotomy, CABG, PTCA, stent procedure) within 90 days prior to enrollment; 7. Implantable cardiac device procedures (e.g. PM, ICD, CRT) within 30 days prior to enrollment; 8. Implanted Left Atrial Appendage Closure device prior to the index procedure; 9. Interatrial baffle, closure device, patch, or patent foramen ovale (PFO) occluder; 10. Subjects with severe valvular disease OR with a prosthetic – mechanical or biological - heart valve (not including valve repair and annular rings); 11. Presence of any pulmonary vein stents; 12. Active systemic infection; 13. Vena cava embolic protection filter devices and/ or known femoral thrombus;

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14. Any previous history of cryoglobulinemia;
15. History of blood clotting or bleeding disease;
16. Any prior history of documented cerebral infarct, TIA or systemic embolism (excluding a post-operative deep vein thrombosis (DVT)) ≤ 180 days prior to enrollment;
17. Subjects who are hemodynamically unstable;
18. The subject is unable or not willing to complete follow-up visits and examination for the duration of the study;
19. Life expectancy ≤ 1 year per investigator's opinion;
20. Women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon investigator's discretion);
21. Unrecovered/unresolved Adverse Events from any previous invasive Procedure;
22. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments; each instance must be brought to the attention of the sponsor to determine eligibility.

Primary Statistical Hypothesis and Statistical Test Methods

Endpoint	Hypothesis	Analysis Method
Primary Safety Endpoint	The primary safety endpoint event-free rate at 12 months post-procedure >86%	Kaplan-Meier rate with pointwise log-log confidence limit
Primary Effectiveness Endpoint	The primary effectiveness event-free rate at 12 months post-procedure >50%	Kaplan-Meier rate with pointwise log-log confidence limit

Sample Size Parameters

[redacted]

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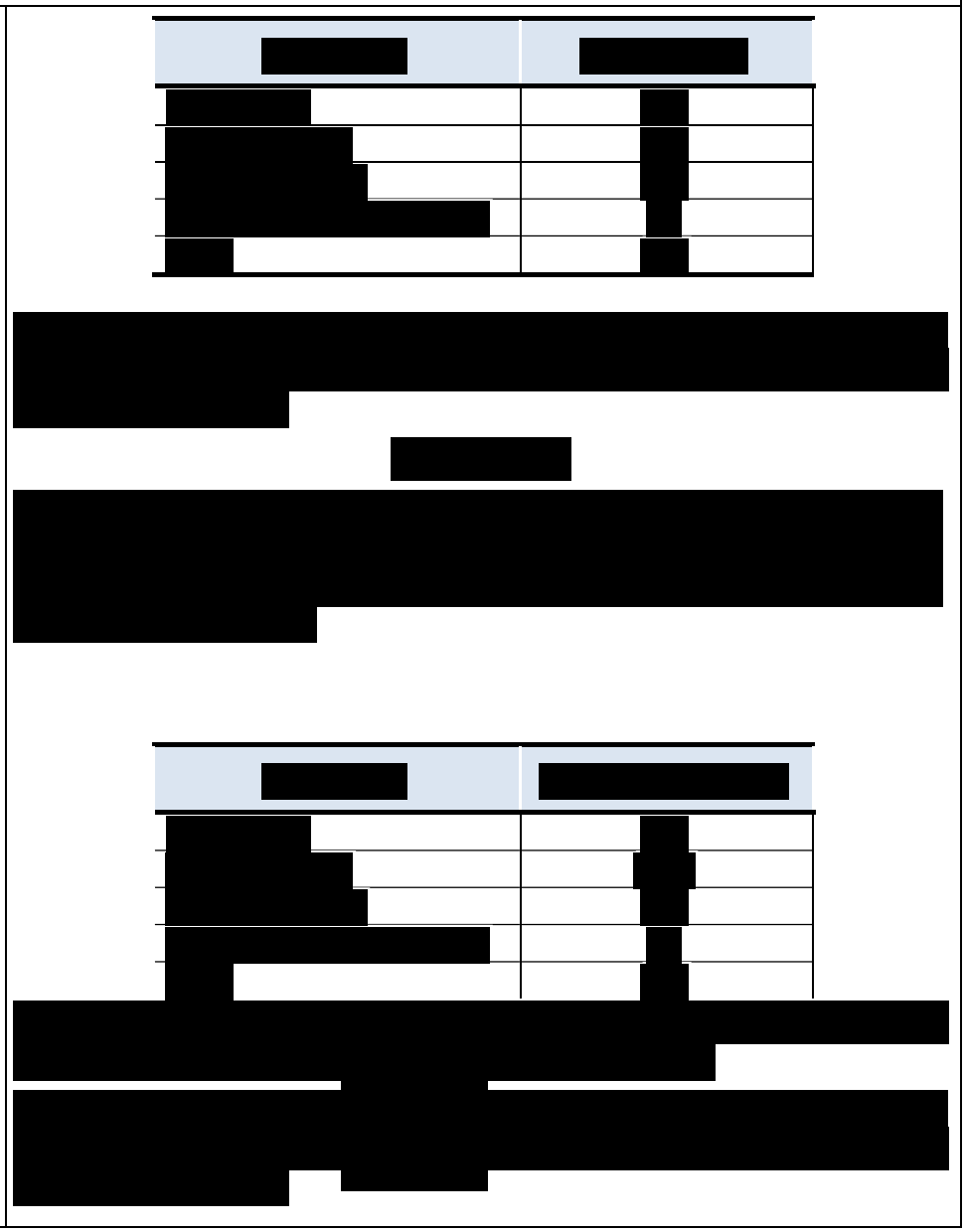

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4. Introduction

4.1. *Background*

Atrial fibrillation (AF) is the most commonly encountered sustained cardiac arrhythmia in clinical practice (1). In the United States, the incidence of atrial fibrillation is estimated to increase from an estimated 2.66 million people in 2010 to as many as 12 million people by 2050 (2). It is also estimated that the number of patients with AF in 2030 in Europe will be 14–17 million and the number of new cases of AF per year at 120,000–215,000 (3). In addition, the prevalence and incidence of AF are increasing over time due to the aging of the population and a substantial increase in the age-specific occurrence of AF (4,5,6).

AF causes symptoms that impair quality of life, increases the risk of stroke fivefold, and increases mortality (7).

There are multiple therapies in current use for the treatment of AF. Treatment options include medical management, pacing, cardioversion, implantable devices, surgery, and ablation therapy to eliminate the arrhythmia (8,9).

Currently, the most recent guidelines form the European Society of Cardiology for the management of AF state that catheter ablation of AF (10) is effective in restoring and maintaining sinus rhythm in patients with symptomatic paroxysmal, persistent, and probably long-standing persistent AF, in general as second-line treatment after failure of or intolerance to antiarrhythmic drug therapy. In particular, it has been increasingly recognized that focal pulmonary vein (PV) triggers of AF can account for 80 to 95 percent of paroxysmal cases that are drug resistant. As outlined in the 2017 Heart Rhythm Society (HRS) consensus document (11), electrical isolation of the pulmonary veins is now recognized as the cornerstone of AF ablation. At most centers where AF ablation is performed, a strategy of creating a series of point-by-point radiofrequency lesions that encircle the PVs is used.

Although great progress has been made in improving the techniques and outcomes of AF catheter ablation, many challenges remain. Two of the current limitations of atrial fibrillation ablation include the use of catheters designed for pinpoint lesions to perform large-area ablations in a point-by-point fashion and the dexterity required to perform such a lesion set.

A cryoballoon system for treatment of AF is comprised of components that deliver cryogenic refrigerant in a controlled fashion, from a reservoir located in a console through a conduit accessory and into a treatment catheter. The treatment catheter has a balloon at its distal end that is delivered to a target location within the patient's heart. Once the balloon is positioned in the antrum of the target PV, refrigerant is delivered to the balloon to extract heat from tissue in contact with the balloon. By navigating the balloon to the ostium of the PV and occluding blood flow, a PV may be isolated with a single 3 to 4-minute application of cryo-energy.

The currently approved cryoablation technology (Arctic Front™/ Arctic Front Advance™ Cryoablation Balloon, Medtronic®) has completed two studies demonstrating effective therapy for PAF management with approximately 70% and 65% efficacy respectively (12,13). In addition to these efficacy and safety results, the simplicity of the procedure and the ability for average skilled interventionalists to match the results of elite RF operators provides cardiologists with the means to address the fast-growing patient numbers. Balloon catheter cryoablation therapy to treat Paroxysmal Atrial Fibrillation (PAF) has gained

significant utilization worldwide, with an estimated 370,000 procedures performed to date (12).

Catheter and sheath performance for cryoablation balloon procedures has not changed since inception, more than ten years ago. Knowing that electrophysiologists are familiar with treating AF with cryo-therapy, the Boston Scientific Cardiac Cryoablation System was designed with a clinical user focus and set out to improve the user experience. This was accomplished by improving balloon stability and achieving continuous inflation and uniform balloon pressure during all phases of the cryoablation, improving sheath maneuverability and incorporating general safety/ workflow improvements over current technology.

Extensive pre-clinical and performance bench testing studies have been performed to date. A first-in-man clinical study was completed on 30 patients with one month follow-up in 2018 and its data has been used to obtain CE-mark. Additionally, data of up to 405 subjects who will undergo treatment with the Boston Scientific Cryoablation System for de-novo PAF are objective of the IDE trial that will enroll patients in the United States, Canada and in Asia. This study seeks to obtain approval for the Boston Scientific Cryoablation System in North America. The present study will provide post market data at support of continued safety and effectiveness assessment for the Cryoablation System, when used under standard of care in Europe.

4.2. *Study Rationale*

The goal of any novel design or therapeutic strategy for AF is to restore normal sinus rhythm and to reduce or eliminate the symptoms due to rapid atrial response.

Boston Scientific developed a Cryoablation Balloon that can maintain constant and stable pressure during the entire procedure. A cryoablation balloon that has been designed to maintain constant pressure is likely to provide improved stability during all phases of the cryoablation, improving user experience and preserving the proven design validated by the Medtronic® Arctic Front Advance™ Catheter.

This post market clinical follow-up study intends to establish the continued safety and effectiveness profile of the Boston Scientific Cryoablation System when used in real-world settings in the treatment of atrial fibrillation. This may include repeated ablations to treat atrial fibrillation, concomitant or delayed adjunctive ablation strategies with other products and use of different diagnostic products to validate the results such as 3D mapping systems.

5. Device Description

5.1. *Commercial Device*

The Boston Scientific Cardiac Cryoablation System (henceforth “Cryoablation System”) is indicated for cryoablation and electrical mapping of the pulmonary veins for pulmonary vein isolation (PVI) in the ablation treatment of atrial fibrillation (AF) as per current and future guidelines and system instructions for use.
The components and accessories of the Cryoablation system and their associated model numbers are listed in Table 5.1-1.

Table 5.1-1: Cryoablation System Components and Accessories

Component	Model Number
POLARx™ Cryoablation Catheter (Cryoablation Catheter)	2315 (Short tip and long tip)
SMARTFREEZE™ Console (Console)	2314
POLARMAP™ Catheter (Cryo Mapping Catheter)	2317 (20mm)
POLARSHEATH™ Steerable Sheath (Cryo Steerable Sheath)	2316
Accessories	
Diaphragm Movement Sensor (DMS)	2314
Inter Connection Box (ICB)	2314
Cryo-Console Foot Switch	2314
Cryo-Cable	2318
Cryo-Catheter Extension Cable	2319
EP Electrical Cable	2320

5.1.1. **Cryoablation Catheter (POLARx ™)**

The Cryoablation Catheter is a component of the Boston Scientific Cardiac Cryoablation System ("Cryoablation System") and is a single use, flexible, over-the-wire balloon catheter used to ablate cardiac tissue. The Cryoablation Catheter is used in conjunction with the Console to induce thermal injury and endocardial tissue necrosis when the balloon is in contact with cardiac tissue and reaches cryoablation temperatures created by a refrigerant injected from the Console into the balloon segment of the POLARx™. The Cryoablation catheter connects to the Console with a Cryo-Cable (for N_2O delivery and removal) and an Extension Cable (for electrical connection via the Interconnection Box). The Cryoablation catheter is designed to be used with a Cryo Mapping Catheter circular mapping catheter deployed within the guidewire lumen during ablation procedures.

During an electrophysiology (EP) ablation procedure, the Cryoablation catheter (including the Cryo Mapping Catheter) is inserted through the Cryo Steerable Sheath (POLARSHEATH™) into the venous system, directed into the left atrium (LA) and towards the ostium of the target pulmonary vein (PV). Once positioning that occludes the PV has been verified, refrigerant is delivered through the Cryo-Cable to the injection coil, which directs the flow of refrigerant toward the interior distal surface of the balloon. This results in a cooled region at the balloon tissue interface, which adheres to the endocardial surface. The low temperature and pressure gradient allows the balloon to thermally create transmural, circumferential tissue necrosis (lesions) and interrupt electrical conduction.

The Cryoablation Catheter is comprised of the following major components, distal to proximal:

- Atraumatic tip
- Double layer balloon system
- Guide wire lumen
- Internal balloon thermocouple
- Injection coil and manifold for delivery of the refrigerant; liquid nitrous oxide (N_2O)
- Catheter shaft; to retrieve the expanded N_2O gas
- Catheter handle
- Distal handle connections

Figure 1: Cryoablation Catheter Distal Tip

Figure 2: Cryoablation Catheter Handle

[redacted]

5.1.2. Cryo Mapping Catheter

The Cryo Mapping Catheter is a single-use, sterile, multi-electrode, diagnostic catheter designed to map cardiac signals during ablation procedures. The catheter is provided in a 20mm diameter with 8 evenly spaced radiopaque electrodes. The proximal end of the

handle contains an electrical connection that integrates with EP lab recording systems. Once deployed through the central guidewire lumen of the Cryoablation Catheter and into the pulmonary vein (PV), a circular shape is established such that the electrodes contact the endocardial surface. This allows for recording and interrogation of electrical conduction between the LA and the pulmonary veins. The Cryo Mapping Catheter also allows for delivery of pacing stimuli used in the interpretation of PV isolation (PVI).

