Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

FROzEN-AF

PY004

CLINICAL INVESTIGATION PLAN

G190060

National Clinical Trial (NCT) Identified Number: NCT04133168

Sponsored By

Boston Scientific Corporation

4100 Hamline Ave. N.

St. Paul, MN 55112

and

Boston Scientific International S.A.

Le Val Saint-Quentin,

2 rue René Caudron,

78960 Voisins le Bretonneux, France

Contact Information

Role	Contact
Clinical Contacts	**Clinical Trial Managers, Protocol Authors** Sarah Kenneweg Clinical Trial Manager 4100 Hamline Ave. N. St. Paul, MN 55112 USA Tel. +1 (510) 701- 1351 Sarah.kenneweg@bsci.com Sheryl McCammon Clinical Trial Manager 4100 Hamline Ave. N. St. Paul, MN 55112 USA Tel. +1 (763) 647- 0113 Sheryl.McCammon@bsci.com Elke Sommerijns Sr. Clinical Trial Manager Guidant Europe, a Boston Scientific Company Green Square, Lambroekstraat 5D 1831 Diegem Belgium Tel. +32 479 76 71 56 Elke.sommerijns@bsci.com
Coordinating Principal Investigator(s)	Kenneth Ellenbogen, MD Kimmerling Professor of Cardiology Chair, Division of Cardiology VCU Pauley Heart Center Medical College of Virginia / VCU School of Medicine Gateway Building 1200E. Marshall Street 3rd Floor – Electrophysiology Division - Room 3-223 Richmond, Virginia 23219 Office (804) 828-7565 E-mail: kenneth.ellenbogen@vcuhealth.org

Executive Steering Committee Members	Ante Anić, MD EP lab, Heart Center, University Hospital Split, Croatia A. Starcevica 25 D, 23000 Zadar, Croatia Telephone: +38523240605 Email: anteanic@gmail.com	Robin Boisseau 9131 Stony Point Parkway Apt 3213 Richmond, VA 23235. Tel: (843) 860-9004 Email: Robin.Boisseau@vcuhealth.org
	Arash Aryana, MD, PhD, FACC, FHRS Medical Director, Cardiovascular Services Mercy General Hospital 3941 J Street, Suite #350 Sacramento, CA 95819 (916) 453 2684 E-mail: a_aryana@outlook.com	Nassir Marrouche, MD Tulane University School of Medicine Cardiology 1430 Tulane Avenue, Box 8548 New Orleans, LA 70112 (804) 988-2025 Email: Nmarrouche@tulane.edu
	Suneet Mittal, MD, FACC, FHRS Director, Electrophysiology Associate Chief of Cardiology Medical Director, Snyder AF Center Director, Cardiac Research 200 West 57th Street, Suite 610 New York, NY 10019 (212) HEART DR (432-7837) Email: MITTSU@Valleyhealth.com	Niraj Varma MD, PhD, FRCP Cardiac Pacing & Electrophysiology Department of Cardiovascular Medicine Cleveland Clinic 9500 Euclid Ave J2-2 Cleveland, OH 44195 (216) 444-2142 Email: varman@ccf.org
	Wilber W. Su, MD, FACC, FHRS Cardiology and Cardiac Electrophysiology Banner– University Medical Group- Heart Center 755 E. McDowell Rd, 4th Floor Phoenix, AZ 85006 (602) 521-3090 Email: wilwsu@gmail.com	This section is intentionally left blank.
Vendors/Labs/External Organizations	A list of vendors/core laboratories/external organizations involved in the trial is maintained by the sponsor.	

Original Release: 30-Jan-2019

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
C	**4-Mar-2019**	**90702637, Rev/Ver AJ**	**NA**	Versions A to C incorporated internal changes prior to FDA submission	NA
D	**9-May-2019**	**90702637, Rev/Ver AJ**		Modifications according to initial FDA IDE review, application # G190060, 5 April 2019	Modifications according to initial FDA IDE review, application # G190060, 5 April 2019
E	**19-Aug-2019**	**90702637, Rev/Ver AJ**		Modifications according to FDA IDE review 3July2019, application # G190060, 3 July 2019	Modifications according to FDA IDE review, application # G190060, 3 July 2019
F	**26-Aug-2019**	**90702637, Rev/Ver AJ**		Updated Table Numbering for Tables 14 through 17	Incorrect table numbering
G	**18-Sep-2019**	**90702637, Rev/Ver AJ**		Modifications according to FDA IDE review, application # G190060, 16 September 2019	Modifications according to FDA IDE review, application # G190060, 16 September 2019
H	**NovNov-2020**	**90702637, Rev/Ver AN**	Throughout	To comply updated BSC template versions (specifically highlighted in green in redlined version)	Per BSC procedures, primarily driven by ISO 14155 changes
H	**Nov-2020**	**90702637, Rev/Ver AN**	9.1	Up to 50 sites in North America, Europe and Asia-Pacific may participate in this study. Up to 10 sites in Europe may contribute to enrollments.	Europe added as a potential geography for study centers within the FROzEN-AF study.
H	**Nov-2020**	**90702637, Rev/Ver AN**	9.3.2	For investigators participating in a geography in which the system is not investigational, a roll-in case may not be required if BSC can confirm the physician has previously treated patients with the system.	Protocol revision H expands the geography to sites in Europe where the product is commercially available.
H	**Nov-2020**	**90702637, Rev/Ver AN**	10.2	For inclusion criteria, "Subjects refractory or intolerant to at least one class I or III antiarrhythmic medication," the following clause was added, "*or contraindicated to any class I or III medications*."	Providing clarification that subjects have either failed, are intolerant or contraindicated to at least one class I or III antiarrhythmic medication for inclusion in the study.
H	**Nov-2020**	**90702637, Rev/Ver AN**	10.2	The defined criteria for PAF documentation for inclusion criteria was updated to the following:	Requires documentation of 2 AF symptomatic recurrences in the medical file but allows ECG documentation to be extended to 12 months.

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
				History of recurrent symptomatic paroxysmal atrial fibrillation (PAF), defined as atrial fibrillation that terminates spontaneously or with intervention (either procedure or drug therapy) within seven days of onset. Minimum documentation includes the following: • a physician's note indicating recurrent self-terminating atrial fibrillation (AF) which includes at least two symptomatic AF episodes within last six months from enrollment, and • one electrocardiographically documented AF episode within 12 months prior to enrollment.	
H	**Nov-2020**	**90702637, Rev/Ver AN**	10.3	Removed the following exclusions: • Age maximum of 75 years • Body Mass index (BMI) ≥ 40	• Inclusion criteria defined of >18 years with no maximum age limit for the randomized studies for which this single-arm trial design is based. • Exclusion criteria for BMI not included in the randomized studies for which this single-arm trial design is based.
H	**Nov-2020**	**90702637, Rev/Ver AN**	12.5.2	Added language to define that if subject enrolled less than 3 weeks prior to the procedure, pre-ablation anticoagulation must be initiated and maintained from point of enrollment to the day of the index procedure and that thrombus screening should be performed for these subjects.	Per protocol, enrollment (subject consent) may occur any time during the 30 days before the index procedure, and clarification added pre-ablation anticoagulation regimen for subjects enrolled less than 3 weeks prior to the procedure.
H	**Nov-2020**	**90702637, Rev/Ver AN**	12.15	Unforeseen Circumstances section added	To provide guidance if patient follow-ups are not possible due to unforeseen circumstances (e.g. COVID-19).
I	**Feb-2022**	**90702637, Rev/Ver AP**	Appendix 27.1	Addition of Appendix 27.1 – POLARx FIT: FROzEN Extension Study	To include a sub-study establishing the safety and effectiveness of Boston Scientific's POLARx Cryoablation System with the POLARx FIT catheter.
I	**Feb-2022**	**90702637, Rev/Ver AP**	Title page and Contact	Added NCT Identified Number and updated BSC Contact Information	Updated contact information to reflect current BSC Study Managers

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
			Information		
I	**Feb-2022**	**90702637, Rev/Ver AP**	Section 7.1	Expanded Device Specification Tables	Expanded device specifications to align with tables in IFUs
I	**Feb-2022**	**90702637, Rev/Ver AP**	Section 8.2, Table 5	Added clarification as to which vascular access complication events would be considered primary safety endpoint events	To remain consistent with the methods used in the meta-analysis performed to determine expected rates and an appropriate performance goal for the primary safety endpoint

2. Protocol Synopsis

Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation **FROzEN-AF**	
Study Objective(s)	To establish the safety and effectiveness of the Boston Scientific Cardiac Cryoablation System for treatment of symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation (AF).
Test Device	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") • Diaphragm Movement Sensor (DMS) • Related Accessories, as listed in protocol section 7.1.7.
Control Device	There are no control devices in this study.
Planned Indication(s) for Use	The Cryoablation System is intended for cryoablation and electrical mapping of the pulmonary veins for pulmonary vein isolation (PVI) in the ablation treatment of patients with paroxysmal atrial fibrillation (PAF). Treatment will occur according to the approved indication for use within each geography and the defined inclusion/exclusion criteria within the protocol.
Study Design	Multi-center, open label, prospective, single arm study to document the safety and performance of Boston Scientific's Cryoablation System. All subjects fitting the enrollment criteria, signing the consent and undergoing the index procedure with the study devices will be followed up for twelve (12) months after the index procedure. FROzEN-AF will be conducted as a post market study in those regions where the device is approved, including Europe.

Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation **FROzEN-AF**	
Planned Number of Subjects	A maximum of 405 subjects treated with the Cryoablation System will be enrolled in the study, inclusive of a maximum of 80 *roll-in* TREATMENT subjects and 325 *non roll-in* TREATMENT subjects.
Planned Number of Investigational Sites / Countries	Up to 50 sites in North America, Europe and Asia-Pacific may participate in this study.. At least 50% of the sites and 50% of the subjects will enroll in the United States, potentially up to 10% of subjects will enroll in 3 to 5 combined sites from Hong Kong and Taiwan. Up to 10 sites in Europe may contribute to enrollments. No study site will be allowed to contribute more than 15% of the required enrollment.
Primary Safety Endpoint	Primary safety event free rate at 12 months post 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 or hospital discharge, whichever is later, include:* • Death • Myocardial infarction (MI) • Transient ischemic attack (TIA) • Stroke/ Cerebrovascular accident (CVA) • Vascular access complications • Mitral or tricuspid valvular damage • Thromboembolism/ Air embolism leading to a life-threatening event such as a ventricular arrhythmia, stroke, pulmonary embolism, or myocardial infarction and, thromboembolic events that result in permanent injury, require intervention for treatment or prolongs or require hospitalization for more than 48 hours • Gastroparesis/injury to vagus nerve • Pneumothorax • Pulmonary edema/heart failure • AV block *Cardiac tamponade/perforation*, occurring up to 30 days post index procedure.

Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation **FROzEN-AF**	
	Chronic primary safety endpoint events, events occurring through 12 months post procedure, include: • Atrial esophageal fistula • Severe Pulmonary vein stenosis (≥ 70% reduction in the diameter of the PV or PV branch from baseline) • Persistent phrenic nerve palsy

Primary Effectiveness Endpoint	Failure free rate at 12 months post procedure.
	Failure defined as:
	• Failure to achieve acute procedural success in the index procedure or repeat procedure during the blanking period
	• Use of amiodarone post index procedure
	• Surgical treatment for AF/AFL/AT post index procedure
	• Use of a non-study ablation catheter for AF targets in the index procedure or repeat procedure during the blanking period
	• More than one repeat procedure with the POLARx catheter during the blanking period (90 days post index procedure)
	• Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia event [≥ 30 seconds in duration from the study specific event monitor, Holter Monitor, or from a 10 second 12-lead Electrocardiography (ECG)] between days 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 days 91 post index procedure and 365 days:
	  • Repeat procedure
	  • Electrical and/or pharmacological cardioversion for AF/AFL/AT
	  • Prescribed any antiarrhythmic drug (AAD)*
	
	*AADs for endpoint will consist of all Class I/III, including Amiodarone, and any Class II/IV medications taken for control of atrial fibrillation (AF)/Atrial tachycardia (AT)/Atrial flutter (AFL) recurrence

Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation **FROzEN-AF**	
Secondary Safety Endpoint	**Safety:** Reportable Adverse Events rates at 12 months. Adverse events will be collected at all subject follow-up visits. Reportable events include: • All Serious Adverse Events • All Study Procedure-Related Adverse Events • All Study Device-Related Adverse Events • All Study Device Deficiencies • Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in Investigator's Brochure or DFU
Secondary Effectiveness Endpoint	Rate of acute procedural success defined as the achievement of electrical isolation of all PVs by using the POLARx Cardiac Cryoablation system only. Electrical isolation of a PV is demonstrated by entrance and exit block.
Additional Endpoints	Additional endpoints and analysis include, but are not limited to: • Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up • Single procedure success defined as freedom from primary effectiveness failure without a repeat procedure • Duration of LA dwell time, defined as time from the Cryoablation Catheter exiting the sheath in the LA to time of final PV isolation • Total Cryoablation time for the index procedure; • Total fluoroscopy time for the index procedure; • Total index procedure time. • Freedom from recurrence of individual types of atrial arrhythmias between 91 and 365 days from index procedure: 1) AF 2) AT 3) AFL • Failure-free rate as defined in primary effectiveness endpoint at 6 months post procedure

Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation **FROzEN-AF**	
	• Failure- free rate as defined in primary effectiveness endpoint when considering AF/AT/AFL episodes reported to the investigators by study specific (event recorder transmissions, 12 lead ECG and Holter) and non-study related devices (other commercial applications for arrhythmia monitoring and detection the subject may access during the study including telemetry, other sources of continuous recording etc.)
PV Stenosis Screening Substudy	Screening for PV stenosis with computed tomography (CT) or cardiac magnetic resonance imaging (MRI) between 3 and 6 months post ablation will be performed in a subgroup of treated subjects. The subgroup will include a minimum of 50 subjects enrolled at up to 8 sites. Sites will be selected among those that use imaging as a standard-of-care for PV stenosis screening after AF ablation. • Each site participating in the sub study will enroll a maximum of 18 substudy subjects.
Patient Disposition and Method of Assigning Patients to Treatment	Any subject that signs the consent form, meets eligibility criteria, has the study device inserted into the body and receives Cryoablation therapy will be assigned to the TREATMENT group. The disposition of all subjects enrolled in the study will be described in tables and diagrams. The data will include number of subjects screened, subjects that fail screening, subjects treated and assessed at each follow-up interval. Subjects who fail screening, or who do not complete the study will be enumerated and the reason(s) for their screening failure or discontinuation from the study will be described.
Follow-up Schedule	Visits schedule: pre-discharge, Day 7, 3 months (blanking period), 6 months, 12 months.
Study Duration	Study is expected to last approximately 24 months (9-12 months for enrollment period with 12 months follow-up).
Participant Duration	The study duration for each subject is expected to be approximately 12 months.

Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation **FROzEN-AF**	
Inclusion Criteria	• History of recurrent symptomatic paroxysmal atrial fibrillation (PAF), defined as atrial fibrillation that terminates spontaneously or with intervention (either procedure or drug therapy) within seven days of onset. Minimum documentation includes the following: o a physician's note indicating recurrent self-terminating atrial fibrillation (AF) which includes at least two symptomatic AF episodes within six months prior to enrollment, and o one electrocardiographically documented AF episode within 12 months prior to enrollment. • No amiodarone use within 90 days prior to enrollment • Subjects who are indicated for an ablation procedure for paroxysmal atrial fibrillation (PAF) according to 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation • Subjects refractory or intolerant to at least one class I or III antiarrhythmic medication or contraindicated to any class I or III medications • Subjects who are willing and capable of providing informed consent • Subjects who are willing and capable of participating in all testing associated with this clinical investigation at an approved clinical investigational center • 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	• Any known contraindication to an AF ablation or anticoagulation • Continuous AF lasting longer than seven (7) days from onset • History of previous left atrial ablation or surgical treatment for AF/ AFL/ AT • Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause • Structural heart disease or implanted devices as described below:

Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation **FROzEN-AF**	
	a. Left ventricular ejection fraction (LVEF) < 40% based on most recent transthoracic echocardiogram (TTE) performed ≤180 days prior to enrollment * b. Left atrial diameter > 5.5 cm OR left atrial volume > 50 ml/m2 indexed based on the most recent TTE performed ≤ 180 days prior to enrollment * c. An implanted pacemaker, ICD, CRT device or an arrhythmia loop recorder d. Previous cardiac surgery: i.e. ventriculotomy or atriotomy (excluding atriotomy for CABG) e. Previous cardiac valvular surgical or percutaneous procedure, or prosthetic valve, including mitral valve clips f. Interatrial baffle, closure device, patch, or patent foramen ovale (PFO) occluder g. Presence of a left atrial appendage occlusion device h. Presence of any pulmonary vein stents i. Coronary artery bypass graft (CABG), PTCA/ PCI/ coronary stent procedures within 90 days prior to enrollment j. Unstable angina or ongoing myocardial ischemia k. Myocardial infarction within 90 days prior to enrollment l. Moderate or severe mitral stenosis [severity assessed on the most recent TTE ≤180 days prior to enrollment as pulmonary artery systolic pressure >30 mmHg(1)] m. Evidence of left atrial thrombus** • Any previous history of cryoglobulinemia • Stage 3B or higher renal disease (estimated glomerular filtration rate, eGFR <45 mL/min) • History of blood clotting or bleeding disease

Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation **FROzEN-AF**	
	• Any prior history of documented cerebral infarct, TIA or systemic embolism [excluding a post-operative deep vein thrombosis (DVT)] ≤180 days prior to enrollment • Active systemic infection • Pregnant, lactating (current or anticipated during study follow up), or women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon physician's discretion) • 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 • Subjects who in the judgment of the investigator have a life expectancy of less than two years **LVEF and LA diameters obtained ≤180 days prior to enrollment will be acceptable, unless a cardiac event has occurred (e.g. MI) between the date of the exam and the enrollment date, otherwise a new echocardiogram (trans-thoracic or trans-esophageal, or intracardiac echo) must be performed to confirm eligibility prior to performing ablation. For TTE, LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used. If both LA diameter and volume are available, only one meeting eligibility criteria is required.* ***The absence of thrombus must be confirmed by means of a trans-esophageal echocardiogram (TEE) within 48 hours prior to the procedure or Intracardiac Echography (ICE) during the procedure in subjects not adequately anticoagulated (see section 12.5.2.) for at least 3 weeks prior to procedure OR with CHA_2DS_2-VASc score (see Appendix 30.4) ≥2 in men and ≥3 in women OR enlarged LA (≥4.5cm). If a thrombus is observed, the subject no longer meets eligibility criteria. When screening for thrombus prior to the index procedure, ensure that the anticoagulation approach as described in section 12.5.2. is followed until the day of the procedure.*
Arrhythmia Monitoring Strategy	This study will employ a rhythm surveillance monitoring strategy consistent with the recommendations in the 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation. A

Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation **FROzEN-AF**	
	wearable arrhythmia/event monitor (e.g. Trans-Telephonic Monitor-TTM) will be used to assess atrial arrhythmia recurrence (including unscheduled visits for symptomatic atrial arrhythmias and 24-hour Holter monitoring at 12 months follow up). Within the first 90 days after the index ablation procedure subjects will be instructed to transmit all symptomatic episodes for detection and treatment of early recurrences. All subjects will be instructed to submit at least two transmissions every month after their 3-month follow-up visit until their 12- month follow-up. All TREATMENT subjects will be provided with 24-Hour Holter Monitors at the 12-month follow-up visit. Core lab will be utilized for reviewing electrocardiographic recordings from the surveillance monitoring, inclusive of data from the wearable arrhythmia/event monitors and in-hospital ECGs.
Statistical Methods	
Primary Statistical Hypothesis	**Hypothesis for primary safety endpoint** • Ho: The primary safety endpoint event-free rate at 12 months post procedure ≤ 89% • Ha: The primary safety endpoint event-free rate at 12 months post procedure > 89% **Hypothesis for primary effectiveness endpoint** • Ho: The 12-month failure-free rate ≤50% • Ha: The 12-month failure-free rate > 50% The performance goal of 50% is based on the minimum chronic acceptable success rate for paroxysmal AF at 12 months follow-up defined in 2017 HRS Consensus document
Statistical Test Method	**Primary safety endpoint** 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

Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

FROzEN-AF

	the observed safety event-free rate will be compared to the performance goal of 89%. 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. **Primary effectiveness endpoint** For the primary effectiveness endpoint, the Kaplan-Meier 12 month (365-day) primary effectiveness event-free rate will be calculated. 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 primary effectiveness event-free rate will be compared to the performance goal of 50%. 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.
Sample Size Parameters	The sample size estimate was obtained using the normal approximation to the binomial distribution and verified through simulations based on Kaplan-Meier methodology. The following assumptions were used in the sample size calculation:

Assumptions	Primary Safety	Primary Effectiveness
Expected rate	94%	60%
Performance goal	89%	50%
Attrition (per year)	10%	10%
Significance level (one-sided)	5%	5%
Power	90%	90%
Sample size	325*	247*

*subjects treated with the ablation system

Data Collection Schedule

Procedure/Assessment	Enrollment *(up to 30 days before Index procedure)*	Baseline *(up to 30 days before Index procedure)*	Index Procedure *(Day 0)*	Blanking Period		Repeat Procedure	Effectiveness Evaluation Period			
				Pre-Discharge *(1-7 days post procedure)*	Day 7 Follow-up Contact *(+/-1 day)*	Repeat Procedure for PAF	Month 3 Follow Up *(91±14 days)*	Month 6 Follow Up *(180±30 days)*	Month 12 Follow Up *(365±30 days)*	Unscheduled Visit
Informed Consent Process, including informed consent signature date	X									
Eligibility Criteria	X	X	X							
Demographics		X								
Medical History		X								
Blood Tests		X[1]								
TTE (medical history)		X[2]								
NIH Stroke Scale (NIHSS)		X[3]		X[3]						
Neurology Consultation[4]				(X)[4]						
Brain MRI Scan[5]				(X)[5]						
Physical Assessment		X					X	X	X	X
Physical Assessment with Cardiovascular/Pulmonary Examination				X[6]						
Quality of Life (AFEQT and EQ-5D-5L)		X					X	X	X	
PV Anatomical Assessment (CT/MRI)		X[7]								
Screening for LA thrombus (TEE or ICE)		X [8]				X[8]				
PV Stenosis Assessment (CT/MRI)				(X)[9]			(X)[9]	(X)[9]	(X)[9]	(X)[9]
PV Stenosis Screening Substudy (CTMRI)		X					X			
Procedural Data			X			X				
12-Lead ECG		X	X	X		X	X	X	X	X
Phrenic Nerve Palsy Assessment			X[10]	(X)[10]		(X)[10]	(X)[10]	(X)[10]	(X)[10]	(X)[10]
Holter Monitor (24 hours)									X	
Arrhythmia/Event Monitor				X			X	X	X	X