Figure 3: Mapping Catheter Assembly

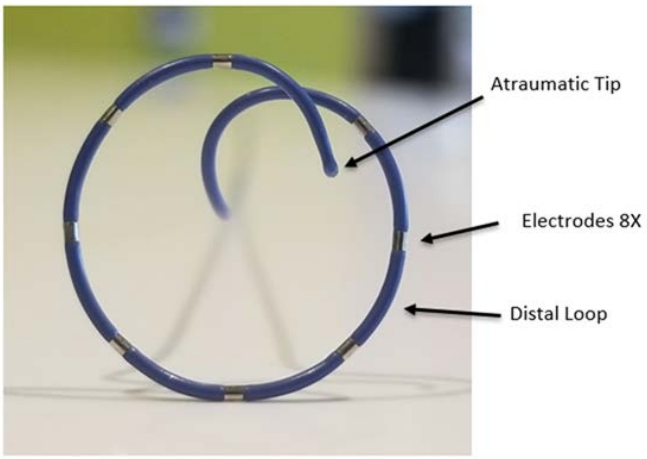


Figure 4: Cryo Mapping Catheter with Electrode Arrangements

Table 5.1-3: Cryoablation Catheter Specifications

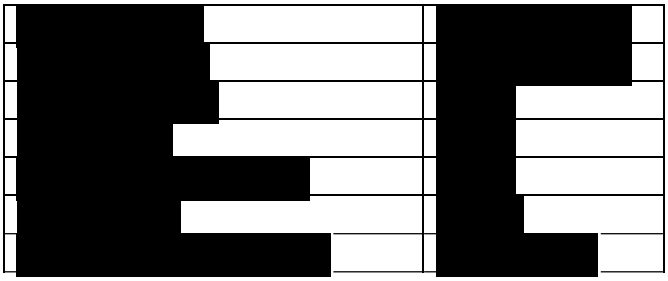
[redacted]

5.1.3. Cryo Steerable Sheath

The Cryo Steerable Sheath is a single use, disposable, steerable percutaneous introducer sheath designed for additional maneuverability of standard catheters that are advanced through the sheath and into cardiac chambers. It is comprised of a composite structured single lumen shaft, an ergonomic handle to provide torque and active deflection, and a hemostasis valve to allow safe introduction, withdrawal, and swapping of catheters and wires while preventing air ingress and minimizing blood loss. A side-port is integrated to allow continuous drip infusion, injection through the center lumen, flushing, aspiration, blood sampling and pressure monitoring.

As a component of the Cryoablation System, the Cryo Steerable Sheath is intended to facilitate the placement of diagnostic and/or therapeutic intracardiac devices during percutaneous catheter ablation procedures. The device is indicated for left-sided cardiac procedures via a transseptal approach.

Table 5.1-4: Cryo Steerable Sheath Specifications



5.1.4. Console

The Console is a device that uses N_2O provided from a refillable cylinder to safely pressurize (inflate) and cool the Cryoablation Catheter to cryogenic ablative temperatures. The Console houses the electrical components and software/firmware needed to perform cryoablation procedures. It controls the delivery, recovery, and disposal of N_2O (cryoablation refrigerant) safely and efficiently. The Console user interface provides a means for initiating and ceasing refrigerant delivery. Once the command is received from the console, N_2O is delivered as a chilled liquid to the Cryoablation Catheter for a programmable time duration. The user interface also displays key information allowing the operator to focus attention on critical tasks and speed up the overall procedure.

Figure 5: Cryo Console

Integration between the Cryoablation Catheter and the Console includes monitoring catheter as well as console functionality, aided by a number of components such as: power cords, extension cables, inter connection box, foot switch, diaphragm movement sensor, esophageal temperature monitor, scavenging hose, wrench and nitrous oxide tanks.

5.1.5. Diaphragm Movement Sensor

The **Diaphragm Movement Sensor (DMS)** is a patch device placed on the patient just below the costal cartilage on the right side and used to monitor a phrenic nerve pacing response. It is connected to the Inter Connection Box (ICB) sending data to be displayed on the user interface of the Console. By integrating the information into the Cryo Console, the user can be informed when the measured pacing response is lower than a pre-determined value set by the physician.

Phrenic nerve monitoring is a known and essential component in determining safety during a cryoablation procedure. The current standard-of-care technique which is used to monitor for phrenic nerve palsy is to have the physician place his/her hand on the subject's abdomen and assess the subject's diaphragmatic movement during the period within the procedure that requires the physician's full attention (when ablation is occurring).
It has been reported with cryoablation balloon technology that the incidence of permanent phrenic nerve injury occurs in up to 0.4% of the cases (10) of patients undergoing a cryoablation procedure. The physician subjectively decides when injury may be occurring based on the change in diaphragmatic movement during respiration. The physician suspends ablation if there is a significant reduction in diaphragmatic movement. This is a

manual and physician dependent technique where the incidence of occurrence is related to experience in the cryoablation procedure.

An accelerometer in the DMS detects any reduction of diaphragmatic movement indicating phrenic nerve impact, thus helping to reduce procedure related adverse events and potentially improve procedural safety. The DMS is connected to the ICB of the Cryo-Console and sends data to be displayed on the Cryo-Console's user interface (see Figure 6 below).

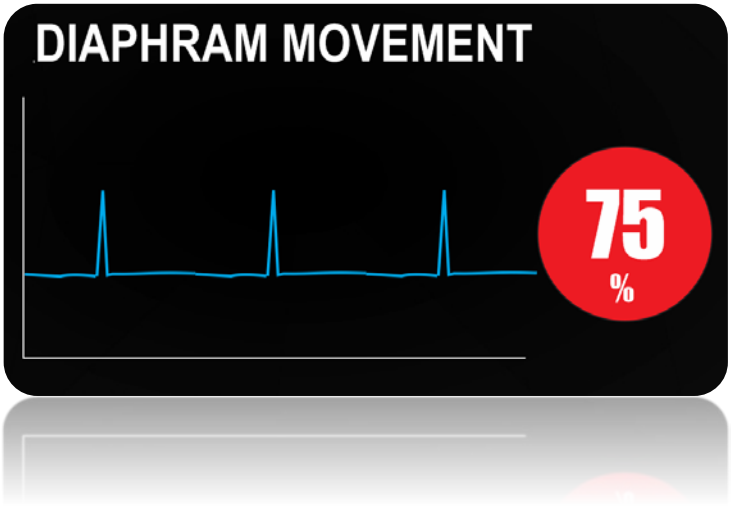


Figure 6: Diaphragm Movement Sensor (DMS) Data Cryo Console Display Phrenic Nerve Pacing Signal & Alert

By integrating the information into the Console, the physician can be informed when the measured pacing response falls below a pre-set value. The pre-determined value is programmed by the physician. The value is displayed as a percentage; with the first physical excursion establishing the baseline at 100%. The measurement display changes from "Blue" to "Red" if the value falls below the physician's programmed pre-set value (see Figure 6 above).

The DMS is designed to be used as an adjunct accessory to continually evaluate diaphragm movement during ablation; as a reminder alert to augment the established clinical practice described above for phrenic nerve assessment. The DMS is not a substitute for physician standard practice of phrenic nerve assessment during a cryoablation; i.e. physician palpation of the diaphragm, or attentive medical practice.

5.1.6. Esophageal temperature monitoring

Esophageal temperature monitoring is a frequently used technique, especially when there is an anatomical concern related to the proximity of the esophagus to the inferior pulmonary veins and posterior wall of the Left Atrium (LA). The esophageal ulceration is generally reversible, with a reported incidence of 17% of patients (10).

This feature integrates the detection of the esophageal temperature and provides a reminder alert to the physician if the esophageal temperature goes below a physician pre-set value.

The measured esophageal temperature turns the measurement display from "Blue" to "Red" if the temperature probe falls below a physician pre-set value. This feature potentially reduces adverse events such as esophageal ulcerations and fistulas. This is a optional safety alert system to the measurement systems used today although the alert is now displayed on the Console.

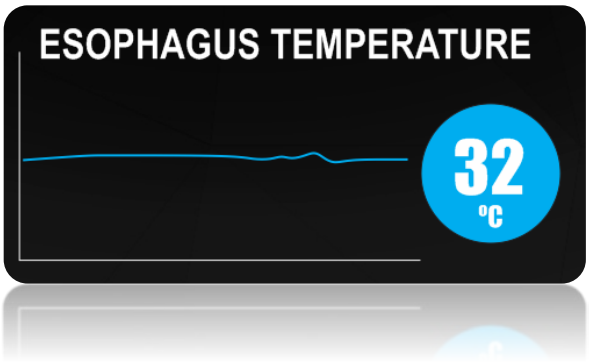


Figure 7: Esophagus Temperature Monitoring Data Display Phrenic Nerve Pacing Signal & Alert

As noted below, the ICB is designed to receive information from other proprietary devices such as an esophageal temperature probe. When connected, the esophageal temperature probe provides monitoring and alert data to the console for display. Esophageal temperature probes are widely available in stand-alone measurement systems and used as such within the EP lab. The Cryterion Medical Esophageal Temperature Sensor Cable enables the connection of a commercially available 400 series temperature probe (for example, Truer Medical 400 Series General Purpose Probes and DeRoyal Temperature Monitoring, Product No. 81-020409) to be connected to the Console

5.1.7. Other Cryoablation System Components

5.1.7.1. Inter Connection Box (ICB)

The ICB interfaces the Cryoablation Catheter with the Console. It receives the Catheter monitoring signals, DMS data, as well as information from other proprietary devices such as an esophageal temperature probe, a tip pressure sensor and various other safety systems. The ICB then transmits this information to the Console for display and user analysis.

5.1.7.2. Console Foot Switch

The Console Foot Switch interfaces with the Console and allows the user to inflate the Cryoablation Catheter, start and stop flow of N_2O (cryoablation) as well as deflate the Cryoablation Catheter at the conclusion of the ablation.

5.1.7.3. Console Scavenging Hose

The Console Scavenging Hose is a flexible N_2O exhaust line that connects to the hospital gas scavenging system and allows removal of N_2O gas.

5.1.7.4. Cryo Cable

The Cryo Cable is a sterile, single-use cable that provides the connectivity between the Cryoablation Catheter to the Console to support the delivery of liquid refrigerant and the evacuation of remaining N_2O gas.

5.1.7.5. Cryoablation Catheter Electrical Cable

The Cryoablation Catheter Electrical Cable is a sterile, single-use cable that provides the connectivity between the Cryoablation Catheter and the Console ICB.

5.1.7.6. Cryo Mapping Catheter EP Electrical Cables

The EP Electrical Cable is a sterile, single-use accessory for the Cryo Mapping Catheter and is designed to interface (connect) the Cryo Mapping Catheter with standard EP recording systems.

6. Study Objectives and Endpoints

6.1. *Study Objective*

This is a Post Market Clinical Follow-up (PMCF) study designed to establish the continued safety and effectiveness profile of the Cryoablation System after receiving CE mark.

The study will also provide information on real-world usage of the Cryoablation System when used to perform pulmonary vein isolation (PVI) for the ablation treatment of atrial fibrillation (AF), according to the current and future guidelines and system indications for use.

This may include (but not limited to) repeated ablations to treat AF, concomitant or delayed adjunctive ablation strategies with other products and use of different diagnostic products to validate the results such as 3D mapping systems.

Collected information and analyses will include, but not limited to, the following:

- Arrhythmia characterisation at the time of enrollment: time since first AF diagnosis, number and duration of reported episodes, prior electrical cardioversions (if any);
- History of prior ablations and repeated ablations during follow-up period;
- Use of anti-arrhythmic drugs (AAD);
- Methods used for verification of procedure success (pulmonary vein isolation): entrance/exit block, adenosine (if used), use of three-dimensional (3D) mapping.

6.2. *Study Endpoints*

6.2.1. Primary Safety Endpoint

The primary safety endpoint will be evaluated by the safety event free rate at 12 months post-index procedure.

Primary safety events will consist of a composite of the following procedure-related and device-related adverse events.

Acute primary safety endpoint events, events occurring up to 7 days post-index procedure or hospital discharge, whichever is later, include:

- Death
- Myocardial infarction (MI)
- Persistent gastroparesis/injury to vagus nerve
- Transient ischemic attack (TIA)
- Stroke/Cerebrovascular accident (CVA)
- Thromboembolism/ Air embolism*
- Cardiac tamponade/perforation
- Pneumothorax
- Serious vascular access complications**
- Pulmonary edema/heart failure
- AV block not attributable to medication effect or vasovagal reaction

*Thromboembolic or air embolic events collected in the study refer to any occlusion of blood vessel(s) that results in clinical symptoms
** Defined as prolongation of hospitalization, requirement of surgical intervention or blood transfusion

Chronic primary safety endpoint events, events occurring through 12 months post-index procedure, include:

- Atrial esophageal fistula
- Pulmonary vein stenosis (≥ 70% reduction of diameter)
- Symptomatic pericardial effusion
- Persistent Phrenic nerve injury***

***A non-recovered phrenic nerve injury at 12 months post-index procedure will count as a chronic primary endpoint. The study will collect information on phrenic nerve palsy observed before the end of the index procedure and, in case it occurred, will track information for potential recovery during the study visits.

6.2.2. Primary Effectiveness Endpoint

Failure free rate at 12 months post-index procedure.

Failure defined as:

- Failure to achieve acute procedural success* in the index procedure;
- More than one repeat procedure during the blanking period (within 90 days post-index procedure);
- Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia event (≥ 30 seconds in duration or from a 10 second 12-lead ECG) between days 91 and days 365 post-index procedure**;
- Any of the following interventions for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between days 91and days 365 post-index procedure:
  - Repeat procedure;
  - Electrical and/or pharmacological cardioversion for AF/AFL/AT;

- Prescribed a higher dose of any AAD*** documented at baseline or a new AAD*** not documented at baseline.

*Acute procedural success is defined as isolation of the all pulmonary veins or anatomical equivalents achieved with the Cryoablation Catheter at the end of the index procedure and as demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion).

**Subjects will be monitored for recurrences of the arrhythmias by means of clinical visits, ECG and 24-hour Holter monitoring. Recurrences documented with other devices only (eg. ILR, PM, ICD, CRT) will not be counted as primary effectiveness endpoint events.

***AADs for endpoint will consist of all Class I/III and any Class II/IV medications taken for control of AF/AFL/AT recurrence

6.2.3. Secondary Effectiveness Endpoint

Documentation and rate of acute procedural success (definition see section 6.2.2.). Electrical isolation of a PV is demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion).

Information on isolation method used per site standard of care will be collected with a minimum by entrance block in all PVs or anatomical equivalents. Additional data, if available, will be collected on Exit Block or Conduction Block verification using 3D mapping.

6.2.4. Additional analyses

Additional analyses include, but are not limited to:

- Procedure times: LA dwell time*, total ablation time, number of cryo applications per vein, time to thaw, total fluoroscopy time and total procedure time;
- Time-To- Isolation per ablation application, if available;
- Freedom from recurrence of individual types of atrial arrhythmias (AF, AFL, AT) between days 91 and days 365 post-index procedure;
- Analysis of ablation techniques (i.e. segmental approach to left common trunk, additional linear ablations, etc.);
- Analysis of different anaesthesia techniques (General anaesthesia with or without intubation versus sedation)
- Freedom from recurrence in subjects with non-common anatomical configurations of PV (e.g. left common trunk);
- Freedom from primary effectiveness failure evaluated in subgroups of subjects (termination of AAD versus continuation of AAD after blanking period);
- For the subgroup of subjects undergoing 3D mapping with the Boston Scientific mapping Rhythmia system and performing a post-procedural map, map information will be collected to determine lesion locations;
- For subjects that will undergo repeat ablation during the course of the clinical follow-up, anatomical location of ablations gaps will be assessed.

*LA dwell time is defined as time from the Cryoablation Catheter introduced in the left atrium (LA) to the last time of Cryoablation Catheter exiting the LA.

Table 6.2-1 Overview of objectives and endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Establish the continued safety of the Cryoablation System	Event free rate of a composite of procedure and device (acute (7 days) and chronic (12 month follow-up)) study specific adverse events	List of events were selected from those typically associated with catheter ablation of AF
Establish the effectiveness of the Cryoablation System	Failure- free rate at 12 months including failure to achieve success at index or repeat procedure in blanking period, documented AF/AT/AFL or interventions to treat these arrhythmias after blanking period, including repeated procedures cardioversion or prescription of new anti-arrhythmic drugs (or higher dose)	Performance goal and expected rates calculated from pivotal studies on AF ablation
Secondary		
Acute procedural success	Success of procedure (PVI)	Component of the primary effectiveness endpoint
Safety endpoint analysis for subgroups (PVI only vs PVI+ additional techniques)	Same as primary Safety endpoint definition, evaluated in specific sub-groups (non powered)	Additional ablations after PVI with other devices are common in standard of care due to non-PV triggers of AF in some subjects.
Additional		
Procedure-related times	LA dwell time, ablation time, number of cryo applications per vein, total fluoroscopy time, total procedure time, time to isolation (if available)	To relate with published data on other AF ablation devices
Single procedure success	Rate of subjects free from AF/AT/AFL undergoing the index procedure ablation only	To assess success rate in subjects who do not undergo a repeated ablation during blanking period
Approach to uncommon anatomies	Analysis of ablation techniques (i.e. segmental) and freedom from recurrence in subjects with non-common anatomical configurations of PV	Over 10 years' experience with the cryoballoon ablation made site able to treat subjects with peculiar anatomical PV configurations. This study wants to collect rate and outcome for this subgroup

7. Study Design

Prospective, non-randomized, multicenter (international), single arm study.

All subjects signing the consent, undergoing the index procedure and treated with the study devices will be followed up for one year.

7.1. *Scale and Duration*

Approximately 25 sites in Europe and Middle East will be included in the study.

A minimum of 200 subjects (with the possibility to expand up to a maximum of 400 subjects) will be enrolled in the study. A minimum of 199 subjects with De Novo treatment (i.e. first treatment for AF in the left atrium) for paroxysmal atrial fibrillation (PAF) will be analyzed to establish the continued safety and effectiveness profile of the Cryoablation System and fulfill the PMCF requirements for the submitted labeling of the Cryoablation System. This number represents the minimum number for the primary endpoint statistical hypothesis testing.

The entire study cohort will provide information on real-world usage of the Cryoablation System and will be analyzed for secondary objectives. These will include subgroup analysis in selected subjects of interest (including (but not limited to) De Novo ablation versus repeated ablations). These analyses will be non-powered but in case some of these subgroups will be poorly represented in the study, Boston Scientific may propose in the future to extend the sample size to up to 400 subjects.

Each subject will be followed at specific time points after the index procedure: pre-discharge, at 3 months (blanking period), 6 months and 12 months post-index procedure. Therefore, the study duration for each subject is expected to be approximately 12 months.

Subjects will be monitored for recurrences of the arrhythmias by means of clinical visits, ECG and 24-hour Holter monitoring.

Study enrollment is expected to be completed in approximately 12 months. Therefore, the total study duration is estimated to be approximately 24 months.

7.2. *Treatment Assignment*

Any subject who signs the consent form will be considered enrolled in the study.

Any subject that signs the consent form, has the study device inserted into the body and undergoes the protocol specific treatment for the intended disease (cryoablation) will be assigned to the treatment group.

Enrollment will progress until reaching a minimum of 200 subjects and a maximum of 400 subjects. A minimum of 199 De Novo (ie. first treatment for AF in the left atrium) TREATMENT subjects with PAF is needed for the assessment of the primary endpoint statistical hypothesis testing (section 11.1).

7.3. *Justification for the Study Design*

Boston Scientific believes that a prospective study on AF treatment with the Cryoablation System device powered for standard safety and effectiveness objective performance criteria is adequate for supporting post market requirements for the assessment of the continued safety and effectiveness of the device after market release in CE mark regions.

According to the most recent guidelines (11) catheter ablation has deemed effective in restoring and maintaining sinus rhythm in subjects with atrial fibrillation. The current study design ensures that the minimal number of subjects with De Novo PAF is reached to ensure testing of the statistical hypothesis and enroll a sufficient number of subjects to allow analysis on real-world usage of the Cryoablation System.

In the context of catheter ablation of AF, adjunctive ablation strategies to PV isolation are currently recommended by clinical guidelines (10) in different conditions including: Cavo-Tricuspid Isthmus ablation, linear ablation lesions in the left atrium or focal ablation of reproducible triggers. These adjunctive strategies can be applied with commercial focal/linear catheters either during a PV isolation procedure or during a repeated procedure, according to site standard of care.

Therefore, the heterogeneous scenarios that an electrophysiologist may encounter when approaching a subject with AF and candidate for catheter ablation could lead to different choices during the procedure.

Accordingly, this study will collect data on instance that may include concomitant or delayed adjunctive ablation strategies with other products and use of different diagnostic products to validate the results such as 3D mapping systems.

8. Subject Selection

8.1. *Study Population and Eligibility*

Subjects enrolled in the POLAR ICE study will be clinically indicated for an ablation procedure for the treatment of atrial fibrillation according to current and future guidelines and system indications for use. Subjects have to meet the study inclusion/exclusion criteria as outlined below in section 8.2 and 8.3. The subjects selected for participation will be from the investigator's general subject population. The investigator or its designee has the responsibility for screening all potential subjects and selecting those who meet study eligibility criteria.

8.2. *Inclusion Criteria*

Subjects who meet all of the following criteria (see Table 8.2-1) may be given consideration for inclusion in this clinical study, provided no exclusion criterion (see Table 8.3-1) is met.

Table 8.2-1: Inclusion Criteria

Inclusion Criteria	1. Subjects indicated for the treatment of AF with the Cryoablation System according to current and future Guidelines and system indications for use; 2. Subjects who are willing and capable of providing informed consent; 3. Subjects who are willing and capable of participating in all testing associated with this clinical study at an approved clinical investigational center; 4. Subjects whose age is 18 years or above, or who are of legal age to give informed consent specific to state and national law.

8.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 8.3-1) cannot be included in this study or will be excluded from this clinical study.

Table 8.3-1: Exclusion Criteria

Exclusion Criteria	1. Any known contraindication to an AF ablation or anticoagulation, including those listed in the instructions for use; 2. Subjects with indication for treatment of AF that is **not** according to current and future Guidelines and system indications for use; 3. Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause; 4. Known or pre-existing severe Pulmonary Vein Stenosis; 5. Evidence of myxoma, LA thrombus or intracardiac mural thrombus; 6. Previous cardiac surgery (e.g. ventriculotomy or atriotomy, CABG, PTCA, stent procedure) within 90 days prior to enrollment; 7. Implantable cardiac device procedure (e.g. PM, ICD, CRT) within 30 days prior to enrollment; 8. Implanted Left Atrial Appendage Closure device prior to the index procedure 9. Interatrial baffle, closure device, patch, or patent foramen ovale (PFO) occluder; 10. Subjects with severe valvular disease OR with a prosthetic – mechanical or biological - heart valve (not including valve repair and annular rings); 11. Presence of any pulmonary vein stents; 12. Active systemic infection; 13. Vena cava embolic protection filter devices and/ or known femoral thrombus; 14. Any previous history of cryoglobulinemia; 15. History of blood clotting or bleeding disease; 16. Any prior history of documented cerebral infarct, TIA or systemic embolism (excluding a post-operative deep vein thrombosis (DVT)) ≤ 180 days prior to enrollment; 17. Subjects who are hemodynamically unstable; 18. The subject is unable or not willing to complete follow-up visits and examination for the duration of the study; 19. Life expectancy ≤ 1 year per investigator's opinion; 20. Women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon investigator's discretion); 21. Unrecovered/unresolved Adverse Events from any previous invasive Procedure; 22. Subjects who are currently enrolled in another investigational study or registry that would directly interfere with the current study, except when the subject is participating in a mandatory governmental registry, or a purely observational registry with no associated treatments; each instance must be brought to the attention of the sponsor to determine eligibility.

9. Subject Accountability

9.1. *Point of Enrollment*

Investigators will select subjects who are appropriate for study inclusion as per eligibility criteria as specified under section 8.2 and 8.3. Subjects who have given written informed consent are considered enrolled in the study. All enrolled subjects will be counted against the enrollment ceiling of maximum 400 subjects. A total of 199 De Novo TREATMENT subjects with paroxysmal atrial fibrillation will serve for PMCF reporting purposes. No study-related activities, testing, procedures, etc. can take place until the Informed Consent Form (ICF) is signed and dated by the subject. Screening tests that are part of standard of care can be used to determine pre-eligibility. Data from exams performed prior to consent/enrollment (e.g. TTE) will be collected as medical history data after the subject is consented/enrolled in the study. It is the investigator's site responsibility to assess eligibility criteria before obtaining the Informed Consent Form.

9.2. *Withdrawal*

All subjects enrolled in the clinical study (including those withdrawn from the clinical study) shall be accounted for and documented. If a subject withdraws from the clinical study, the reason(s) shall be reported. Withdrawn subjects will not be replaced.

Reasons for withdrawal include but are not limited to physician discretion, subject choice to withdraw consent, lost to follow-up, or death. While study withdrawal is discouraged, subjects may withdraw from the study at any time, with or without reason, and without prejudice to further treatment. All applicable case report forms up to the point of subject withdrawal and a "End of Study" form must be completed.
Every effort should be made to obtain full information on any ongoing reportable adverse events up to the point of withdrawal. All open reportable adverse events should be closed or documented as chronic. Data collected up to the point of subject withdrawal may be used, unless any local regulations apply. Additional data may no longer be collected after the point at which a subject has been withdrawn from the study or withdraws his/her consent, for whatever reason. If such withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's permission to follow his/her status/condition.

9.3. *Lost to Follow-Up*

A subject will be considered lost to follow-up if he/she fails to return to scheduled visits as per Data Collection Schedule (Table 10.1-1), and is unable to be contacted by the study site staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject to reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.

- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (3 attempts, including telephone calls and/or a certified letter to the participant's last known mailing address or local equivalent methods, where possible). These contact attempts must be documented in the subject's medical record or study file and in the "End of Study" eCRFs.
- Should the subject continue to be unreachable, he or she will be considered lost to follow-up from the study.

9.4. *Subject Status and Classification*

Consent Ineligible (Screening Failures)

A subject who has given written informed consent but is found not to meet eligibility criteria before undergoing the index procedure and before having the study device inserted in the body, will be classified as "Consent Ineligible".

Subjects determined to be Consent Ineligible count towards the enrollment ceiling but will not be used for analysis of the endpoints. The original signed and dated Informed Consent must be maintained in the center's subject file. A subject identification number (ID) will be assigned in the EDC system.

For consent ineligible subjects, at the minimum the following forms must be completed:

- Enrollment eCRFs;
- Adverse Event eCRFs for any reportable event (as defined in section 17) that occurs after signing the Informed Consent, up to the point of subject withdrawal;
- Protocol Deviation eCRF, if applicable;
- End of Study eCRF.

Intent

A subject who has given written informed consent, meets eligibility criteria, but does not have any study devices inserted into the body will be classified as "INTENT". This includes subjects that had been prepared for the procedure (e.g. medication administered) and/or who had non-study devices inserted into the body. Subjects that are enrolled in the study but do not undergo ablation procedure within 90 days from consent signature date must not be reconsented and will be withdrawn from the study and classified as "INTENT". These subjects won't be allowed to be re-enrolled in the study.

There are no follow-up requirements for Intent subjects. Intent subjects will count towards the enrollment ceiling but will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the center's subject file. A subject ID will be assigned in the EDC system.