Procedure/Assessment	**Enrollment** *(up to 30 days before Index procedure)*	**Baseline** *(up to 30 days before Index procedure)*	**Index Procedure** *(Day 0)*	**Blanking Period**		**Repeat Procedure**	**Effectiveness Evaluation Period**			
				Pre-Discharge *(1-7 days post procedure)*	**Day 7 Follow-up Contact** *(+/-1 day)*	**Repeat Procedure for PAF**	**Month 3 Follow Up** *(91±14 days)*	**Month 6 Follow Up** *(180±30 days)*	**Month 12 Follow Up** *(365±30 days)*	**Unscheduled Visit**
Documentation of intervention for AF/AT/AFL (if any)						X	X	X	X	X
Medications	Prior and current AAD medications and Anticoagulant therapy regimen from Enrollment through End of Study Visit									
Protocol deviations	From Enrollment through End of Study Visit									
Adverse Event Assessment	Continuous from Enrollment through End of Study Visit									

[1] Blood tests up to 90 days prior to enrollment,

[2] TTE either new or from medical file, ≤180 days prior to enrollment;

[3] NIH Stroke Scale (NIHSS) performed at baseline and at the pre-discharge visit

[4] Neurology consult is only required if NIH scale worsens from the previous assessment

[5] Brain DW-MRI scan required if neurology consultation determines possibility of new stroke

[6] Physical Assessment at discharge to include a Cardiovascular/Pulmonary Examination including: weight, resting heart rate, systolic and diastolic blood pressure, O_2 saturation, lung auscultation (includes respiratory rate and respiratory rhythm), and temperature,

[7] Performed before the case (CT/MRI);

[8] TEE within 48 hours prior to the procedure or ICE during procedure

[9] Assessed in case of suspected PV stenosis;

[10] Screening for phrenic nerve palsy will be performed during ablation, and prior to leaving the EP lab at the completion of the ablation procedure in all subjects. Assessment at discharge and at follow-up visits is only applicable for subjects who had phrenic nerve palsy detected at the index procedure.

Abbreviations: IP = index procedure, NIH = National Institutes of Health, ECG = electrocardiogram, ICE= Intracardiac Echography; PV=pulmonary vein, TTM = trans-telephonic monitor, TTE = trans-thoracic echocardiogram, TEE = trans-esophageal echocardiogram, CT = Computed Tomography, MRI = Magnetic Resonance Imaging, FU = follow-up.

3. Table of Contents

4. Table of Figures

5. Table of Tables

6. Introduction

6.1. *Background*

Atrial fibrillation (AF) is the most commonly encountered sustained cardiac arrhythmia in clinical practice (2). 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 (3). It currently affects approximately 2.3 million people in North America (4). 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 (5,6,7). Among Medicare beneficiaries, incident AF is common and increases as individuals age with incidence rates per 1,000 person-years reported at ages 70-74 of 18.8, increasing to 28.8 for persons 75-79 and 38.3 for persons 80-84. Similarly, the overall prevalence among Medicare beneficiaries age 70-74 is about 6% increasing to over 13% for individuals 80 years of age and older (8).

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

There are multiple therapies in current use for the treatment of AF; however, it is recognized that many of these therapies are suboptimal for most patients. Treatment options include medical management, pacing, cardioversion, implantable devices, surgery, and ablation therapy to eliminate the arrhythmia (9,10.11). 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, 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 (14).

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 in 2018 and its data is being used to obtain CE-mark.

The data of up to 405 subjects who will undergo treatment with the Boston Scientific Cryoablation System for de-novo PAF will be evaluated in this IDE trial. This study seeks to obtain approval for the Boston Scientific Cryoablation System in North America.

6.2. *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. Accordingly, the present IDE study aims at collecting clinical data to establish the safety and one-year effectiveness profile of the Cryoablation System for treatment of symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation.

7. Device Description

7.1. *Boston Scientific Cardiac Cryoablation System*

The Boston Scientific Cardiac Cryoablation System (henceforth “Cryoablation System”) is intended for treatment of symptomatic, drug refractory, recurrent, paroxysmal AF.
The individual devices within the Cryoablation system and their associated model numbers are listed in Table 1.
Treatment will occur according to the approved indication for use within each geography and the defined inclusion/exclusion criteria within the protocol. A copy of the DFU will be provided in local language as required per national regulations.
FROzEN-AF will be conducted as a post market study in those regions where the device is approved, including Europe. For countries where commercially available, please refer to country-specific commercially available DFU.

Table 1: Cryoablation System

Individual Devices within the System	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
Diaphragm Movement Sensor (DMS)	2314
Inter Connection Box (ICB)	2314
Esophageal Temperature Sensor Cable	2314
Cryo-Console Foot Switch	2314
Cryo-Cable	2318
Cryo-Catheter Extension Cable	2319
Cryo Mapping Catheter EP Electrical Cable	2320

7.1.1. POLARx Cryoablation Catheter

The Cryoablation Catheter 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 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: POLARx Cryoablation Catheter Distal Tip

Figure 2: POLARx Cryoablation Catheter Handle

Table 2: POLARx Cryoablation Catheter Specifications

Catheter Shaft Size	11.8 Fr	
Catheter Overall Length	134 cm	
Catheter Tip Outer Diameter (OD)	9 Fr	
Compatible Introducer Sheath	Compatible with POLARSHEATH Sheath 12F Steerable Sheath	
Guidewire Lumen Inner Diameter (ID)	Compatible with POLARMAP Mapping Catheter and guidewires ≤ 0.035	
Inflated Balloon Dimensions	Diameter	28 mm

	Catheter Effective Length	99 cm
	Short Tip	5 mm
	Long Tip	12 mm
Thermocouples	Internal to Balloon	
Environmental Parameters	Storage	15°C to 25°C (59°F to 77°F)
	Transit	-30°C to 60°C (-22°F to 140°F) 15% to 90% relative humidity
	Operation	15°C to 30°C (59°F to 86°F)

7.1.2. **POLARMAP Cryoablation Mapping Catheter**

The POLARMAP Cryoablation Mapping Catheter is a single-use, sterile, multi-electrode, diagnostic catheter designed to map cardiac signals during ablation procedures. The catheter is 20mm in 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 Cryoablation Mapping Catheter also allows for delivery of pacing stimuli used in the interpretation of PV isolation (PVI).

Figure 3: Mapping Catheter Assembly

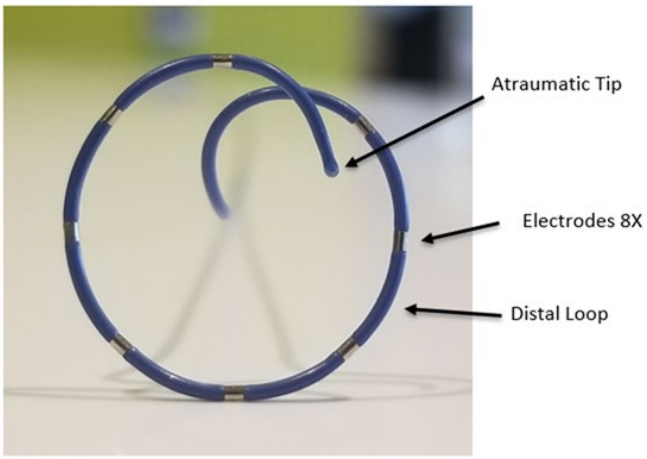


Figure 4: POLARMAP Cryoablation Mapping Catheter with Electrode Arrangements

Table 3: POLARMAP Cryoablation Mapping Catheter Specifications

POLARMAP Shaft Size	3.3 Fr (1.1 mm or 0.043 inches)	
Compatible Mating Device Minimum Internal Diameter	3.4 Fr. (1.2 mm or 0.044 inches)	
Loop Diameter	20 mm (0.79 inches)	
POLAR Shaft Length	Overall 166: cm	
	Effective: 149 cm	
Electrodes	8 electrodes	
Electrode Size	1 mm	
Electrode Spacing	6 mm	
Environmental Parameters	Storage	15°C to 25°C (59°F to 77°F)
	Transit	-30°C to 60°C (-22°F to 140°F) 15% to 90% relative humidity
	Operation	15°C to 30°C (59°F to 86°F)

7.1.3. POLARSHEATH Cryoablation Steerable Sheath

The POLARSHEATH Cryoablation 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 Cryoablation 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 4: POLARSHEATH Cryoablation Steerable Sheath Specifications

Sheath Overall Length	82 cm (32.3 in)	
Sheath Usable Length	68 cm (26.8 in)	
Sheath Inner Diameter	12.7 Fr	
Sheath Outer Diameter	15.9 Fr	
Usable Dilator Length	85 cm (33.5 in)	
Radiopaque Markers	2.5mm proximal to sheath tip	
Guidewire Compatibility	0.81 mm (0.032 in) and 0.89 mm (0.035 in)	
Environmental Parameters	Storage	15° C to 25° C (59° F to 77° F)

	Transit	-30° C to 60° C (-22° F to 140° F) 15% to 90% relative humidity
	Operation	15° C to 30° C (59° F to 86° F)

7.1.4. **SMARTFREEZE Cryoablation System Console**

The SMARTFREEZE Cryoablation System 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 and 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: SMARTFREEZE Cryoablation System Console

Integration between the Cryoablation Catheter and the Console includes monitoring catheter as well as console functionality, aided by a number of accessory devices that make up the overall system such as: power cords, extension cables, connection box, foot switch, diaphragmatic movement sensor, esophageal temperature sensor cable. In addition, the system incorporates a number of non-medical device items such as a scavenging hose, wrench, and nitrous oxide tank.

7.1.5. **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 Cryoablation 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 patient's chest and assess the patient'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 phrenic nerve injury ranges from 2.7% - 11.2% 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 Cryoablation Console and sends data to be displayed on the Cryoablation Console's user interface (see Figure 6 below).

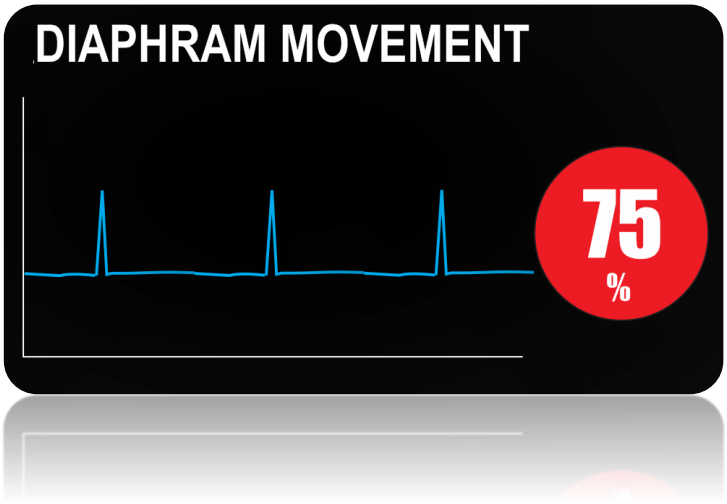


Figure 6: Diaphragm Movement Sensor (DMS) Data Cryoablation Console Display Phrenic Nerve Pacing Signal & Alert

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 a 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.

7.1.6. **Esophageal Temperature Sensor Cable**

Esophageal temperature monitoring is a frequently used technique; used more so 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 incidence of esophageal ulceration is generally reversible, with a reported incidence of 17% of patients.

As noted above, 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 **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.

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 (see Figure 7 below). This feature potentially reduces adverse events such as esophageal ulcerations and fistulas. This is a redundant safety alert system to the measurement systems used today although the alert is now displayed on the Console.

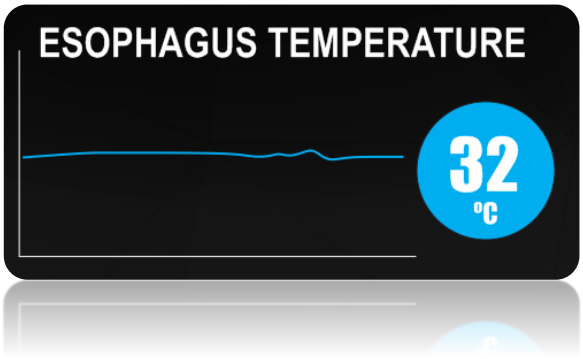


Figure 7: Esophagus Temperature Monitoring Data Display

7.1.7. **Other Cryoablation System Devices**

7.1.7.1. Inter Connection Box

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.

7.1.7.2. 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.

7.1.7.3. Cryoablation 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.

7.1.7.4. Cryoablation Catheter Extension Cable

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

7.1.7.5. Cryoablation Mapping Catheter EP Electrical Cable

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

7.2. ***Intended Use and Contraindications***

The Cryoablation System is intended for treatment of symptomatic, drug refractory, recurrent, paroxysmal AF.

7.2.1. **POLARx Cryoablation Catheter**

The POLARx Cryoablation Catheter is a single use, flexible, over-the wire balloon catheter intended to ablate cardiac tissue.

Use of the Cryoablation Catheter is contraindicated as follows:

- In patients with an active systemic infection, as this may increase the risk for endocarditis and sepsis.
- In patients with a myxoma or an intracardiac thrombus, as the catheter could precipitate an embolic event.
- In patients with a prosthetic valve (mechanical or tissue)

- In the ventricle of the heart where the device may become entrapped in a valve or chordae structures.
- In patients with a recent ventriculotomy or atriotomy, as this may increase the risk of cardiac perforation or embolic event.
- In patients with pulmonary vein stents, as the catheter may dislodge or damage the stent.
- In patients with cryoglobulinemia, as the cryoablation application may lead to vascular injury.
- In conditions where insertion into or manipulation in the atrium is unsafe, as this may increase the risk of perforation or systemic embolic event.
- In patients with intra-atrial septal patch or surgical intervention in or adjacent to the intra-atrial septum.
- In patients with an interatrial baffle or patch, as the transseptal puncture could fail to close.
- In patients with hypercoagulopathy or an inability to tolerate anticoagulation therapy during an electrophysiology procedure
- In patients with a contraindication to an invasive electrophysiology procedure where insertion or manipulation of a catheter in the cardiac chambers is deemed unsafe.

7.2.2. **POLARMAP Cryoablation Mapping Catheter**

During an ablation procedure when PVs are isolated, the Cryoablation Mapping Catheter is intended to obtain electrograms and provide pacing in cardiac structures in the atrial regions of the heart.

Use of the POLARMAP Mapping Catheter is contraindicated as follows:

- In patients with an active systemic infection as this may increase the risk for endocarditis and sepsis.
- In patients with a myxoma or an intracardiac thrombus as the catheter could precipitate an embolic event.
- In patients with a prosthetic heart valve (mechanical or tissue).
- In the ventricle of the heart where the device may become entrapped in a valve or chordae structures.
- In patients with a recent ventriculotomy or atriotomy as this may increase the risk of cardiac perforation or embolic event.
- In patients with pulmonary vein stents as the catheter may dislodge or damage the stent.
- In patients with cryoglobulinemia as the cryoablation application may lead to vascular injury.
- In conditions where insertion into or manipulation in the atrium is unsafe as this may increase the risk of perforation or systemic embolic event.
- In patients with intra-atrial septal patch or other surgical intervention in or adjacent to the intra-atrial septum.
- In patients with a contraindication to an invasive EP procedure where insertion or manipulation of a catheter in the cardiac chambers is deemed unsafe.

7.2.3. **POLARSHEATH Cryoablation Steerable Sheath**

The Cryoablation Steerable Sheath is intended to facilitate the placement of diagnostic and/ or therapeutic intracardiac devices during percutaneous catheter ablation procedures. The sheath deflection facilitates catheter positioning.
Use of the POLARSHEATH is contraindicated as follows:

- In patients with an active systemic infection as this may increase the risk for endocarditis and sepsis.
- In patients where vascular access is unobtainable, or the femoral vein is known to be obstructed.
- In conditions where insertion into or manipulation in the atrium is unsafe as this may increase the risk of perforation or systemic embolic event.
- In the ventricle of the heart where the device may become entrapped in a valve or chordae structures.
- In patients with a prosthetic heart valve (mechanical or tissue)
- In patients with a recent ventriculotomy or atriotomy as this may increase the risk of cardiac perforation or embolic event.
- In patients with pulmonary vein stents as the sheath may dislodge or damage the stent.
- In patients with an interatrial baffle or patch as the transseptal puncture could fail to close.
- In patients with hypercoagulopathy or an inability to tolerate anticoagulation therapy during an electrophysiology procedure.
- In patients with a contraindication to an invasive electrophysiology procedure where insertion

7.2.4. **SMARTFREEZE Cryoablation System Console**

The SMARTFREEZE Cryoablation System Console is a component of the Cryoablation System which is intended for cryoablation and electrical mapping of the pulmonary veins for pulmonary vein isolation (PVI) in the ablation treatment of paroxysmal atrial fibrillation.

Use of the SMARTFREEZE Cryoablation System is contraindicated as follows:

- In patients with an active systemic infection as this may increase the risk for endocarditis and sepsis.
- In patients with a prosthetic valve (mechanical or tissue)
- In patients with a myxoma or an intracardiac thrombus as the catheter could precipitate an embolic event.
- In the ventricle of the heart where the device may become entrapped in the valve or chordae structures.
- In patients with a recent ventriculostomy or atriotomy because this may increase the risk of cardiac perforation or embolic event.
- In patients with pulmonary vein stents as the catheter may dislodge or damage the stent.
- In patients with cryoglobulinemia as the application of cryogenic energy may

lead to vascular injury.

- In conditions where insertion into or manipulation in the atria is unsafe as this may increase the risk of perforation or systemic embolic event.
- In patients with an interatrial baffle or patch as the transseptal puncture could fail to close.
- In patients with hyper-coagulopathy or an inability to tolerate anticoagulation therapy during an electrophysiology procedure.
- In patients with a contraindication to an invasive electrophysiology procedure where insertion or manipulation of a catheter in the cardiac chambers is deemed unsafe.

8. Study Objectives and Endpoints

8.1. *Study Objective*

To establish the safety and effectiveness of the Boston Scientific Cardiac Cryoablation System for treatment of symptomatic, drug refractory, recurrent, PAF. The following endpoints will be evaluated to establish the safety and effectiveness of the Cryoablation System for the treatment of symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation.

8.2. *Primary Safety Endpoint*

Primary safety event free rate at 12 months post 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 or hospital discharge, whichever is later, include:

- Death
- Myocardial infarction
- Transient ischemic attack (TIA)
- Stroke/ Cerebrovascular accident (CVA)
- Vascular access complications
- Mitral or tricuspid valvular damage
- Thromboembolism/ Air embolism leading to a life-threatening event such as a ventricular arrhythmia, stroke, pulmonary embolism, or myocardial infarction and, thromboembolic events that result in permanent injury, require intervention for treatment or prolongs or require hospitalization for more than 48 hours
- Gastroparesis/ injury to vagus nerve
- Pneumothorax
- Pulmonary edema/ heart failure
- AV block

Cardiac tamponade/perforation, occurring up to 30 days post index procedure.

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

- Atrial esophageal fistula
- Severe pulmonary vein stenosis (≥ 70% reduction in the diameter of the PV or PV branch from baseline)
- Persistent phrenic nerve palsy*

*A non-recovered phrenic nerve palsy 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.

Table 5: Primary Safety Endpoint Components Definitions*

Term	Definition
Atrioesophageal Fistula	An atrioesophageal fistula is defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium, such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT scan or MRI scan is the most common method of documentation of an atrioesophageal fistula.
AV block	A conduction disturbance that results in the partial inability of an electrical impulse generated in the atria to reach the ventricles.
Cardiac tamponade/perforation	Cardiac tamponade/perforation is defined as 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.
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 left bundle branch block, 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.
Pericardial Effusion	A collection of fluid or blood in the pericardial space around the heart or in pleural space around the lungs.
Phrenic nerve palsy	Phrenic nerve palsy is defined as absent phrenic nerve function as assessed by a sniff test. A phrenic nerve palsy is considered to be permanent when it is documented to be present 12 months or longer following ablation.
Pneumothorax	Collapse of the lung due to an abrupt change in the intrapleural pressure within the chest cavity.
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
Pulmonary Vein Stenosis (Severe)	Pulmonary vein stenosis is defined as a reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as mild <50%, moderate 50%–70%, and severe ≥70% reduction in the diameter of the PV or PV branch. A severe PV stenosis will count toward the primary safety endpoint.
Stroke/Cerebrovascular accident (CVA)	Stroke diagnostic criteria: • 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) • Stroke: (diagnosis as above, preferably with positive neuroimaging study); o Minor–Modified Rankin score <2 at 30 and 90 days† o Major–Modified Rankin score ≥2 at 30 and 90 days
Thromboembolism	The blockage of a blood vessel lumen by 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. Transient ischemic attack: new focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), always within 24 hours; neuroimaging without tissue injury
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	Vascular access complications include the 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.

8.3. *Primary Effectiveness Endpoint*

Failure-free rate at 12 months post procedure.

Failure is defined as:

- Failure to achieve acute procedural success in the index procedure or repeat procedure during the blanking period
- Use of amiodarone post index procedure
- Surgical treatment for AF/AFL/AT post index procedure
- Use of a non-study ablation catheter for AF targets in the index procedure or repeat procedure during the blanking period
- More than one repeat procedure with the POLARx catheter during the blanking period (90 days post index procedure)
- Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia event (≥ 30 seconds in duration from the study-specific event monitor, Holter Monitor, 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 and 365 days post procedure:
    - Repeat procedure
    - Electrical and/or pharmacological cardioversion for AF/AFL/AT
    - Prescribed any anti-arrhythmic drug (AAD)**

*12-lead ECGs performed during scheduled or unscheduled visits and assessed by the ECG core lab will count for primary effectiveness endpoint assessment. Additional documentation of arrhythmias coming from sources different from those listed above will be collected and analyzed separately.