For intent subjects, at the minimum the following forms must be completed:

- Enrollment and Baseline eCRFs;
- Adverse Event eCRFs for any reportable event (as defined in section 17) that occurs after signing the Informed Consent, up to the point of subject withdrawal;
- Protocol Deviation eCRF, if applicable;
- End of Study eCRF.

Attempt

A subject who has given written informed consent, and has any study device inserted into the body but does not receive any Cryoablation application will be classified as "ATTEMPT." Attempts subjects will count towards the enrollment ceiling and will be used for analysis of the endpoints as per section 11.3.1. The original signed Informed Consent must be maintained in the center's subject file. A subject ID will be assigned in the EDC system. These subjects won't be allowed to be re-enrolled in the study.

Attempt subjects will be followed up to 7 days after index procedure or until discharge, whichever is later, for safety purposes. All applicable case report forms in the EDC system will be completed. The original signed Informed Consent and any relevant documentation must be maintained in the center's subject file.

For attempt subjects, at the minimum the following forms must be completed:

- Enrollment and Baseline eCRFs;
- Index Procedure eCRFs;
- Pre-Discharge eCRFs and Day 7 follow-up contact eCRF (if applicable);
- Adverse Event eCRFs or Device Deficiency eCRF for any reportable event (as defined in section 17) that occurs after signing the Informed Consent, up to the point of subject withdrawal;
- Protocol Deviation eCRF, if applicable;
- End of study eCRF.

Treatment

Any subject who has given written informed consent and has the specified study device inserted into the body and received at least one Cryoablation application will be classified as "TREATMENT". These subjects are followed in accordance with the Data Collection Schedule (Table 10.1-1) and included in all study analyses. A subject ID will be assigned in the EDC system. For TREATMENT subjects, all applicable case report forms per the protocol will be completed. Treatment subjects do count towards the enrollment ceiling and will be used for analyses of the endpoints. The original signed Informed Consent and any relevant documentation must be maintained in the center's subject file.

9.5. *End-of-Study Definition*

The clinical study is considered completed when subjects are no longer being examined or the last subject's last study visit has occurred. The subject's end of study is defined as completion of the last visit or procedure as shown in the Data Collection Schedule (Table 10.1-1) in the study.

10. Study Methods

10.1. *Data Collection*

Each Treatment subject will be followed at index procedure, at pre-discharge visit, at the month 3 follow-up, month 6 follow-up and month 12 follow-up. To reliably capture subject status at study end, the month 12 follow-up must be scheduled within 365 ± 30 days following the index procedure. The data collection schedule is shown in Data Collection Schedule (Table 10.1-1).

Table 10.1-1: Data Collection Schedule

Procedure / Assessment	Enrollment Baseline	Index Procedure *(Day 0)*	Blanking period			Effectiveness Evaluation period			Repeat (additional) ablation procedure
			Pre-Discharge *(0-7 days post procedure)*	Day 7 contact [4] *(day 7 + 7 days)*	Month 3 Follow-Up *(91±14 days)*	Month 6 Follow-Up *(180±30 days)*	Month 12 Follow-Up *(365±30 days)*	Additional Follow-up	
Informed consent process, including informed consent signature date	X								
Eligibility criteria	X								
Demographics	X								
Medical history	X								
LVEF, LA diameter and LA volume	X[1]								
Physical assessment	X		X		X	X	X	(X)	
LA assessment[3] imaging and thrombus assessment	(X)[2]								(X)[2]
Procedural Data		X							X
3D Mapping information		(X)							(X)
12-Lead ECG	X	X	X		X	X	X	(X)	X
Holter Monitor (24 hours) [6]					(X)	X	X	(X)	
Documentation of intervention for AF/AT/AFL (if any)			X		X	X	X	(X)	
Medications	X	X	X		X	X	X	(X)	X
Protocol Deviations	X	X	X	X	X	X	X	(X)	X
Adverse Event Assessment	X[5]								

X: Required; (X): Optional, per site standard of care;
[1] Per investigator's method. It is recommended to have the assessment within 180 days prior to enrollment;
[2] Assessment of left atrium anatomy, pulmonary veins anatomy and rule-out presence of thrombus is strongly recommended and to be performed according to site's standard of care practice - Assessments can be performed using CT, MRI, pulmonary venogram, ICE, TEE or other;
[3] It is recommended to have the LA assessment performed within 180 days prior to enrollment;
[4] If subject is discharged prior to day 7 post-index procedure, a (telephone) contact at day 7 (+ 7 days) is required to assess any post-discharge adverse events and complications;
[5] Adverse event assessment will be performed as from enrollment until study completion;
[6] A 24H Holter monitor is required at 6 and 12 months follow-up for all subjects.

10.2. *Study Candidate Screening*

Investigators are responsible for screening all subjects and selecting those subjects who are appropriate for study inclusion, as per eligibility criteria (see section 8).

The subjects selected for participation should be from the investigator's general subject population. The investigator is expected to follow standard of care testing to diagnose and screen subjects for inclusion in the study.

Prior to have any study related activities performed, subjects must give written informed consent to the study, as per section 10.3 and section 18.

10.3. *Enrollment and Informed Consent*

Subjects who provide written informed consent are considered enrolled in the study. As soon as informed consent is obtained, subject's eligibility criteria can be determined. Therefore, the investigator or designee needs to implement the consent process to verify and document if the subject meets the eligibility criteria. Informed consent is required for all subjects prior to their participation in the study. No study-specific procedures can be conducted prior to consent.

The subject should be given ample time to consider participation and ask questions if necessary. An approved informed consent form (ICF) shall be signed and dated by the subject or legally authorized representative. The original, signed document is to be kept with the subject's file and a copy must be provided to the subject. The index procedure must be performed within 90 days post ICF signature. In case the index procedure has not been performed within this time period, the subject will be classified as Intent (see section 9.4). The intent subject cannot be considered for re-enrollment as re-enrollment is not allowed for any subjects in this study. The site will ensure that originally signed ICFs and documentation of the ICF signature process are filed in subjects' files and that the subject's participation into the study is documented per hospital process (e.g.in the medical file). Originally signed ICFs and the ICF process documentation will be made available for review at Monitoring Visits.

For additional information regarding the informed consent process, refer to section 18.

10.4. *Baseline Visit*

The following assessments must be performed during the baseline visit. These assessments shall be recorded on the respective eCRF.

- Visit date;
- Documentation of Informed Consent process, including Informed Consent Form signature date;
- Eligibility criteria check;
- Demographics – including age at time of consent, gender, race, ethnicity;
- Medical history – including, but not limited to:
    - Underlying Cardiovascular disease (if any) and history of cardiac events;

- Arrhythmia history;
- Non-cardiac comorbidities;
- Prior surgical interventions and/or cardiac procedures;

- LVEF, left atrial diameter, left atrial volume (if available), as per investigator's method. It is recommended to have the assessment within 180 days prior to enrollment
- Physical Assessment – including height, weight, resting heart rate, systolic and diastolic blood pressure;
- Rhythm at the time of the visit (via 12-lead ECG);
- Current Anti-Arrhythmic Drugs and Anticoagulation medication regimen.

The assessment of LA anatomy* and the screening for potential LA thrombi prior to the procedure is strongly recommended to be performed according to the site's standard of care practice, however it is recommended to follow the indications from the HRS consensus statement for AF ablation (11).

This includes:

- Cardiac MRI, spiral CT scan, TEE, ICE or pulmonary venogram, to assess PV anatomy and PV dimension.
- Cardiac examination (TEE or ICE preferred) to rule out presence of left atrial thrombus**.

*It is recommended to perform the LA anatomy assessment within 180 days prior to enrollment

** If a thrombus is observed prior to ablation, the subject no longer meets eligibility criteria and shall not have the ablation procedure performed: the subject will then be withdrawn from the study, classified as Consent Ineligible and no further follow-up is required.

10.4.1. **Medications**

10.4.1.1. Anti-Arrhythmic Drugs

Information on all Anti-arrhythmic drug (AAD) medications will be collected on the eCRF starting from baseline visit. During the entire course of the study, details on changes will be specified on the eCRF. Post-index procedure AADs are allowed per investigator's discretion during the blanking period (90 days post-index procedure). According to HRS consensus guidelines (11), it is recommended to stop the administration of AAD for any atrial tachyarrhythmia after blanking period. If the investigator determines that the subject must be prescribed an increased dosage of AAD or a new AAD for treatment of any atrial tachyarrhythmia after the blanking period, the subject will be considered a Primary Effectiveness Failure.

AADs for endpoint will consist of all Class I/III and any Class II/IV medications taken for control of AF/AFL/AT recurrence.

10.4.1.2. Anticoagulation

The use of anticoagulation up to the procedure (including up to transseptal puncture) is per standard of care of the investigator. Information on anticoagulation therapy, pre and post index procedure will be collected in the eCRF.

It is recommended that heparin is administered prior to or immediately following transseptal puncture during ablation procedure and adjusted to achieve and maintain an ACT of at least 300 seconds. The ACT levels should be checked at a 15-30 minutes interval during the duration of the procedure.

10.5. *Ablation Procedure (Day 0)*

10.5.1. General Info

The study-related ablation procedure, from transseptal access in the left atrium until end of the ablation procedure must be performed by study-delegated investigators trained in electrophysiology (EP). Any procedure activity as of first skin puncture and prior to transseptal access can be performed by a physician who is not a study investigator under the supervision of the study investigator. Any reportable safety events that occur must be reported on the Adverse Event eCRF. The index ablation procedure must be performed within 90 days of a subject's enrollment into the study.

10.5.1.1. Esophagus Management

Information on esophagus management, if any, will be collected in the eCRF (e.g. temperature monitoring, esophageal deviation). It is highly recommended to perform temperature monitoring. If temperature monitoring is performed, monitoring will be performed via the Smartfreeze Console using compatible commercially available products, if available.

10.5.1.2. Phrenic Nerve Activity Monitoring

During ablation, phrenic nerve activity monitoring will be performed according to the standard of care at the site. It is highly recommended to use the Diaphragm Movement Sensor. If the Diaphragm Movement Sensor (DMS) is used, data will be collected in the eCRF. If a reduction in phrenic response is detected, the operating physician will continue to closely monitor phrenic nerve activity and pacing capture, and will consider immediately interrupting cryoablation. In case of phrenic nerve injury at the procedure the subject status and potential resolution of the adverse event will be monitored during the course of the study.

10.5.1.3. Pulmonary Vein Isolation

The goal of the ablation procedure is electrical isolation of all pulmonary veins or anatomical equivalents. Electrical isolation of the veins must be demonstrated at minimum with evidence of entrance block in all of the pulmonary veins using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion).

If the subject is in AF prior to the ablation, it will be up to the investigator's discretion whether to cardiovert or proceed with the procedure with the subject in AF. Electrocardiographic documentation of the subject's rhythm prior to ablation will be collected.

10.5.1.4. Cryoablation System Preparation

All devices should be prepared as described in the Instructions for use.

The Console will create a record for each ablation attempted, including (but not limited to) Ablation Duration and Cryoballoon Temperature. Esophagus Temperature and DMS activity data will also be collected if esophageal probe and DMS are connected.

In order to accurately capture information relevant to the study, the following information must be entered into the Console at each index procedure:

Prior to Ablation:

- On the subject information screen, enter the subject's identification (subject ID is provided by the EDC system when enrolling the subject) and the operating physician's name.
- If the physician decides to use DMS it should be connected to the subject during right PV ablations (for data acquisition). The DMS is an adjunctive sensor designed to monitor a phrenic nerve pacing response. Standard of care methods for evaluating phrenic nerve function and determining when intervention is needed (e.g. palpation, ICE) should always be applied during right pulmonary vein ablations. The DMS is not intended as a substitute for such standard of care methods.
- It is recommended to update the console timer preferences:
    - Cooling timer to: -40°C
    - Thaw timer to: 0°C

In case the DMS is used, the steps reported in the instructions for use (IFU) will be followed.

10.5.2. **Cryoablation protocol**

Preparation activities should be performed as follows:

1. Assessment of presenting rhythm by 12-lead ECG
2. Baseline the fluoroscopy exposure time (Time 0).
3. Place additional diagnostic catheters, for example in the coronary sinus or for pacing the phrenic nerve, at the discretion of the physician.
4. Per institutional protocol, complete transseptal access (single or double).
5. Per the IFU, prepare the Cryo Steerable Sheath. Insert the Cryo Steerable Sheath over the guidewire and advance the sheath across the atrial septum.
6. Per the IFU, prepare the Cryoablation Catheter and the Cryo Mapping Catheter. Insert the Cryo Mapping Catheter into the Cryoablation Catheter. Insert the Cryoablation Catheter into the Cryo Steerable sheath and advance it into the left atrium.
7. Baseline the LA dwell time.

Following the step-wise approach for the ablation procedure is recommended:

8. Navigating and positioning of the balloon
    a. Advance the Cryo Mapping Catheter and Cryoablation Catheter under fluoroscopic guidance to the proximity of the target PV
    b. Inflate the balloon while remaining outside of the target PV
    c. Occlude blood flow by advancing the balloon as necessary but remain outside of the tubular portion of the vein. Confirm and grade the occlusion (per physician's assessment)
    d. Verify balloon position for complete PV occlusion. Verification may be performed with fluoroscopy and/or contrast injection or other technique (per investigator's discretion).
9. Cryo Ablation of all target PVs
    a. Perform cryo ablation as per IFU. A minimum ablation time of TTI + 120sec is highly recommended, where possible. If no PV potential is visible, a minimum ablation time of 180sec is highly recommended.
    b. During each ablation application: annotate the anatomical location of ablation, the time-to-isolation* (as observed on the PolarMap EGMs and representing the time point when electrical activity disappears) and the ablation duration.

        * Time-to-isolation is required to be captured through the console, when available.
    c. Wait for the thawing phase to be completed prior to manipulating the Cryoablation Catheter.
    d. As needed, perform additional cryoablation in the same PV, adjusting the position of the Cryoablation Catheter, if necessary.
10. Confirmation of isolation of the PV at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion) is required for all pulmonary veins or their anatomical equivalent.