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

8.4. *Secondary Safety Endpoints:*

Reportable Adverse Events rates at 12 months.

Adverse events will be collected at all subject follow-up visits. Reportable events include:

- All Serious Adverse Events
- All Study Procedure-Related Adverse Events
- All Study Device-Related Adverse Events
- All Study Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in DFU/Investigator's Brochure

8.5. *Secondary Effectiveness Endpoints:*

Rate of Acute Procedural Success defined as the achievement of electrical isolation of all PVs by using the Cardiac Cryoablation system only.; Electrical isolation of a PV is demonstrated by entrance and exit block.

8.6. *Additional Endpoints*

Additional endpoints and analyses include, but are not limited to:

- Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up
- Single procedure success, defined as freedom from primary effectiveness failure without a repeat procedure
- Duration of LA dwell time, defined as time from the Cryoablation Catheter exiting the sheath in the LA to time of final PV isolation
- Total Cryoablation time for the index procedure
- Total fluoroscopy time for the index procedure;
- Total index procedure time
- Freedom from recurrence of individual types atrial arrhythmias between 91 and 365 days post index procedure: 1) AF 2) AT 3) AFL
- Failure- free rate as defined in primary effectiveness endpoint when considering AF/AT/AFL episodes reported to the investigators by study specific (event recorder transmissions, 12 lead ECG and Holter) and non-study related devices (other commercial applications for arrhythmia monitoring and detection the subject may access during the study including telemetry, other sources of continuous recording etc.)
- Freedom from primary effectiveness failure at six (6) months will be included s in the final study report as a “proof-of-concept” analysis to potentially show the ability to predict 1-year effectiveness results using 6-month effectiveness data

Table 6: Overview of Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Establish the safety of the Cryoablation System	Composite of acute and 12-month 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 repeated procedure in blanking period, amiodarone post procedure,	Performance goal and expected rates calculated from a meta-analysis of pivotal and IDE studies on AF ablation

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	documented AF/AT/AFL or interventions to treat these arrhythmias after blanking period, including repeated procedures cardioversion or pharmacologic treatment	
Secondary		
Acute procedural success	Rate of acute procedural success defined as the achievement of electrical isolation of all PVs by using the POLARx Cardiac Cryoablation System only. Electrical isolation of a PV is demonstrated by entrance and exit block.	Component of the primary effectiveness endpoint
Adverse events reporting	Reportable Adverse Events rates at 12 months	Complete overview of the safety events collected in the study
Additional		
Recurrence of individual arrhythmia types	Freedom from recurrence of AF/AT/AFL	Component of the primary effectiveness endpoint
Quality of life assessment	Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up	Consistent with the objective of AF ablation to improve quality of life and reduce AF-associated symptoms
Single procedure success	Freedom from primary effectiveness failure without a repeat procedure .	To assess success rate after a single procedure
Establish the effectiveness of the Cryoablation System at 6 months	Failure free rate at 6 months post index procedure	Post hoc ancillary analysis to establish if the effectiveness profile of the device at 1 year could be predicted by 6 months data.
Procedure-related times	LA dwell time, ablation time, fluoroscopy time, index procedure time	To relate with published data on other AF ablation devices

9. **Study Design**

The FROzEN-AF study is a prospective, non-randomized, multi-center, investigation being conducted to establish the safety and effectiveness of the Cryoablation System in subjects with symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation.

9.1. *Scale and Duration*

A maximum of 405 subjects treated with the Cryoablation System will be enrolled in the study, inclusive of a maximum of 80 *roll-in* TREATMENT subjects and 325 *non roll-in* TREATMENT subjects undergoing the index ablation procedure (per subject status classification, section 11.5)

Fifty (50) *non roll-in* TREATMENT subjects will participate in a PV Stenosis Screening Substudy at up to 8 study sites. The substudy will include a baseline and a 3 to 6 months CT/MRI imaging data post index procedure to evaluate the potential extent of PV stenosis. Each site participating to the substudy will enroll a maximum of 18 substudy subjects.

Up to 50 sites in North America, Europe and Asia-Pacific may participate in this study. At least 50% of the sites and 50% of the subjects will enroll in the United States and potentially up to 10% of subjects will enroll in 3 to 5 combined sites from Hong Kong and Taiwan. Up to 10 sites in Europe may contribute to enrollments. To reduce the impact of individual center bias, no study site will be allowed to contribute more than 48 subjects (average 15% of the 325 study *non roll-in* TREATMENT subjects).

The enrollment period for this study is expected to last between 9 to 12 months. Each subject will be followed at specified time points after the ablation procedure (index procedure), with a follow-up duration of 12 months. A study subject's participation will be considered complete when all protocol required visits have been completed as indicated in Figure 8. The total study duration is estimated to be approximately 24 months. Subjects may be requested to consent to provide long term follow-up data, if needed for post-approval requirements.

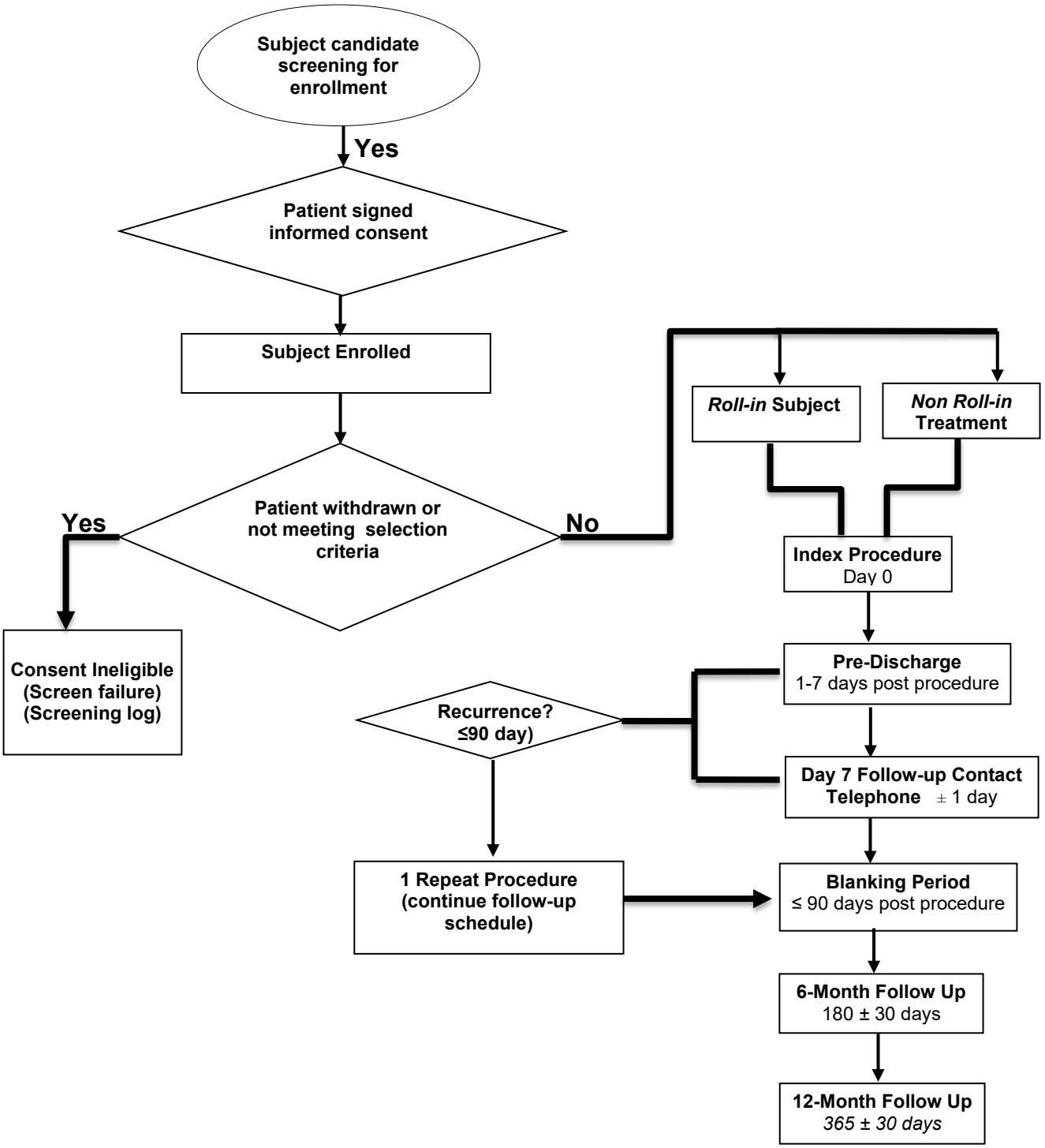


Figure 8: FROzEN-AF Study Design

9.2. *Treatment Assignment*

All screened subjects who sign the informed consent will be considered enrolled. Data will be collected during the baseline visit, the ablation (index) procedure, the pre-discharge visit, the Day 7 telephone contact/follow up, month 3 follow up, the month 6 follow up and during the month 12 follow up. In case unscheduled visits or additional ablation procedures take place, this data will also be collected. Please refer to section 12 for an overview of data to be collected during these visits.

Subjects will be classified based on Subject Status and Classification as per section 11.5.

9.2.1. **Treatment**

All enrolled subjects who undergo the ablation procedure will be treated with the Cryoablation System.

It is recommended that each investigational center will be limited to 2 active ablating investigators. Additional investigators may participate for completion of subject follow-up visits if appropriately delegated (section 12.6.1) and trained to complete the assigned tasks.

9.3. *Justification for the Study Design*

9.3.1. **Single-Arm Study design**

Boston Scientific believes that a prospective non-randomized IDE trial with the Cryoablation System as treatment device and powered for standard safety and effectiveness objective performance criteria is reasonable to obtain approval of the Cryoablation System.

The rationale for a non-randomized trial includes, the formal equivalence of the system design with the existing Medtronic® Arctic Front Advance™ Catheter in terms of delivered therapy and temperature profiles, as proven by extensive bench testing done with the Boston Scientific Cryoablation System.

Additionally, the current understanding in the field of catheter ablation of PAF and presence of an additional seven products approved by the FDA for the PAF ablation indication from four different manufacturers makes the field mature enough to consider a single arm design adequate for this study. Inherent limitations of single arm trials compared to a randomized clinical trial (RCT) will be addressed by appropriately limiting bias and confounders in the present protocol. This includes definition of inclusion/exclusion criteria to match the population enrolled in other IDE trials on PAF ablation and taking measures for subject screening and arrhythmia recurrence surveillance.

9.3.2. ***Roll-ins*** **and** ***Non Roll-in*** **Treatment Subjects**

To help facilitate investigators' familiarity with the new investigational system and avoid learning curve bias, *roll-in* subjects will be enrolled at each study site. Each ablating physician will need to treat 1 (one) *roll-in* subject with the Cryoablation System per definition of *Treatment* in section 11.5.

After completing the treatment *roll-in* case, BSC will provide the investigator with authorization to proceed with the treatment of the non *roll-in* subjects.

All safety and effectiveness data will be collected and reported for all subjects; however, the data will not be included in the endpoint analyses for *roll-in* cases.

In order to avoid potential bias, it is recommended the number of authorized active ablating physicians per investigational site performing the index procedure is restricted to 2.

For investigators participating in a geography in which the system is not investigational, a roll-in case may not be required if the physician has previous experience treating patients with the Cryoablation System.

10. Subject Selection

10.1. *Study Population and Eligibility*

Subjects enrolled in the FROzEN-AF study will be clinically indicated for an ablation procedure for the treatment of symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation. Subjects should meet the study inclusion/exclusion criteria as outlined below in section 10.2 and 10.3. The subjects selected for participation will be from the investigator's general patient population. The investigator or its designee has the responsibility for screening all potential subjects and selecting those who meet study inclusion/exclusion.

10.2. *Inclusion Criteria*

Subjects who meet all the following criteria (see **Table 7**) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see section 10.3) is met.

Table 7: Inclusion Criteria

Inclusion Criteria	• History of recurrent symptomatic paroxysmal atrial fibrillation (PAF), defined as atrial fibrillation that terminates spontaneously or with intervention (either procedure or drug therapy) within seven days of onset. Minimum documentation includes the following: o a physician's note indicating recurrent self-terminating atrial fibrillation (AF) which includes at least two symptomatic AF episodes within six months prior to enrollment, and o one electrocardiographically documented AF episode within 12 months prior to enrollment. • Subjects who are indicated for an ablation procedure for paroxysmal atrial fibrillation (PAF) according to 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation

	• No amiodarone use within 90 days prior to enrollment • Subjects refractory or intolerant to at least one class I or III antiarrhythmic medication or contraindicated to any class I or III medications • Subjects who are willing and capable of providing informed consent • Subjects who are willing and capable of participating in all testing associated with this clinical investigation at an approved clinical investigation center • Subjects whose age is 18 years or above, or who are of legal age to give informed consent specific to state and national law

10.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (see **Table 8**) cannot be included in this study or will be excluded from this clinical study.

Table 8: Exclusion Criteria

Exclusion Criteria	• Any known contraindication to an AF ablation or anticoagulation • Continuous AF lasting longer than seven (7) days from onset • History of previous left atrial ablation or surgical treatment for AF/ AFL/ AT • Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause • Structural heart disease or implanted devices as described below: a. Left ventricular ejection fraction (LVEF) < 40% based on the most recent TTE performed ≤180 days prior to enrollment* b. Left atrial diameter > 5.5 cm OR left atrial volume > 50 ml/m2 indexed based on the most recent TTE performed ≤ 180 days prior to enrollment* c. An implanted pacemaker, ICD, CRT device or an arrhythmia loop recorder d. Previous cardiac surgery: i.e. ventriculotomy or atriotomy (excluding atriotomy for CABG) e. Previous cardiac valvular surgical or percutaneous procedure, or prosthetic valve, including mitral valve clips f. Interatrial baffle, closure device, patch, or PFO occluder

	g. Presence of a left atrial appendage occlusion device h. Presence of any pulmonary vein stents i. Coronary artery bypass graft (CABG), PTCA/ PCI/ coronary stent procedures within 90 days prior to enrollment j. Unstable angina or ongoing myocardial ischemia k. Myocardial infarction within 90 days prior to enrollment l. Moderate or severe mitral stenosis[severity assessed on the most recent TTE ≤180 days prior to enrollment as Pulmonary artery systolic pressure >30 mm Hg(1)] m. Evidence of left atrial thrombus** • Any previous history of cryoglobulinemia • Stage 3B or higher renal disease (estimated glomerular filtration rate, eGFR <45 mL/min) • History of blood clotting or bleeding disease • Any prior history of documented cerebral infarct, TIA or systemic embolism (excluding a post-operative DVT) ≤180 days prior to enrollment • Active systemic infection • Pregnant, lactating (current or anticipated during study follow up), or women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon physician's discretion) • 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 • Subjects who in the judgment of the investigator have a life expectancy of less than two years **LVEF and LA diameters obtained ≤180 days prior to enrollment will be acceptable, unless a cardiac event has occurred (e.g. MI) between the date of the exam and the enrollment date, otherwise a new echocardiogram (trans-thoracic or trans-esophageal, or intracardiac echo) must be performed to confirm eligibility prior to performing ablation. For TTE, the LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used. If both LA diameter and volume are available, only one meeting eligibility criteria is required.*

	***The absence of thrombus must be confirmed by means of a TEE within 48 hours prior to the procedure or ICE during procedure in subjects not adequately anticoagulated (see section 12.5.2.) for at least 3 weeks prior to the procedure OR with CHA_2DS_2-VASc score (see Appendix 30.4) ≥2 in men and ≥3 in women OR enlarged LA (≥4.5cm). If a thrombus is observed, the subject no longer meets eligibility criteria. When screening for thrombus prior to the index procedure, ensure that the anticoagulation approach as described in section 12.5.2. is followed until the day of the procedure.*

11. Subject Accountability

11.1. *Point of Enrollment*

Subjects who have signed and dated the Informed Consent Form are considered enrolled in the study. All TREATMENT subjects (per definition in section 12.3) will be counted against the enrollment ceiling of 325 subjects. 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 SOC can be used to determine pre-eligibility. Study 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 and document them for each screened patient in the study Screening and Enrollment Log.

11.2. *Enrollment Controls*

Subject study-specific ID will be generated through the Electronic Data Capture (EDC) system used for this study. This database will also be utilized to provide the sites with subject classification assignments (including *roll-in* subjects) once a subject has provided written informed consent. Enrollment controls will be put in place to ensure no more than 48 (average 15% of the 325 TREATMENT subjects) will occur at a single site. In addition, BSC will communicate the process that will be followed for enrolling subjects as the enrollment ceiling of 325 TREATMENT subjects is approached to prevent exceeding this enrollment ceiling.

11.3. *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 investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's documented permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal may include physician discretion, subject choice to withdraw, 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. In the event a subject does decide to withdraw from the study, every effort should be made to obtain

full information on any on-going reportable Adverse Events up to the point of withdrawal. 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. Data collected up to the point of subject withdrawal may be used, unless any local regulations apply which require removal of the data.

If the withdrawal is due to the investigator's discretion, the investigator is obligated to follow all open reportable Adverse Events until they can be considered as closed or chronic.

All open reportable adverse events should be closed or documented as chronic. If the withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's documented permission to follow his/her status/condition.

Withdrawn subjects will not be replaced.

All applicable electronic case report forms (eCRFs) up to the point of subject withdrawal/lost to follow up and an "End of Study" eCRF must be completed.

11.4. *Lost to Follow-Up*

A participant will be considered lost to follow-up if he or she fails to return after documented attempts to attend a scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant 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 participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (at minimum 3 telephone calls and a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up from the study.

All applicable electronic case report forms (eCRFs) up to the point of subject withdrawal/lost to follow up and an "End of Study" eCRF must be completed.

11.5. *Subject Status and Classification*

As subjects are evaluated, enrolled and treated in the study, they will be grouped into one of the following categories. Categorization will help determine how data gathered from them will be stored and evaluated.

Consent Ineligible (Screening Failures)

A subject who has signed informed consent but is found not to meet eligibility criteria will be classified as "Consent Ineligible". There are no Follow Up reporting requirements for consent ineligible subjects. Subjects determined to be Consent Ineligible do not count towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the center's patient file. A subject Identification Number (ID) will be assigned in the EDC system.

For consent ineligible subjects the following forms must be completed:

- Enrollment and End of Study
- Adverse Event forms for any reportable event, as defined in section 21 for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal

Roll-in and non *roll-in* subjects will be further classified as Intent, Attempt, and Treatment as described below.

Intent

A subject who signs informed consent, meets eligibility criteria, but does not have any study investigational devices inserted into the body will be classified as "INTENT". Subjects that are enrolled in the study but do not undergo ablation procedure within 30 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 not count towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the center's patient file. A subject ID will be assigned in the EDC system.

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

- Enrollment and baseline forms such as, but not limited to: informed consent, enrollment information and other related forms;
- End of Study form;
- Adverse Event forms for any reportable event, as defined in section 21 for any adverse event that occurs after signing the Informed Consent, up to the point of subject withdrawal

Attempt

A subject who signs informed consent, meets eligibility criteria, and has any study device inserted into the body but does not receive any Cryoablation application will be classified as "ATTEMPT." Attempt subjects do not count towards the enrollment ceiling. Attempt subjects and will be used for analysis of the primary and secondary safety endpoint and additional analyses of safety data but will not be used for analysis of the primary and secondary effectiveness endpoints or additional analyses of effectiveness data (additional analysis include subgroup, multivariable, and center pooling analyses). The original signed Informed Consent must be maintained in the

center's patient 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 the 12 month visit. All applicable case report forms per the protocol will be completed. The original signed Informed Consent and any relevant documentation must be maintained in the center's patient file.

Treatment

Any subject that signs the consent form, meets eligibility criteria 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 follow-up schedule 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 patient file.

It is the investigational sites's responsibility to list all Screen Failures, Consent Ineligible (screening failure), Intent, Attempt and Treatment subjects on the Screening and Enrollment Log.

11.6. *End-of-Study Definition*

A clinical trial is considered completed when participants are no longer being examined or the last participant's last study visit has occurred. The end of the study is defined as completion of the last visit or procedure shown in the Data Collection Schedule in the trial globally.

12. Study Methods

12.1. *Data Collection*

Each Treatment subject will be followed at index procedure, at pre-discharge visit, at the month 3 follow up, at the month 6 follow up and at 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. If the subject needs to undergo an additional ablation procedure in the LA during the follow-up period, then this additional ablation procedure will need to be captured in the EDC database. The data collection schedule is shown in **Table 9.**

Table 9: Data Collection Schedule

Procedure/Assessment	Enrollment *(up to 30 days before Index procedure)*	Baseline *(up to 30 days before Index procedure)*	Index Procedure *(Day 0)*	Blanking Period		Repeat Procedure	Effectiveness Evaluation Period			
				Pre-Discharge *(1-7 days post procedure)*	**Day 7 Follow-up Contact** *(+/-1 day)*	**Repeat Procedure for PAF**	**Month 3 Follow Up** *(91±14 days)*	**Month 6 Follow Up** *(180± 30 days)*	**Month 12 Follow Up** *(365±30 days)*	**Unscheduled Visit**
Informed Consent Process, including informed consent signature date	X									
Eligibility Criteria	X	X	X							
Demographics		X								
Medical History		X								
Blood Tests		X[1]								
TTE (medical history)		X[2]								
NIH Stroke Scale (NIHSS)		X[3]		X[3]						
Neurology Consultation[4]				(X)[4]						
Brain MRI Scan[5]				(X)[5]						
Physical Assessment		X					X	X	X	X
Physical Assessment with Cardiovascular/Pulmonary Examination				X[6]						
Quality of Life (AFEQT and EQ-5D-5L)		X					X	X	X	
PV Anatomical Assessment (CT/MRI)		X[7]								
Screening for LA Thrombus (TEE or ICE)		X [8]				X[8]				
PV Stenosis Assessment (CT/MRI)				(X)[9]			(X)[9]	(X)[9]	(X)[9]	(X)[9]
PV Stenosis Screening Substudy (CT/MRI)		X					X			
Procedural Data			X			X				
12-Lead ECG		X	X	X		X	X	X	X	X
Phrenic Nerve Palsy Assessment			X[10]	(X)[10]		(X)[10]	(X)[10]	(X)[10]	(X)[10]	X[10]
Holter Monitor (24 hours)									X	
Arrhythmia/Event Monitor				X			X	X	X	X