Note: If at any time during the ablation procedure the investigator is unable to continue the ablation with the designated study catheter (for the PV isolation), the investigator may complete the case with a device determined best for the subject. The case will represent an acute procedural failure (per protocol definition), regardless of achievement of PVI with other catheters. The point at which failure was determined as well as the rationale (including a device deficiency or adverse event, if any) must be documented in the EDC system. A protocol deviation will be documented in the EDC system.

10.5.2.1. Cryoablation-specific recommendations

Investigators may deliver one or more cryo applications per each pulmonary vein (or their anatomical equivalent) in order to achieve PVI.

In order to preserve subject's safety, it is recommended to adhere to the following indications:

- Terminate ablation if, in case of temperature monitoring, esophagus temperature falls below 20°C. Do not start a 2nd ablation until esophagus temperature returns at baseline levels.
- Terminate ablation if an impairment of diaphragmatic movement is detected by the operating investigator during ablation. Do not start a 2nd ablation until phrenic nerve activity returns at baseline levels.
- Do not apply more than 2 consecutive ablations in the same PV location*
- Do not apply more than 4 total ablations in a single PV*

* Ablations inferior to 60 seconds in duration are not considered in the total ablation count. Multiple ablations superior to these recommended numbers are reasonable in case of segmental ablations of large common trunk.

10.5.3. Additional ablation(s)

Additional ablation outside PVI for AF treatment or treatment of other arrhythmias could be done. This includes non-PV foci that initiate AF (including locations in the LA, LAA, RA, or SVC), targeting complex fractionated electrograms or ganglionated plexi or performing left atrial mitral isthmus or roof lines. Data will be collected in the eCRF.

The Cryoablation System cannot be used for the ablation of other arrhythmia(s)/additional line(s) or applications outside the PVs. For this purpose another commercially available catheter will be used.

If the subject presents with AF after all ablations are complete, cardioversion should be performed and will be noted. Cardioversions during the Index procedure do not signify procedural failures and are not to be reported as adverse events. Induction of or spontaneous conversion to AF during the procedure will not be considered an adverse event.

10.5.4. 3D mapping

Three-dimensional (3D) mapping may be used during the procedure. If 3D mapping is performed, a commercially available device will be used, and the information should be collected on the eCRF including but not limited to: mapping catheter, 3D mapping system, mapping times.

In case a post PVI map is collected, information on lesion and/or presence of conduction gaps should be collected for each PV. Potential gaps or poor lesion extension will be collected including localization information: vein and anatomical location.

10.5.5. Data Collection

The following data ***related to the procedure*** will be collected:

- Date of procedure
- Identification of study devices for the following:

- Cryoablation Catheter
- Cryo Mapping Catheter
- Cryo Steerable Sheath
- Console
- Related accessories

- Identification of non-study devices (if applicable):
  - Any additional sheaths/introducers used during the procedure including manufacturer, model and type
  - Any additional catheter(s) used during the procedure including manufacturer, model, and type (e.g. CS catheter)
  - Mapping system, if used (manufacturer, model and software version) and appropriate interface cables (manufacturer, model and type)
- Presenting rhythm at the beginning of the procedure (by means of a 12-lead ECG)
- Method of delivering sedation or anesthesia for the procedure
- Method of transseptal access to left atrium: single or double
- Method of evaluating phrenic nerve function and determining when intervention is needed

Specific to the ***PVI ablation*** the following information will be collected (including, but not limited to):

- Per each ablation application:
  - Acute Time-to-Isolation (if available)
  - Minimum balloon temperature
  - Time to thaw
  - Duration of each cryo application
  - DMS and Esophageal temperature, if available
  - Reason, if any, for premature interruption of the ablation
  - If ablation was followed by a verification of entrance block and if successful or not.

- For each pulmonary vein or anatomical equivalent:
  - PV isolation success, at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion) documented through EGMs printed from recording system and/or in medical file
- Any other ablation performed during the index procedure (before, during or after PVI)

At the ***end of the procedure***, the following information will be collected:

- Total procedure time, defined as time elapsed from time first access sheath insertion into the subject until the last catheter removed;
- Total Fluoroscopy time measured from baseline fluoroscopy time (Time 0);
- Total Cryoablation time (duration of all cryo applications);
- Duration of LA dwell time, defined as time from the Cryoablation Catheter introduced in the LA (exiting the sheath) to the last time of Cryoablation Catheter exiting the LA;
- Rhythm at end of case (documented by means of a post-ablation EGM/12-lead ECG);
- Cardioversion(s) performed during the procedure, if any;
- Assessment of reportable Adverse Events including resolution of ongoing events, if applicable/Device Deficiencies;
- Assessment of phrenic nerve palsy (method per investigator's discretion, eg. through fluoroscopy of diaphragm movement);
- Protocol Deviations, if applicable.

The ablation data report collected through the Console will be exported to external media, printed, signed by the investigator and stored as source data.

10.6. *Pre-Discharge (0-7days post index procedure)*

The pre-discharge follow-up visit should be completed before the subject is discharged from the hospital. The visit should occur within seven days post-index procedure. If the subject is to remain in the hospital beyond seven days post-index procedure, then the pre-discharge follow-up visit should be conducted before the eighth day.

Data collection during the Pre-Discharge visit will be recorded on the respective eCRF.

Data collection includes:

- Date of visit;
- Physical assessment including at minimum resting heart rate, weight, systolic and diastolic blood pressure;
- Rhythm at time of visit (by means of a 12-lead ECG);
- Documentation of intervention of AF, AFL, AT, if any;
- New, discontinued or changes to current Anti-Arrhythmic Drugs and Anticoagulation medication regimen;
- Protocol Deviations, if applicable;
- Reportable Adverse Events, including resolution of ongoing events, if applicable.

In cases of phrenic nerve palsy at the index procedure, the subject should be assessed to evaluate if the event resolved (method per investigator's discretion).

10.7. *Day 7 Follow-up Contact (eg. Phone call – window of + 7 days)*

In case the subject is discharged prior to 7 days post-index procedure, a (telephone) contact at day 7 (+ 7days) is required to assess if any adverse events, complications etc. have occurred since hospital discharge.

10.8. *Month 3 Follow-up (91 ± 14 days) (in-clinic visit)*

The Month 3 follow-up should be completed between 77 and 105 days post-index procedure.

Due to the range for the visit completion and the endpoint requirement for medication, AAD medication changes made during the Month 3 Follow-up visit will be counted as being made within the blanking period.

Data collection during the Month 3 follow-up visit will be recorded on the respective eCRF.

Data collection includes:

- Date of visit;
- Physical assessment including at minimum resting heart rate, weight, systolic and diastolic blood pressure;
- Rhythm at time of visit (by means of a 12-lead ECG);
- Holter monitor (24 hours) (optional, per standard of care);
- Documentation of intervention of AF, AFL, AT, if any;
- New, discontinued or changes to current Anti-Arrhythmic Drugs and Anticoagulation medication regimen;
- Protocol deviations, if any;
- Reportable Adverse Events, including resolution of ongoing events, if applicable.

  In cases of a pre-existing and unresolved phrenic nerve palsy the subject should be assessed to evaluate if the event resolved (method per investigator's discretion).

10.9. *Month 6 Follow-up (180 ± 30 days) (in-clinic visit)*

The Month 6 follow-up should be completed between 150 and 210 days post-index procedure.

Data collection during the Month 6 follow-up visit will be recorded on the respective eCRF.

Data collection includes

- Date of visit;
- Physical assessment including at minimum resting heart rate, weight, systolic and diastolic blood pressure;
- Rhythm at time of visit (by means of a 12-lead ECG);

- Holter monitor (24 hours) (required);
- Documentation of intervention of AF, AFL, AT, if any;
- New, discontinued or changes to current Anti-Arrhythmic Drugs and Anticoagulation medication regimen;
- Protocol deviations, if any;
- Reportable Adverse Events, including resolution of ongoing events, if applicable.

  In cases of a pre-existing and unresolved phrenic nerve palsy the subject should be assessed to evaluate if the event resolved (method per investigator's discretion).

10.10. *Month 12 Follow-up (365 ± 30 days) (in-clinic visit)*

The Month 12 follow-up should be completed between 335 and 395 days post-index procedure.

Data collection during the Month 12 follow-up visit will be recorded on the respective eCRF.

Data collection includes

- Date of visit;
- Physical assessment including at minimum resting heart rate, weight, systolic and diastolic blood pressure;
- Rhythm at time of visit (by means of a 12-lead ECG);
- Holter monitor (24 hours) (required);
- Documentation of intervention of AF, AFL, AT, if any;
- New, discontinued or changes to current Anti-Arrhythmic Drugs and Anticoagulation medication regimen;
- Protocol deviations, if any;
- Reportable Adverse Events, including resolution of ongoing events, if applicable.

  In cases of a pre-existing and unresolved phrenic nerve palsy the subject should be assessed to evaluate if the event resolved (method per investigator's discretion).

10.11. *Additional Follow-up*

An additional follow-up visit at the investigational site is any subject visit triggered by subject symptoms that is not already defined as one of the study visits.

Data collection during the additional follow-up visit will be recorded on the respective eCRF.

Data collection should include:

- Date of visit;
- Physical assessment including at minimum resting heart rate, weight, systolic and diastolic blood pressure;

- Rhythm at time of visit (by means of a 12-lead ECG);
- Holter monitor (24 hours) (per standard of care);
- Documentation of intervention of AF, AFL, AT, if any;
- New, discontinued or changes to current Anti-Arrhythmic Drugs and Anticoagulation medication regimen;
- Protocol deviations, if any;
- Reportable Adverse Events, including resolution of ongoing events, if applicable.

  In cases of a pre-existing and unresolved phrenic nerve palsy the subject should be assessed to evaluate if the event resolved (method per investigator's discretion).

10.12. *Repeat (or additional) ablation procedure*

It is known that during the first 90 days post-index procedure (blanking period), subjects can suffer from recurrences of atrial tachycardias (AF, AFL, AT). Within the blanking period, one repeat ablation procedure, using a commercially available ablation system, is allowed. More than one repeat ablation procedure during the blanking period, or a repeat ablation procedure performed after blanking period will count as a failure for the primary effectiveness endpoint.

During the repeat ablation procedure, the anatomical location of potential ablation gaps in the pulmonary veins will be assessed.

In case a repeat ablation procedure occurs during the 12 month follow-up period, the data of this procedure will be entered in the 'Additional Procedure' eCRF. In case this ablation procedure is performed to treat a supraventricular arrhytmia, including AF, AFL or AT, following detailed information about this repeat ablation procedure will be collected:

- Was the ablation procedure performed in the LA?;
- For repeat ablation procedures performed in the LA: was this repeat ablation procedure performed to treat atrial fibrillation? If no, specify the arrhythmia type;
- For ablations in the LA collect potential results of imaging (e.g. CT/MRI/ICE) performed per standard of care, including data to rule out thrombus prior to ablation or asses PV stenosis;
- The use of anticoagulation up to the procedure (including up to transseptal puncture) is per standard of care of the investigator. Information on anticoagulation therapy, pre and post repeat procedure will be collected in the eCRF.

  It is recommended that heparin is administered prior to or immediately following transseptal puncture during ablation procedure and adjusted to achieve and maintain an ACT of at least 300 seconds. The ACT levels should be checked at a 15-30 minutes interval during the duration of the procedure.
- If a 3D mapping system is used for this repeat procedure, additional info should be collected on the location and number of gaps;
- Rhythm at the beginning (12-lead ECG) and the end of the repeat procedure (documented by means of a post-ablation EGM/12-lead ECG);

- Reportable Adverse Events, including resolution of ongoing events, if applicable/Device Deficiencies;

  In cases of a pre-existing and unresolved phrenic nerve palsy the subject should be assessed to evaluate if the event resolved (method per investigator's discretion);

- Protocol deviations, if applicable.

10.13. *Study Completion*

All TREATMENT subjects will be followed for 12 months after the index procedure. Data collection will continue up to the point of the Month 12 follow-up visit, including the Holter monitor. The End of Study eCRF will have to be completed at study completion.

10.14. *Source Documents*

It is preferable that original source documents are maintained, when available. In lieu of original source documents, certified copies are required to be maintained. A certified copy is a copy (irrespective of the type of media used) of the original record that has been verified (i.e., by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original. Source documentation includes but is not limited to those items noted in Table 10.14-1.

Table 10.14-1: Source Documentation Requirements

Requirement	Disposition
Informed Consent documentation process	Retain at Center
Medical history documents pertaining to eligibility criteria	Retain at Center
Documentation of demographics data	Retain at Center
Physical assessment	Retain at Center
Medication regimen and Changes	Retain at Center
Medical history	Retain at Center
Documentation of isolation confirmation for each Pulmonary Vein	Retain at Center
Printed and signed PDF Console Export Case Data	Retain in subject binder
12-Lead ECGs data including ongoing rhythm	Retain at Center
Signed Technical Source Form	Retain in subject binder
Imaging, per standard of care	Retain at Center
Holter report	Retain in subject binder
Adverse Events	Retain at Center
In the event of a subject death (if requested: • Death narrative • Relevant medical records • Death Certificate • Autopsy report	Submit one copy to BSC, Retain one copy at center

11. Statistical Considerations

11.1. *Endpoints*

11.1.1. Primary Safety Endpoint

The primary safety endpoint will be evaluated by the safety event free rate at 12 months post-index procedure.

Primary safety events will consist of a composite of the following device and procedure-related and device-related adverse events.