Procedure/Assessment	Enrollment *(up to 30 days before Index procedure)*	Baseline *(up to 30 days before Index procedure)*	Index Procedure *(Day 0)*	Blanking Period		Repeat Procedure	Effectiveness Evaluation Period			
				Pre-Discharge *(1-7 days post procedure)*	**Day 7 Follow-up Contact** *(+/-1 day)*	**Repeat Procedure for PAF**	**Month 3 Follow Up** *(91±14 days)*	**Month 6 Follow Up** *(180± 30 days)*	**Month 12 Follow Up** *(365±30 days)*	**Unscheduled Visit**
Documentation of Intervention for AF/AT/AFL (if any)						X	X	X	X	X
Medications	Prior and current AAD medications and Anticoagulant therapy regimen from Enrollment through End of Study Visit									
Protocol Deviations	From Enrollment through End of Study Visit									
Adverse Event Assessment	Continuous from Enrollment through End of Study Visit									

[1] Blood tests up to 90 days prior to enrollment,
[2] TTE either new or from medical file, ≤180 days prior to enrollment;
[3] NIH Stroke Scale (NIHSS) performed at baseline and the pre-discharge visit.
[4] Neurology consult is only required if NIH scale worsens from the previous assessment
[5] Brain DW-MRI scan required if neurology consultation determines possibility of new stroke
[6] Physical assessment at discharge will also include a cardiovascular/pulmonary examination: weight, resting heart rate, systolic and diastolic blood pressure, O_2 saturation, lung auscultation (includes respiratory rate and respiratory rhythm), and temperature
[7] Performed before the case (CT/MRI);
[8] TEE 48 hours prior to the procedure or ICE during the procedure
[9] Assessed in case of suspected PV stenosis;
[10]Screening for phrenic nerve palsy will be performed during ablation, and prior to leaving the EP lab at the completion of the ablation procedure in all subjects. Assessment at discharge and at follow-up visits is only applicable for subjects who had phrenic nerve palsy detected at the index procedure.
Abbreviations: IP = index procedure, NIH = National Institutes of Health, ECG = electrocardiogram, ICE= Intracardiac Echograp PV=pulmonary veins, TTM = trans-telephonic monitor,
TTE = trans-thoracic echocardiogram, TEE = trans-esophageal echocardiogram, CT = Computed Tomography, MRI = Magnetic Resona Imaging, FU = follow-up.

12.2. *Study Candidate Screening*

Investigators are responsible for screening all subjects and selecting those who are appropriate for study inclusion. The subjects selected for participation should be from the investigator's general patient population. The investigator is expected to follow standard of care testing to diagnose and screen subjects for inclusion in the study.

12.2.1. **Screening and Enrollment Log**

A *Screening and Enrollment Log* will be maintained to document select information about candidates who fail to meet the general and specific selection criteria, including those enrolled in the study and classified either as Consent Ineligible, Intent, Attempt or Treatment subjects.

12.3. *Enrollment and Informed Consent*

Subjects who provide consent are considered enrolled in the study. In order to determine eligibility of a subject, the investigator or designee needs to implement the consent process and verify/document the subject meets the inclusion/exclusion criteria. Informed consent is

required for all subjects prior to their participation in the study. No study-specific procedures should 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 personally signed and dated by the subject. 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 30 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 11.5). 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 will be made available for review at Interim Monitoring Visits (IMVs).

For additional information regarding the informed consent process, refer to section 22.

12.4. ***Baseline Visit***

Enrolled subjects will have baseline data collected. The data collection at baseline includes:

- Visit date
- Documentation of Informed Consent process, including Informed Consent Form signature date
- Check of Eligibility Criteria*
- Demographic data, including: age at time of consent, gender, race and ethnicity
- Physical assessment including: weight, height, resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (by means of a 12-lead ECG)
- Medical history, including, but not limited to:
    - Evidence of PAF in the medical history should be documented as per the inclusion criteria. Treatment history (drug, cardioversion, etc.) should be documented.
    - Underlying cardiovascular disease, if any; including but not limited to hypertension, dyslipidemia, coronary artery disease
    - Prior history of cardiac events including: acute myocardial infarction, CVA, or TIA
    - Prior surgical interventions and/or cardiac procedures including: Percutaneous Trans Catheter Angioplasty (PTCA), Coronary Artery Bypass Graft (CABG), pacemaker (PM) implantation, implantable cardioverter-defibrillator (ICD) implant, Cardiac Resynchronization Therapy (CRT) implant, cardiac valve interventions, left atrial appendage closure (LAAC), patent foramen ovale (PFO) intervention, heart transplant or procedures for implantation of other intracardiac devices
    - Detailed history of all arrhythmias

- Non-cardiac comorbidities, including but not limited to: Chronic Obstructive Pulmonary Disease, Diabetes, Hepatic Disease, Neurologic Disease, Renal Disease, Bleeding Disorders/Clot disorders, Sleep Disordered Breathing

- The following instrumental assessments will be performed or data from existing information will be collected:
  - TTE (most recent, either assessed at baseline visit or from medical file if date if not > 180 days prior to enrollment). Data will include: LVEF, left atrial diameter or left atrial volume**, pulmonary artery pressure**
  - Cardiac MRI or spiral CT scan, to assess PV anatomy and PV dimension.
  - TEE or ICE to rule out presence of left atrial thrombus. See section 12.5.2. Anticoagulation, Thrombus Screening.

  In the event a subject has an adverse event related to the TTE, TEE, ICE or CT/MRI scan, they shall remain in the study until the event is resolved.

- Pregnancy test (urine or blood), if applicable***
- Blood tests****
- Quality of Life assessment through AFEQT and EQ-5D-5L questionnaires
- Conduct a baseline National Institute of Health Stroke Scale (NIHSS), see Appendix 30.2.
- AAD history and most recent dose prior to enrollment; stop date of amiodarone (if applicable)
- Current AAD and anticoagulation medication regimen
- Reportable Adverse Events, if applicable
- Protocol Deviations, if applicable

* LVEF and LA diameters obtained ≤ 180 days prior to enrollment will be acceptable, unless a cardiac event has occurred (e.g. MI) between the date of the exam and the enrollment date, otherwise a new echocardiogram (trans-thoracic or trans-esophageal, or intracardiac echo) must be performed to confirm eligibility prior to performing ablation. LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used. If both LA diameter and volume are available, only one meeting eligibility criteria is required.

**Moderate to Severe mitral stenosis (severity will be assessed as pulmonary artery systolic pressure > 30 mmHg).

***A pregnancy test (method of assessment per investigators' discretion) must be performed for women of childbearing potential. Women of child bearing potential will be required to verify entrance criteria prior to the procedure by providing documentation of a negative pregnancy test. A negative pregnancy test conducted as standard of care *within 7 days prior to enrollment* will be acceptable.

****Laboratory blood tests (other than a pregnancy blood test) obtained ≤ 90 days prior to enrollment will be acceptable.

12.5. *Medications*

12.5.1. **Anti-Arrhythmic Drugs**

12.5.1.1. AADs prior to index procedure

Inclusion criteria require the subject to be refractory or intolerant to at least one class I or III antiarrhythmic medication and amiodarone to be stopped three months before enrollment. Prior and current AAD therapy will be collected in the EDC system.
If applicable, administration of amiodarone and stop date will be entered in EDC.

12.5.1.2. AADs post index procedure during the 90-day blanking period

Blanking period is defined as the time between Index procedure and 90 days post Index procedure. Post-procedure AADs are allowed per physician's discretion during the blanking period. New AADs should not be prescribed unless considered medically necessary. If treatment with AAD is prescribed during the blanking period, it is recommended that a Class I or III AAD be selected according to the ACC/AHA/ESC 2014 Guidelines for the Management of Patients with AF. No amiodarone use is permitted post procedure. After the index procedure, the investigator should remove subjects from AADs to appropriately assess the subject for early arrhythmia recurrence that may require a repeat ablation procedure within the blanking period (on or before day 90).

12.5.1.3. AADs post 90 days blanking period

Investigators must stop administration of AADs for any atrial tachyarrhythmia after the blanking period. If the investigator determines that the subject must be prescribed any dose of 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/AT/AFL recurrence.*

Treatment with Class II/IV medications for conditions other than control of atrial arrhythmia recurrence is also permitted and will be documented. Every effort should be made to keep those drugs at a stable dose over the entire course of the study.

12.5.2. **Anticoagulation**

The following anticoagulation protocol is required for this study. An *adequate anticoagulation regimen* is represented by one of the 4 approaches listed in the paragraph titled "Pre-ablation".

Pre-ablation.

Physicians can follow either an uninterrupted anticoagulation approach (Recommended), based on uninterrupted warfarin or NOAC, or minimally interrupted NOAC or an interrupted anticoagulation approach with adequate bridge with LMWH (Low Molecular Weight Heparin).

- Uninterrupted anticoagulation approach (recommended) includes one of the following options:

1) Uninterrupted treatment with warfarin or NOAC*, requiring continued treatment including the day of the index procedure
2) Minimally interrupted NOAC, requiring continued treatment but allowing to stop NOAC 12 to 24 hours before the index procedure (e.g. holding the morning dose the day of the procedure)

- Interrupted anticoagulation approach includes one of the following options.

3) If patient is on Warfarin, this should be stopped 5 days prior to the ablation procedure and bridged with LMWH. LMWH should be stopped 12 hours prior ablation.
4) If patient is on NOAC, this should be stopped 5 days prior to the ablation procedure and bridged to Warfarin or bridged with LMWH. LMWH should be stopped 12 hours prior ablation. At the time NOAC is stopped, INR value should be checked, if applicable, to ensure the Time of Therapeutic Range (TTR) are achieved with normalized ratio (INR) between 2.0 and 3.0.

* Includes any of the FDA approved NOAC (dabigatran, edoxaban, apixaban or rivaroxaban)
Anticoagulation guidelines that pertain to cardioversion of AF should be adhered.

If at the time of enrollment, a patient has not been anticoagulated as defined above in the pre-ablation anticoagulation, anticoagulation must be initiated and maintained from point of enrollment to the time of the index procedure. In the event that the patient has not been anticoagulated for at least 3 weeks prior to the index procedure, thrombus screening must be conducted as outlined in Section 12.5.3.

Intra ablation:

- Heparin should be administered prior to transseptal puncture during AF catheter ablation procedures and adjusted to achieve and maintain an ACT of at least 300 seconds. The ACT level should be checked at 10-15 minute intervals until therapeutic anticoagulation is achieved, and then at 15–30 minute intervals for the duration of the procedure.

After ablation:

- Systemic anticoagulation with warfarin or a NOAC is recommended for at least 2 months post catheter ablation of AF.
- Adherence to AF anticoagulation guidelines is recommended for patients who have undergone an AF ablation procedure, regardless of the apparent success or failure of the procedure.

Decisions regarding continuation of systemic anticoagulation more than 2 months post ablation should be based on the patient's stroke risk profile and not on the perceived success or failure of the ablation procedure.

12.5.3. **Thrombus Screening**

The absence of thrombus must be confirmed by means of a TEE within 48 hours prior to the procedure or ICE during the procedure in subjects not adequately anticoagulated (see section 12.5.2) for at least 3 weeks prior to procedure *OR with CHA_2DS_2-VASc score (see Appendix 30.4) ≥2 in men and ≥3 in women OR enlarged LA (≥4.5cm)*. When screening for thrombus prior to the index procedure, ensure that the anticoagulation approach as described in Section 12.5.2 is followed until the day of the procedure.