Acute primary safety endpoint events, events occurring up to 7 days post-index procedure or hospital discharge, whichever is later, include:

- Death
- Myocardial infarction (MI)
- Persistent gastroparesis/injury to vagus nerve
- Transient ischemic attack (TIA)
- Stroke/Cerebrovascular accident (CVA)
- Thromboembolism/ Air embolism*
- Cardiac tamponade/perforation
- Pneumothorax
- Serious vascular access complications**
- Pulmonary edema/heart failure
- AV block not attributable to medication effect or vasovagal reaction

* Thromboembolic or air embolic events collected in the study refer to any occlusion of blood vessel(s) that results in clinical symptoms
** Defined as prolongation of hospitalization, requirement of surgical intervention or blood transfusion

Chronic primary safety endpoint events, events occurring through 12 months post-index procedure, include:

- Atrial esophageal fistula
- Pulmonary vein stenosis (≥ 70% reduction of diameter)
- Symptomatic pericardial effusion
- Persistent Phrenic nerve injury***

***A non-recovered phrenic nerve injury at 12 months post-index procedure will count as a chronic primary endpoint. The study will collect information on phrenic nerve palsy observed before the end of the index procedure and, in case it occurred, will track information for potential recovery during the study visits.

11.1.1.1. Hypotheses

For all Cohorts:

H_o: The primary safety endpoint event-free rate at 12 months post procedure ≤ 86%

H_a: The primary safety endpoint event-free rate at 12 months post procedure > 86%

11.1.1.2. Sample Size

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

11.1.1.3. Statistical Methods

The 12 month (365-day) primary safety event-free rate will be calculated using Kaplan-Meier methodology. Subjects who withdraw from the study prior to 12 months without experiencing an event will be censored on the date of withdrawal. The 95% one-sided lower confidence limit of the observed safety event-free rate will be compared to the performance goal of 86%. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected. The lower confidence limit will be calculated as the pointwise confidence limit using the log-log methodology.

11.1.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint will be evaluated by the failure-free rate at 12 months post-index procedure in each cohort.

Failure defined as:

- Failure to achieve acute procedural success* in the index procedure;
- More than one repeat procedure during the blanking period (within 90 days post-index procedure);
- Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia event (≥ 30 seconds in duration or from a 10 second 12-lead ECG) between days 91 and days 365 post-index procedure**.
- Any of the following interventions for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between days 91 and days 365 post-index procedure:
    - Repeat procedure
    - Electrical and/or pharmacological cardioversion for AF/AFL/AT
    - Prescribed a higher dose of any AAD*** documented at baseline or a new AAD*** not documented at baseline

* Acute procedural success is defined as isolation of the all pulmonary veins or anatomical equivalents achieved with the POLARx Cryoablation balloon at the end of the index procedure and as demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion)

** Subjects will be monitored for recurrences of the arrhythmias by means of clinical visits, ECG and 24-hour Holter monitoring. Recurrences documented with other devices only (eg. ILR, PM, ICD, CRT) will not be counted as primary effectiveness endpoint events

*** AADs for endpoint will consist of all Class I/III and any Class II/IV medications taken for control of AF/AT/AFL recurrence

11.1.2.1. Hypotheses

H_o: The failure-free rate at 12 months post procedure ≤ 50%

H_a: The failure-free rate at 12 months post procedure > 50%

11.1.2.2. Sample Size

[redacted]

[redacted]

[redacted]

[redacted]

11.1.2.3. Statistical Methods

The 12 month (365-day) primary effectiveness failure-free rate will be calculated using Kaplan-Meier methodology. Subjects who withdraw from the study prior to 12 months without experiencing an event will be censored on the date of withdrawal. The 95% one-sided lower confidence limit of the observed effectiveness failure-free rate in each cohort will be compared to the corresponding performance goal. If the lower confidence limit is greater than the performance goal, the null hypothesis will be rejected. The lower confidence limit will be calculated as the pointwise confidence limit using the log-log methodology.

11.2. *Data Analyses*

11.2.1. Secondary Effectiveness Endpoint

Documentation and rate of acute procedural success (definition see section 11.1.2.). Electrical isolation of a PV is demonstrated at minimum by entrance block using the Cryo Mapping Catheter (Other techniques of assessment are per investigator's discretion).

Information on isolation method used per site standard of care will be collected with a minimum by entrance block in all PVs or anatomical equivalents. Additional data, if available, will be collected on Exit Block or Conduction Block verification using 3D mapping.

11.2.2. Interim Analyses

No formal interim analyses are planned for the purpose of stopping the study early for declaring effectiveness or for futility. Analysis of each endpoint will be performed when all applicable data for that endpoint has been collected. Analyses of acute data (procedural safety and acute procedural success) may be performed and used for publication purposes after completion of study enrollment, index procedure, 7 day and 3 month follow-up of all subjects. A study report will be completed when the first 199 De Novo treatment subjects with paroxysmal atrial fibrillation qualifying for primary endpoint analyses will complete the follow-up of 12 months.

11.2.3. Subgroup Analyses

Additional ancillary analyses on specific subgroup of subjects, may be presented.

These analyses will include but not limited to the following:

- Age (<60 versus ≥ 60 years);
- Gender (Male versus Female);
- Monitoring (Subjects with data from continuous ECG recording systems (eg. ILR, PM, ICD, CRT) versus those without).

11.2.4. Pooling Analysis

Center-to-center heterogeneity will be assessed for the primary endpoints by performing a random effects logistic regression analysis. Centers with less than five enrollments will be combined to form "supercenters". Small centers will be combined until the newly created supercenter has five enrollments, and then a new supercenter will be created. Centers will be deemed to be heterogeneous if the variance of the random center effect is found to significantly differ from zero. A significance level of 15% will be used for this test.

11.2.5. Multivariable Analyses

For each primary endpoint, univariate analyses of the following covariates will be performed, and any found to be significantly associated with the outcome at the .15 alpha

level will be included as covariates in a multivariate regression model. Backward selection with 0.15 alpha level stay criterion will be used to determine the final multivariate model. The list of baseline covariates includes, but is not necessarily limited to:

- Subject demographics (e.g. age, gender)
- Subject baseline characteristics (e.g. LVEF and LA diameter)
- Procedural techniques (e.g., esophageal temperature monitoring,)

An additional multivariable analysis will be performed to assess on the effect of cryo dosing parameters on acute (procedure duration, dwell time, acuite success, acute adverse events) and chronic parameters (freedom from effectiveness failure). Cryo dosing parameters to be assessed for use in the model will be considered: number of cryo applications, time to isolation, ablation duration, sequence of veins approached and consecutive applications in the same vein. Additional subject variables such as PV anatomy and baseline characteristics will also be assessed for inclusion in the model.

11.2.6. **Additional Analyses**

Additional analyses include, but are not limited to:

- Procedure times: LA dwell time*, total ablation time, number of cryo applications per vein, time to thaw, total fluoroscopy time and total procedure time;
- Time-To-Isolation per ablation application, if available;
- Freedom from recurrence of individual types of atrial arrhythmias (AF, AFL, AT) between days 91 and days 365 post-index procedure;
- Analysis of ablation techniques (i.e. segmental approach to left common trunk, additional linear ablations, etc.);
- Analysis of different anaesthesia techniques (General anaesthesia with or without intubation versus sedation)
- Freedom from recurrence in subjects with non-common anatomical configurations of PV (e.g. left common trunk);
- Freedom from primary effectiveness failure evaluated in subgroups of subjects (termination of AAD versus continuation of AAD after blanking period);
- For the subgroup of subjects undergoing 3D mapping with the Boston Scientific mapping Rhythmia system and performing a post-procedural map, map information will be collected to determine lesion locations;
- For subjects that will undergo repeat ablation during the course of the clinical follow-up, anatomical location of ablations gaps will be assessed.

* LA dwell time is defined as time from the Cryoablation Catheter introduced in the left atrium (LA) to the last time of Cryoablation Catheter exiting the LA.

11.2.7. Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

11.3. *General Statistical Methods*

11.3.1. Analysis Sets

Effectiveness endpoint analyses will use all available data from all eligible TREATMENT subjects. Eligible TREATMENT subjects for the primary effectiveness endpoint includes all TREATMENT subjects who do not have an implantable continuous ECG recording system (eg. Pacemakers, arrhythmia loop recording systems, ICD, CRT). Eligible TREATMENT subjects for the secondary effectiveness endpoint will include all TREATMENT subjects.

Primary safety endpoint analyses will use data from all available TREATMENT subjects. Safety analysis for ATTEMPT subjects will be limited to the Acute primary safety endpoint events (per definition in section 6.2.1.).

11.3.2. Control of Systematic Error/Bias

Selection of subjects will be made from the Investigator's population. All subjects that have signed the ICF will be enrolled in the study.

11.3.3. Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will initially not be allowed to enroll more than 10% of the 199 subjects (20 subjects) meeting enrollment criteria. Enrollment up to a total of 30 subjects meeting the enrollment criteria during the enrollment period will be allowed **after sponsor approval**. Enrollment of an amount of study subjects in excess of such approved number of 30 total subjects must first be approved by Sponsor, notified to Institution's IRB/EC/REB, as applicable, and requires an amendment of exhibit A of the clinical study agreement.

12. Data Management

12.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system, recommended within 10 business days.

The clinical database will reside on a production server hosted by Medidata EDC System. All changes made to the clinical data will be captured in an electronic audit trail and available for review by the sponsor or its representative. The associated Rave software and database have been designed to meet regulatory compliance for deployment as part of a

validated system compliant with laws and regulations applicable to the conduct of clinical studies pertaining to the use of electronic records and signatures. Database backups are performed regularly.

The Investigator provides his/her electronic signature on the appropriate electronic case report forms (eCRFs) in compliance with local regulations. A written signature on printouts of the eCRFs must also be provided if required by local regulation. Changes to data previously submitted to the sponsor require a new electronic signature by the Investigator acknowledging and approving the changes.

Visual and/or electronic data review will be performed to identify possible data discrepancies. Manual and/or automatic queries will be created in the Medidata EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database in a timely manner.

CRF Completion Guidelines will be created by Boston Scientific and provided to all sites.

12.2. *Data Retention*

The Principal Investigator or his/her designee or Investigational site will maintain all essential study documents and source documentation that support the data collected on the study subjects in compliance with applicable regulatory requirements.

The Principal Investigator or his/her designee will take measures to prevent accidental or premature destruction of these documents. If for any reason the Principal Investigator or his/her designee withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility and BSC must receive written notification of this custodial change. Sites are required to inform Boston Scientific in writing where paper or electronic files are maintained in case files are stored off site and are not readily available.

12.3. *Technical Source Forms*

The Technical Source Form (TSF) is the approved document to capture protocol required data elements that are not duplicated in any other source documents. This form requires review and approval by the investigator and is to be used by the study sites as a source document.

Collection and completion of all information on the Technical Source Form is the responsibility of the appropriately delegated site personnel.

At the conclusion of the procedure, the completed technical source form must be signed (and initialed as needed) by the following people:

- the Delegated Site Personnel completing the forms;
- the Delegated Investigator conducting and/or supervising the case.

13. Deviations

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. An investigator shall notify the sponsor and the reviewing EC of any deviation from the investigational plan to protect

the life or physical well-being of a subject in an emergency, and those deviations which affect the scientific integrity of the clinical study. Such notice shall be given as soon as possible, but no later than 5 working days after the emergency occurred, or per prevailing local requirements, if sooner than 5 working days.

All deviations from the investigational plan, with the reason for the deviation and the date of occurrence, must be documented and reported to the sponsor using EDC. Sites may also be required to report deviations to the EC, per local guidelines and government regulations.

Deviations will be reviewed and evaluated on an ongoing basis and, as necessary, appropriate corrective and preventive actions (including EC notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

14. Compliance

14.1. *Statement of Compliance*

This study will be conducted in accordance with the spirit of ISO 14155 (Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice), the relevant parts of the ICH Guidelines for Good Clinical Practices, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and regulations. The study shall not begin until the required approval/favorable opinion from the EC and/or regulatory authority has been obtained, if appropriate. Also, the study shall not begin prior to issuance of the site Authorization to Enroll, as provided by the sponsor. Any additional requirements imposed by the EC or regulatory authority shall be followed, if appropriate.

14.2. *Investigator Responsibilities*

The Principal Investigator of an investigational site is responsible for ensuring that the study is conducted in accordance with the Clinical Study Agreement, the clinical investigation plan, the spirit of ISO 14155, ethical principles that have their origins in the Declaration of Helsinki, any conditions of approval imposed by the reviewing EC, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

The Principal Investigator's responsibilities include, but are not limited to, the following.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Provide his/her qualifications and experience to assume responsibility for the proper conduct of the study and that of key members of the site team through up-to-date curriculum vitae or other relevant documentation and disclose potential conflicts of interest, including financial, that may interfere with the conduct of the clinical study or interpretation of results.
- Make no changes in or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency; document and explain any deviation from the approved protocol that occurred during the course of the clinical study.

- Create and maintain source documents throughout the clinical study and ensure their availability with direct access during monitoring visits or audits; ensure that all clinical-study-related records are retained per requirements.
- Ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.
- Record, report, and assess (seriousness and relationship to the device/procedure) every adverse event as applicable per the protocol and observed device deficiency.
- Report to sponsor, per the protocol requirements, all SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE.
- Report to the EC and regulatory authorities any SAEs and device deficiencies that could have led to a SADE and potential/USADE or UADE, if required by applicable laws or regulations or this protocol or by the EC, and supply BSC with any additional requested information related to the safety reporting of a particular event.
- Allow the sponsor to perform monitoring and auditing activities, and be accessible to the clinical research monitor or auditor and respond to questions during monitoring visits or audit(s).
- Allow and support regulatory authorities and the EC when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local EC requirements.
- Provide adequate medical care to a subject during and after a subject's participation in a clinical study in the case of adverse events, as described in the Informed Consent Form (ICF).
- Inform the subject of the nature and possible cause of any adverse events experienced.
- As applicable, provide the subject with necessary instructions on proper use, handling, storage, and return of the device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical study, including the need for additional medical care that may be required.
- Provide the subject with well-defined procedures for possible emergency situations related to the clinical study, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical studies, as needed.
- Ensure that clinical medical records are clearly marked to indicate that the subject is enrolled in this clinical study.
- Ensure that, if appropriate, subjects enrolled in the clinical study are provided with some means of showing their participation in the clinical study, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided).
- Inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical study.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical study while fully respecting the subject's rights.

- Ensure that an adequate study site team and facilities exist and are maintained and documented during the clinical study.

14.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator or trained sub-investigator is responsible for providing appropriate training, ensuring delegates are competent to perform the tasks they have been delegated and ensuring adequate supervision of those to whom tasks are delegated. Where there is a sub-investigator at a site, the sub-investigator should not be delegated the primary supervisory responsibility for the site. The investigator is accountable for regulatory violations resulting from failure to adequately supervise the conduct of the clinical study.

14.3. *Ethics Committee*

The investigational site will obtain the written and dated approval/favorable opinion of the EC for the clinical study before recruiting subjects and implementing all subsequent amendments, if required.

A copy of the written EC and/or competent authority (CA) approval of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study. Prior approval must also be obtained for other materials related to subject recruitment or which will be provided to the subject.

Any amendment to the protocol will require review and approval by the EC before the changes are implemented to the study. All changes to the ICF will be EC approved; a determination will be made regarding whether a new ICF needs to be obtained from participants who provided consent, using a previously approved ICF.
Annual EC approval and renewals will be obtained throughout the duration of the study as required by applicable local/country laws or regulations or EC requirements. Copies of the study reports and the EC continuance of approval must be provided to the sponsor.

14.4. *Sponsor Responsibilities*

All information and data sent to BSC concerning subjects or their participation in this study will be considered confidential by BSC and will be kept confidential in accordance with all applicable laws and regulations. Only authorized BSC personnel and/or a BSC representative including, but not limited to Contract Research Organization (CRO), will have access to this information. Authorized regulatory personnel have the right to inspect and copy all records pertinent to this study. Study data collected during this study may be used by BSC for the purposes of this study, publication, and to support future research and/or other business purposes, such as overseeing and improving the performance of its device, new medical research and proposals for developing new medical products and procedures. All data used in the analysis and reporting of this study or shared with a third-party researcher will be without identifiable reference to specific subjects.

Information received during the study will not be used to market to subjects; subject names will not be placed on any mailing lists or sold to anyone for marketing purposes.

14.4.1. Role of Boston Scientific Representatives

Boston Scientific personnel can provide technical support to the investigator and other health care personnel (collectively HCP) as needed during index procedure, testing required by the protocol, and follow-ups. Support may include HCP training, addressing HCP questions, or providing clarifications to HCPs concerning the operation of BSC equipment/devices (including programmers, analyzers, and other support equipment).

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during index procedure, assist with the conduct of testing specified in the protocol, and interact with the subject to accomplish requested activities.

Typical tasks may include the following:

- Setting up, calibrating and/or operating parameters to investigator-requested settings of the Console during the preparation and execution of the mapping and ablation procedure;
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel;
- Interaction with Boston Scientific noninvasive equipment (Console and applicable accessories) and interpretation of information contained therein to support the collection of required information by the delegated site staff;
- Print out reports/export data directly from the console and provide original printouts or electronic data reports to clinical site as source documentation;
- Provide technical expertise/support to subjects during office visits and/or during teleconference calls/electronic communications with the principal investigator or their delegated site staff and the subject.

In addition, BSC personnel may perform certain activities to ensure study quality. These activities may include the following:

- Observing testing or medical procedures to provide information relevant to protocol compliance
- Reviewing collected data and study documentation for completeness and accuracy

Boston Scientific personnel will not do the following.

- Practice medicine;
- Provide medical diagnosis or treatment to subjects;
- Discuss a subject's condition or treatment with a subject;
- Record data on source documents;
- Independently collect critical study data (defined as primary or secondary endpoint data);
- Enter data in electronic data capture systems or on paper case report forms.

14.5. *Insurance*

Where required by local/country regulation, proof and type of insurance coverage, by BSC for subjects in the study will be obtained.

15. Monitoring

Monitoring will be performed during the study to assess continued compliance with the protocol and applicable regulations. In addition, the clinical research monitor verifies that study records are adequately maintained, that data are reported in a satisfactory manner with respect to timeliness, adequacy, and accuracy, and that the Principal Investigator continues to have sufficient staff and facilities to conduct the study safely and effectively. The Principal Investigator/institution guarantees direct access to original source documents by BSC personnel, their designees, and appropriate regulatory authorities.

The study may also be subject to a quality assurance audit by BSC or its designees, as well as inspection by appropriate regulatory authorities. It is important that the Principal Investigator and relevant study personnel are available during on-site monitoring visits or audits and that sufficient time is devoted to the process.

16. Potential Risks and Benefits

16.1. *Instructions for Use*

Please refer to the Instructions for Use for an overview of anticipated adverse (device) effects, and risks associated to the commercial device(s).

16.2. *Risks associated with Participation in the Clinical Study*

There are no specific tests outside those recommended as standard practice for catheter ablation of AF required by this clinical study protocol. Therefore, there is no foreseen increased risk to subjects for participating in the study.

16.3. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, using the devices in accordance with their applicable Instructions for Use, performing procedures in the appropriate hospital environment, following recommended standard practices/guidelines, adherence to subject selection criteria, close monitoring of the subject's physiologic status during research procedures and/or follow-ups and by promptly supplying BSC with all pertinent information required by this protocol.

16.4. *Anticipated Benefits*

Subjects may or may not receive any benefit from participating in this study as compared to the current standard of care received for treatment of AF. Potential benefits of the Cryoablation System for the subject may include the following:

- Complete or partial reduction in symptoms related to AF
- Complete or partial reduction in the number of cardioversions, medications a subject is taking, and in the number of hospitalizations related to AF

16.5. *Risk to Benefit Rationale, if applicable*

Risk management activities, including Hazard Analyses (HA) and Failure Mode Effects Analyses (FMEA), have been performed on the Cryoablation System, steerable sheath and extension cable to identify and analyze known and foreseeable hazards (in both normal and fault conditions) and reasonably foreseeable sequences or combinations of events that could result from using this product and the risks associated with each hazard. Mitigations have been implemented in the design, processes, and/or labeling and directions for use of the product to reduce the residual risk of each hazard as necessary and practicable. The HA has been reviewed and approved and the remaining risks are acceptable when weighed against the intended benefits to the subject.

17. Safety Reporting

17.1. *Reportable Events by investigational site to Boston Scientific*

It is the responsibility of the investigator to assess and report to BSC any event which occurs in any of following categories of reportable events:

- All Serious Adverse Events, including all events leading to death;
- All Thromboembolic Events;
- All Study Procedure Related AEs (index and repeat procedure);
- All BSC commercialized device-related adverse events;
- All Study Device-Related Adverse Events;
- All Study Related Device Deficiencies;
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in the IFU.

Any reportable adverse event (per definition above), experienced by the study subject after written informed consent must be recorded in the eCRF.

Whenever possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms. If it is unclear whether or not an event fits one of the above categories, or if the event cannot be isolated from the device or procedure, it should be submitted as an adverse event and/or device deficiency.

Death should not be recorded as an SAE but should only be reflected as an outcome of one (1) specific SAE (see Table 17.2-1 for Safety definitions).

If the subject experiences a new arrhythmia between index procedure and end of study, and the investigator considers this adverse event to be procedure related, it needs to be reported.

The following clinical events will not be considered adverse events for this clinical study:

- Pre-existing diseases or conditions (including AF, AFL, AT) will not be reported as adverse events unless there has been a substantial increase in severity or frequency of the problem as compared to the subject's baseline which cannot be attributed to the expected progression of the disease or condition;

- A recurrence of an arrhytmia should be reported on the "AF recurrence" CRF and should not be recorded as an adverse event, unless it meets seriousness criteria as per table 17.2-1;
- Pre-planned hospitalizations at time of enrollment or for a pre-existing condition;
- If an additional ablation procedure is required, this additional ablation procedure should not be considered as an Adverse Event, unless associated with subject worsening condition or a new diagnosis. If the investigator considers this event to be related to any procedure, the event needs to be reported. In this case, the additional ablation procedure should be reported in the Adverse Event eCRF as corrective action of the specific Procedure Related Adverse Event reported for the worsening condition or new diagnosis.

Refer to Instructions for Use for the known risks associated with the commercial device(s).

17.2. *Definitions and Classification*

Adverse event definitions are provided in Table 17.2-1. Administrative edits were made on the safety definitions from ISO 14155 and MEDDEV 2.7/3 for clarification purposes.

Table 17.2-1: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, whether or not related to the study medical device. **NOTE 1**: This includes events related to the study medical device or comparator. **NOTE 2**: This definition includes events related to the procedures involved. **NOTE 3**: For users or other persons, this definition is restricted to events related to the study medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of the study medical device **NOTE 1**: This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of the study medical device. **NOTE 2**: This definition includes any event resulting from use error or intentional abnormal use of the study medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Note: This definition meets the reporting objectives and requirements of ISO 14155 and MEDDEV 2.7/3. Adverse event that: a) Led to death, b) Led to serious deterioration in the health of the subject as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, or

Table 17.2-1: Safety Definitions

Term	Definition
	3) in-patient hospitalization or prolongation of existing hospitalization, or 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function c) Led to fetal distress, fetal death, or a congenital abnormality or birth defect. **NOTE 1:** Planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered a serious adverse event.
Serious Adverse Device Effect (SADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.
Unanticipated Adverse Device Effect (UADE) *Ref: 21 CFR Part 812*	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.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of the study medical device related to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

17.3. *Relationship to Device(s)*

The Investigator must assess the relationship of the reportable AE to the device or procedure. See criteria in Table 17.3-1:

Table 17.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref: MEDDEV 2.7/3*	Relationship to the device or procedures can be excluded when: - the event is not a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has no temporal relationship with the use of the study device or the procedures; - the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event; - the event involves a body-site or an organ not expected to be affected by the device or procedure; - the serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the study device used for diagnosis, when applicable; harms to the subject are not clearly due to use error; - In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.
Unlikely Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.
Probably Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the study device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Table 17.3-1: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the study device or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with the study device use/application or procedures; - the event involves a body-site or organ that -the study device or procedures are applied to; -the study device or procedures have an effect on; - the serious event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible); - other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the study device used for diagnosis, when applicable; - In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

17.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 17.4-1.

Adverse events and device deficiencies must always be reported through the eCRF system. In the event that an alternative method of reporting is necessary (i.e. the eCRF system is unavailable), please report the adverse event or device deficiency to Boston Scientific by sending the Event Notification Form via email to the following email address:

[redacted]

Table 17.4-1: Investigator reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline post-market studies*** (MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Unanticipated Adverse Device Effect / Unanticipated Serious Adverse Device Effect	Complete AE eCRF page with all available new and updated information.	• Within 1 business day of first becoming aware of the event. • Terminating at the end of the study.
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 10 business days after becoming aware of the event or as per local/regional regulations. • All death events must be reported within 3 calendar days • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 2 business days of first becoming aware of the event or as per local/regional regulations. • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Device Deficiency that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate is considered a reportable event.	Complete DD eCRF with all available new and updated information.	• Within 2 business days of first becoming aware of the event. Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor

Event Classification	Communication Method	Communication Timeline post-market studies* (MEDDEV 2.12/2: GUIDELINES ON A MEDICAL DEVICE VIGILANCE SYSTEM)
Adverse Event including Adverse Device Effects	Complete AE eCRF page, which contains such information as date of AE, treatment of AE resolution, assessment of seriousness and relationship to the device.	• In a timely manner (e.g. recommend within 30 business days) after becoming aware of the information • Reporting required through the end of the study
	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	

17.5. *Boston Scientific Device Deficiencies*

All device deficiencies (including but not limited to failures, malfunctions, use errors, product nonconformities, and inadequacy in the information supplied by the manufacturer) associated with the study devices will be documented and reported to BSC (as per table 17.4-1). If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the device(s) will be provided upon request. If it is not possible to return the device, the investigator should document why the device was not returned and the final disposition of the device. Device deficiencies should also be documented in the subject's source records.

Device deficiencies are not adverse events. However, an adverse event that results from a device deficiency, would be recorded as an adverse event on the appropriate eCRF in addition to completing a Device Deficiency eCRF.

17.6. *Reporting to Regulatory Authorities / ECs / Investigators*

BSC is responsible for reporting adverse event information to all participating Principal Investigators, ECs and regulatory authorities, as applicable.

The Principal Investigator is responsible for informing the EC, and regulatory authorities of UADEs and SAEs as required by local/regional regulations.

17.7. *Subject Death Reporting*

A subject death during the study should be reported to Boston Scientific as soon as possible and, in any event, within three (3) calendar days of site notification. The site's EC must be notified of any deaths in accordance with that site's EC policies and procedures.

Upon request of sponsor, notification of death must include a detailed narrative (death letter) that provides detailed information describing the circumstances surrounding the death. A death narrative in the local language is acceptable, if accompanied by a translation in English. The details listed below should be addressed in the death narrative, in order for BSC to understand the circumstance surrounding the death:

- Date and time of death;
- Place death occurred;
- Immediate cause of death;
- Rhythm at the time of death, if known (include any available documentation);
- Whether the death was related to the study devices, clinical study, procedure, or subject condition;
- Whether or not the death was witnessed;
- Whether the subject had worsening heart failure;
- Any other circumstances surrounding the death;
- Approximate time interval from the initiating event to death (temporal course) – items to consider include, but are not limited to: information regarding last time subject was seen by investigator, last office visit, etc.
- Investigator or sub-Investigator signature and date.

Also submit the following documentation, upon request from sponsor:

If the subject expired in the hospital:

- A copy of the medical records for that admission (e.g., H&P, consults, test results, operative reports, and/or progress notes from the hospital chart);
- Death certificate (if available);
- Autopsy report (if applicable);

If the subject expired outside of the hospital (e.g., home):

- A copy of the most recent clinic visit (if not already submitted to Boston Scientific);
- Death certificate (if available);
- If applicable, the Boston Scientific catheters should be returned promptly to Boston Scientific CRM/EP for analysis.

18. Informed Consent

Subject participation in this clinical study is voluntary. Informed Consent is required from each subject or his/her legally authorized representative. The Investigator is responsible for ensuring that Informed Consent is obtained prior to the use of any study devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with the principles of the Declaration of Helsinki, ISO 14155, any applicable national regulations, and local Ethics Committee and/or Regulatory authority, as applicable. The ICF must be accepted by BSC or its delegate (e.g. CRO), and approved by the site's EC, or central EC, if applicable.

Boston Scientific will provide a study-specific template of the ICF to investigators participating in this study. The ICF template may be modified to meet the requirements of the investigative site's EC. Any modification requires acceptance from BSC prior to use

of the form. The ICF must be in a language understandable to the subject and if needed, BSC will assist the site in obtaining a written consent translation. Translated consent forms must also have EC approval prior to their use. Privacy language shall be included in the body of the form or as a separate form as applicable.

The process of obtaining Informed Consent shall at a minimum include the following steps, as well as any other steps required by applicable laws, rules, regulations and guidelines:

- be conducted by the Principal Investigator or designee authorized to conduct the process,
- include a description of all aspects of the clinical study that are relevant to the subject's decision to participate throughout the clinical study,
- avoid any coercion of or undue influence of subjects to participate,
- not waive or appear to waive subject's legal rights,
- use native language that is non-technical and understandable to the subject or his/her legal representative,
- provide ample time for the subject to consider participation and ask questions if necessary,
- ensure important new information is provided to new and existing subjects throughout the clinical study.

The ICF shall always be signed and personally dated by the subject or legal representative competent to sign the ICF under the applicable laws, rules, regulations and guidelines and by the investigator and/or an authorized designee responsible for conducting the informed consent process. If a legal representative signs, the subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows. The original signed ICF will be retained by the site and a copy of the signed and dated document and any other written information must be given to the person signing the form.

Failure to obtain subject consent will be reported by BSC to the applicable regulatory authority according to their requirements (e.g., FDA requirement is within 5 working days of learning of such an event). Any violations of the informed consent process must be reported as deviations to the sponsor and local regulatory authorities (e.g. EC), as appropriate.

If new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the affected subject(s) in written form via a revised ICF or, in some situations, enrolled subjects may be requested to sign and date an addendum to the ICF. In addition to new significant information during the course of a study, other situations may necessitate revision of the ICF, such as if there are amendments to the applicable laws, protocol, a change in Principal Investigator, administrative changes, or following annual review by the EC. The new version of the ICF must be approved by the EC. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's EC. The EC will determine the subject population to be re-consented.

19. Committees

19.1. *Safety Monitoring Process*

BSC Safety Trial Operations reviews all reported adverse events and device deficiencies on a regular basis and, as required, with BSC Medical Safety per the study specific safety plan. During scheduled monitoring activities, clinical research monitors will support this continuous review through their review of source documents and other data information. The BSC Medical Safety group includes physicians with expertise in Electrophysiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

19.2. *Steering Committee*

A Steering Committee composed of the sponsor's Clinical Management and other prominent Electrophysiologists from around Europe has been convened for this study. Responsibilities for the Committee may include oversight of the overall conduct of the study with regard to protocol development, study progress, subject safety, overall data quality and integrity, and first line review and final decision making of independent medical reviewer recommendations, as well as disseminating any study results through appropriate scientific sessions and publications. Steering Committee members may participate in the review and approval of all requests for data analysis, abstract and manuscript preparation, and submission.

20. Suspension or Termination

22.1 Premature Termination of the Study

Boston Scientific reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or business reasons and reasons related to protection of subjects. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

22.1.1 Criteria for Premature Termination of the Study

Possible reasons for premature study termination include, but are not limited to, the following:

- The occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Boston Scientific to suspend or discontinue development/marketing of the device.

22.2 Termination of Study Participation by the Investigator or Withdrawal of EC Approval

Any investigator, or associated EC or regulatory authority may discontinue participation in the study or withdraw approval of the study, respectively, with suitable written notice to

Boston Scientific. Investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

22.3 Requirements for Documentation and Subject Follow-up

In the event of premature study termination a written statement as to why the premature termination has occurred will be provided to all participating sites by Boston Scientific. The EC and regulatory authorities, as applicable, will be notified. Detailed information on how enrolled subjects will be managed thereafter will be provided.

In the event an EC terminates participation in the study, participating investigators, associated ECs, and regulatory authorities, as applicable, will be notified in writing. Detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

In the event a Principal Investigator terminates participation in the study, study responsibility will be transferred to another investigator, if possible. In the event there are no opportunities to transfer Principal Investigator responsibility; detailed information on how enrolled subjects will be managed thereafter will be provided by Boston Scientific.

The Principal Investigator or his/her designee must return all study-related documents and devices, if supplied by Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

22.4 Criteria for Suspending/Terminating a Study Site

Boston Scientific reserves the right to stop the inclusion of subjects at a study site at any time after the study initiation visit if no subjects have been enrolled for a period beyond 12 months after site initiation, or if the site has multiple or severe protocol violations/noncompliance without justification and/or fails to follow remedial actions.

In the event of termination of site participation, all devices and testing equipment, as applicable, will be returned to BSC unless this action would jeopardize the rights, safety or well-being of the subjects. The EC and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

21. Publication Policy

BSC requires disclosure of its involvement as a sponsor or financial supporter in any publication or presentation relating to a BSC study or its results. BSC will submit study results for publication (regardless of study outcome) following the conclusion or termination of the study. Boston Scientific adheres to the Contributorship Criteria set forth in the Uniform Requirements of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org). In order to ensure the public disclosure of study results in a timely manner, while maintaining an unbiased presentation of study outcomes, BSC personnel may assist authors and investigators in publication preparation provided the following guidelines are followed:

- All authorship and contributorship requirements as described above must be followed.

- BSC involvement in the publication preparation and the BSC Publication Policy should be discussed with the Coordinating Principal Investigator(s) and/or Executive/Steering Committee at the onset of the project.
- The First and Senior authors are the primary drivers of decisions regarding publication content, review, approval, and submission.

The data, analytic methods, and study materials for this clinical study may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

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23. Abbreviations and Definitions

23.1. *Abbreviations*

Abbreviations are shown in Table 23.1-1.

Table 23.1-1: Abbreviations

Abbreviation/Acronym	Term
AAD	Anti-Arrhythmic Drugs
ADE	Adverse Device Effect
AE	Adverse Event
AF	Atrial Fibrillation
AFL	Atrial Flutter
AT	Atrial Tachycardia
CA	Competent Authority
CABG	Coronary artery bypass grafting
CRF	Case Report Form
CVA	Cerebrovascular Accident
DD	Device Deficiency
DMS	Diaphragm Movement Sensor
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ICB	Inter Connection Box
ICE	Intracardiac Echo
ICF	Informed Consent Form
IFU	Instructions for Use
LA	Left Atrium
MI	Myocardial Infarction
MRI	Magnetic Resonance Imaging
N_2O	Nitrous Oxide
PAF	Paroxysmal Atrial Fibrillation

Table 23.1-1: Abbreviations

Abbreviation/Acronym	Term
PeAF	Persistent Atrial Fibrillation
PFO	Patent Foramen Ovale
PMCF	Post Market Clinical Follow-up
PTCA	Percutaneous transluminal coronary angioplasty
PV	Pulmonary Vein
PV	Pulmonary Venogram
PVI	Pulmonary Vein Isolation
RA	Right Atrium
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TEE	Trans-esophageal echocardiography
TIA	Transient Ischemic Attack
TSF	Technical Source Form
TTE	Trans-Thoracic echocardiography
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect

23.2. *Definitions*

Terms are defined in Table 23.2-1.

Table 23.2-1 Definitions

Term	Definition
Activated Coagulation/Clotting Time	ACT is a test that is used to monitor the effectiveness of high dose heparin therapy.
Arterial-Venous Fistula	Abnormal communication between an artery and a vein.
Atrioesophageal Fistula	A connection between the atrium and the lumen of the esophagus.
Attempt Subject	Any subject that signs the consent form, and has any study device inserted into the body but does not receive any Cryoablation application.
AV block	A conduction disturbance that results in the partial inability of an electrical impulse generated in the atria to reach the ventricles.
Blanking Period	90-day period between ablation procedure and the initiation of the Effectiveness Evaluation Period during which up to one additional ablation procedure can be performed and subjects can be prescribed antiarrhythmic drugs as determined necessary by the investigator.
Cardiac tamponade/ perforation	The development of a significant pericardial effusion during or within 30 days of undergoing an AF ablation procedure. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1-cm or more pericardial effusion as documented by echocardiography.
Embolism	The sudden blocking of an artery by a clot or foreign material which has been brought to its site of lodgment by the blood current.
Enrolled Subject	A subject who has given written informed consent to participate in the study.
Hematoma	A localized collection of blood, usually clotted, in an organ, space or tissue, due to a break in the wall of a blood vessel.
Intent Subject	Any subject that signs the consent form but does not have any study devices inserted into the body. Subjects who are enrolled in the study but do not undergo ablation procedure within 90 days from consent signature date may not be reconsented and will be withdrawn from the study.

Term	Definition
In-patient Hospitalization	Hospitalizations ≥24 hours in duration or <24 hours with medical intravenous therapy or surgical intervention
Myocardial infarction (in the context of AF ablation)	The presence of any one of the following criteria: (1) detection of ECG changes indicative of new ischemia (new STT wave changes or new LBBB) that persist for more than 1 hour; (2) development of new pathological Q waves on an ECG; (3) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality
Occlusion Grade	Score 4 = excellent (full retention of contrast medium without visible outflow) Score 3 = moderate (incomplete occlusion with slight leakage of contrast medium) Score 2= poor (presence of sustained and massive leakage of contrast medium) Score 1 = very poor (immediate rapid outflow from the PV).
Paroxysmal Atrial Fibrillation (PAF)	Recurrent symptomatic Atrial Fibrillation that terminates spontaneously or with intervention within seven days of onset.
Pericardial Effusion	A collection of fluid or blood in the pericardial space around the heart or in pleural space around the lungs.
Pericarditis	Inflammation of the pericardium surrounding the heart. Pericarditis should be considered a major complication following ablation if it results in an effusion that leads to hemodynamic compromise or requires pericardiocentesis, prolongs hospitalization by more than 48 hours, requires hospitalization, or persists for more than 30 days following the ablation procedure.
Pneumothorax	Collapse of the lung due to an abrupt change in the intrapleural pressure within the chest cavity.
Primary Effectiveness Failure	A TREATMENT subject with • Acute procedure failure • More than one repeat procedure during the blanking period • Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia event (≥ 30 seconds in duration from an event monitor or Holter, or from a 10 second 12-lead ECG) between 91 and 365 days post index procedure Any of the following interventions for atrial fibrillation, or new onset of atrial flutter or atrial tachycardia between 91 days and 365 days post index procedure: • Repeat procedure • Electrical and/or pharmacological cardioversion for AF/AT/AFL • Prescribed a higher dose of any AAD documented at baseline or a new AAD not documented at baseline
Procedural Success	Pulmonary vein isolation achieved with the Boston Scientific cryoablation system as demonstrated by entrance block at the minimum.
Prolonged Hospitalization	Hospitalization ≥72 hours after the study procedure for reasons other than anticoagulation
Pseudoaneurysm	A dilation of an artery with disruption of one or more layers of its walls.
Pulmonary Vein Stenosis (Significant)	Pulmonary vein stenosis is defined as a reduction of the diameter of a PV or PV branch. For the primary safety endpoint of this study, significant pulmonary vein stenosis is defined as symptomatic and requiring intervention.
Pulmonary edema/heart failure	Ineffective pumping of the heart leading to an accumulation of fluid in the lungs. Typical symptoms include shortness of breath with exertion, difficulty breathing when lying flat and leg or ankle swelling.

Term	Definition
Source Data	All information in original records of clinical findings, observations, or other activities in a clinical study, necessary for the reconstruction and evaluation of the clinical study (original records or certified copies).
Source Document	Printed, optical or electronic document containing source data. Examples: Hospital records, laboratory notes, device accountability records, radiographs, records kept at the investigation site, and at the laboratories involved in the clinical study.
Stroke/Cerebrovascular accident (CVA)	Rapid onset of a focal or global neurological deficit with at least one of the following: change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke. Duration of a focal or global neurological deficit ≥24 hours; OR <24 hours if therapeutic intervention(s) were performed (e.g., thrombolytic therapy or intracranial angioplasty); OR available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death. No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences). Confirmation of the diagnosis by at least one of the following: neurology or neurosurgical specialist; neuroimaging procedure (MRI or CT scan or cerebral angiography); lumbar puncture (i.e., spinal fluid analysis diagnostic of intracranial hemorrhage)
Symptomatic AF	Required symptom(s) of AF that were experienced by the subject, made them seek medical attention, and were concurrent with a documented episode by ECG, event monitoring and/or Holter monitor. Symptoms may have included palpitations, irregular pulse (i.e. rapid, racing, pounding, fluttering, bradycardic), dizziness, weakness, chest discomfort, and breathlessness.
Thrombus	An aggregation of blood factors, primarily platelets and fibrin with entrapment of cellular elements, frequently causing vascular obstruction at the point of its formation.
Thromboembolism	The blockage of a blood vessel lumen by air or solid material such as device fragments, blood clot or other tissues that have migrated from another anatomic site.
Transient Ischemic Attack (TIA)	New focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), always within 24 hours; neuroimaging without tissue injury
Treatment Subject	Any subject that signs the consent form, and has the specified study devices inserted into the body and undergoes protocol specific treatment for the intended disease.
Vagal Nerve Injury/Gastroparesis	Vagal nerve injury is defined as injury to the vagal nerve that results in esophageal dysmotility or gastroparesis. Vagal nerve injury is considered to be a major complication if it prolongs hospitalization, requires hospitalization, or results in ongoing symptoms for more than 30 days following an ablation procedure
Vascular access complications	Development of a hematoma, an AV fistula, or a pseudoaneurysm. A major vascular complication is defined as one that requires intervention, such as surgical repair or transfusion, prolongs the hospital stay, or requires hospital admission.