12.6. ***Index (Ablation) Procedure***

12.6.1. **General Info**

- Authorized ablating physicians

The study-related ablation procedure, from transseptal access in the left atrium until end of the ablation procedure must be performed by investigators trained in Electrophysiology (EP), trained to the FROzEN-AF clinical protocol and authorized by BSC to handle investigational devices. The index ablation procedure must be performed within 30 days of a subject's enrollment into the study. To avoid potential bias, it is recommended the number of *active* ablating physicians performing the index procedure per investigational site is restricted to 2. Boston Scientific will therefore authorize a maximum of 2 *active* ablating physicians per site except in regions where the Cryoballoon System is commercially available.

- De novo procedures

For the purposes of this protocol, de novo procedures are defined as AF procedures in which there has been no prior ablation in the Left Atrium (LA). According to subject selection criteria, all Index procedures in this study are de-novo as history of previous left atrial ablation or surgical treatment for AF/ AFL/ AT constitute an exclusion criterion.

- Esophagus management

Esophagus management must be performed by means of temperature monitoring via the Console using commercially available products. A commercially available temperature probe compatible with the Cryoablation system, will be used with measurements acquired and displayed through the Console. If the esophageal temperature falls below 20°C during cryoablation applications, the ablation will be stopped until esophageal temperature returns to baseline.

- Phrenic nerve activity monitoring
    - Index Procedure:
        - During ablation phrenic nerve activity monitoring will be performed. The phrenic nerve will be paced with a focal or circular catheter, higher than the ablation position during all right sided vein ablations. 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

- After ablation, prior to leaving the EP lab, fluoroscopy of diaphragm movement will be performed at the completion of the ablation procedure

- Discharge:
  - All patients presenting with phrenic nerve palsy at the end of the index procedure will be re-assessed at the discharge visit for phrenic nerve palsy via sniff test or an inhalation-exhalation chest radiography of the diaphragm
- At Follow-up Visits:
  - Patients with unresolved phrenic nerve palsy detected at discharge visit, should be assessed by means of sniff test or an inhalation -exhalation chest radiography of the diaphragm to evaluate if the event resolved

- Three-dimensional electroanatomic mapping

3D electro-anatomical mapping is not recommended in this study. If 3D mapping is performed, a commercially available device will be used, and the following information will be collected: mapping catheter, 3D mapping system and mapping times.

12.6.1.1. Pulmonary Vein Isolation

The goal of the ablation procedure is electrical isolation of all clinically relevant PVs. Electrical isolation of the veins must be demonstrated by entrance and exit block.

If the subject is in AF prior to the ablation, it will be up to the physician'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.

12.6.1.2. Cryoablation System Preparation

The Console will create a record for each ablation attempted, including Ablation Duration, Cryoballoon Temperature, Esophagus Temperature (if connected) and DMS activity data. In order to accurately capture information relevant to the study, the following information must be input into the Console at each index procedure:

Prior to Ablation:

- On the subject information screen, enter the subject's identification (code provided by the EDC system when enrolling the patient) and the operating physician name.
- For the purpose of this study, the DMS must 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.

1. Place a disposable ECG electrode just below the right side costal cartilage.
2. Snap the DMS onto the electrode.
3. Ask the patient to cough and verify that signal is visible on the console screen. Adjust the position of the electrode if necessary.

   Prior to performing the ablation, pace the phrenic nerve with a focal or circular catheter positioned superior to the ablation location (e.g. superior vena cava). Adjust the pacing settings and catheter location as necessary to attain phrenic nerve capture. Typically, high output at 20 mA and 800 – 1000 milliseconds (ms) may be needed.

   NOTE: Avoid or minimize use of paralytics if general anesthesia is used as paralytics may interfere with pacing capture of the phrenic nerve.
4. While pacing the phrenic nerve, adjust the DMS gain and sensitivity levels within the Settings screen to maximize the DMS signal level in the display window. Reduce the gain if the DMS signal appears saturated. Stop pacing until needed for the ablation.
5. Set the DMS threshold (within the Settings screen) for which the DMS notification will be displayed. The suggested DMS threshold setting is 65%, but. the threshold can be adjusted per physician discretion.
   - The movement amplitude measured by the DMS at the initiation of cryoablation is used as the baseline value and is displayed as 100%.
   - If the phrenic nerve pacing response decreases during cryoablation, the DMS amplitude will correspondingly decrease. The console will display the DMS amplitude as a percentage of the baseline value. For example, 80% displayed on the console indicates the DMS amplitude is 80% of the baseline valve and that movement amplitude is reduced by 20%.
6. In case of a DMS notification, continue to closely monitor phrenic nerve activity and pacing capture, and consider immediately interrupting cryoablation.

During Each Ablation Application:

- Annotate the ablation site, mark the Time-To-Isolation, and set the Ablation Duration.

12.6.1.3. Cryoablation protocol

The ablation procedure should follow this recommended sequence: Prepare patient with conscious sedation or general anaesthesia. Prepare the vascular access sites per physician preference. Follow anticoagulation protocol in section 12.5.2.

1. Intracardiac echo (ICE) may be performed to support the procedure. Record any observation of cardiac structural damage, any evidence of pericardial effusion, or any visible anomalies on the CRF.
2. Place additional diagnostic catheters, for example in the coronary sinus or for pacing the phrenic nerve, at the discretion of the physician.
3. Per institutional protocol, complete transseptal access (single or double).
4. Baseline the fluoroscopy exposure time.
5. Per the DFU, prepare the steerable sheath. Insert the steerable sheath over the guidewire and advance the sheath across the atrial septum.
6. Per the DFU, prepare the cryoablation catheter and the mapping catheter. Insert the mapping catheter into the cryoablation catheter. Insert the Cryoablation Catheter into the steerable sheath and advance it into the left atrium.
7. Baseline the LA dwell time.
8. Advance the mapping catheter into the targeted PV and attain baseline electrograms, including confirming conduction between LA and PV.
9. Inflate the cryoballoon and occlude the targeted PV. Confirm and grade the occlusion using fluoroscopy with contrast injection.
10. Position the esophagus temperature probe as directly posterior to the cryoballoon as possible.
11. If the selected vessel is a right PV, start phrenic nerve pacing prior to starting the cryoablation.
12. Start the cryoablation and observe the electrograms for changes in conduction. Identify Time-To-Isolation and set ablation duration as required by the dosing strategy document (document 92355401 provided separately). Investigators may apply a different dosing than the one provided in this document for reasons including technical difficulties, anatomical challenges, or concerns for subject welfare.
13. Upon completing the ablation, determine if entrance and exit block were achieved. If entrance and exit block are not confirmed, ablate the PV again as required by the dosing strategy document (document 92355401). Investigators may apply a different dosing than the one provided in this document for reasons including technical difficulties, anatomical challenges, or concerns for subject welfare. If entrance and exit block are confirmed, reposition the system to target another PV.

12.6.1.4. PV isolation verification

Electrograms from the POLARMAP mapping catheter will be used to assess entrance and exit block into/from the PVs. The PV will only be considered isolated if entrance and exit block are confirmed. Electrogram data must be documented.

12.6.1.5. Additional ablation(s)

Additional ablation of non-PV foci that initiate AF (including locations in the LA, RA, or SVC), targeting complex fractionated electrograms or ganglionated plexi or performing left atrial mitral isthmus or roof lines are not allowed in this protocol.

Additional ablation of the cavo-tricuspid isthmus (CTI) with a conventional market approved RF catheter is allowed only in case a typical atrial flutter is documented in prior patient history or occurs during the case (either spontaneously or inducible).

The Cryoablation System cannot be used for the ablation of other arrhythmia(s)/additional line(s) or applications outside the PVs.

It is not allowed to perform concomitant procedures during the ablation procedure (e.g. ICD implant, PM, LAAC).

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.

If at any time during the ablation procedure the investigator is unable to continue the ablation with the designated investigational catheter (for the PV isolation), the investigator may consider the case a procedural failure and complete the case with a device determined best for the subject. The point at which failure was determined as well as the rationale must be documented. A protocol deviation will be documented in the EDC system.

12.6.2. **Index procedure collected data**

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

- Date of procedure
- Identification of all investigational study devices:
    - Cryoablation Catheter
    - Cryo Mapping Catheter
    - Cryo Steerable Sheath
    - Console and all investigational accessory devices
- Identification of non-study devices if applicable:
    - Additional sheaths/introducers used during the procedure including manufacturer, model and type
    - Additional catheter(s) used during the case other than Cryoablation Catheter including manufacturer, model, and type (e.g. mapping catheter and CS catheter)
    - Mapping system and mapping catheter (manufacturer and model); if RHYTHMIA HDx™ is used (manufacturer, model and software version)

- 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 access to left atrium single or double transseptal
- Method of evaluating phrenic nerve function and determining when intervention is needed
- Collection of ACT levels

Specific to the ***PVI ablation*** the following information will be collected:

- Pre-ablation electrograms with baseline entrance and exit conduction for each PV
- Occlusion score for each cryo application
- Time-to-Isolation (if achieved), minimum balloon temperature, and duration of each cryo application.
- Total number and total duration of cryo applications per PV
- Post-ablation electrograms of entrance/exit block for each PV

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
- Total Cryoablation time (duration of all cryo applications)
- Duration of LA dwell time defined as time from the Cryoablation Catheter exiting the sheath in the LA to time of final PV isolation.
- 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 through fluoroscopy of diaphragm movement.
- Protocol Deviations, if applicable

After removal from the subject, all investigational catheters should be inspected by the investigational site staff, and if any abnormalities are noted on the catheter, it must be documented. All investigational catheters, steerable sheaths and extension cables opened and/or used during the procedure must be returned to the sponsor. Failure to return an

investigational device will result in a protocol deviation. All other control ablation or diagnostic catheters may be disposed of per standard EP practice. All adverse experiences with a BSC product, including those commercially available, during the ablation procedure must be promptly reported to BSC and documented on the eCRF.

- The Export Case Data (the data collected through the Console) will be saved and stored to external media, as provided by the sponsor;
- Console Report
- The EP Lab Procedure Report will be printed and stored in the center's patient file. Please refer to **Table 10** for an overview of source document requirements.

12.7. ***Pre-Discharge Visit***

The pre-discharge follow-up visit (1 to 7 days post procedure) should be done before hospital discharge, but 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.

The data collection at Pre-Discharge includes:

- Date of visit
- Physical assessment with cardiovascular/pulmonary examination including:
    - Weight,
    - Resting heart rate,
    - Systolic and diastolic blood pressure,
    - O_2 saturation,
    - Lung auscultation (includes respiratory rate and respiratory rhythm),
    - Temperature
- Rhythm at time of visit (by means of a 12-lead ECG)
- Conduct an NIH Stroke Scale (NIHSS) (see Appendix 30.2)
- In cases of phrenic nerve palsy at the index procedure, patients should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Provide subjects with arrhythmia/event monitor and operating instructions;
- Perform a cardiac MRI or spiral CT if PV stenosis is suspected at any time throughout the follow-up period. Recommend using the same imaging modality used at baseline
- New, discontinued or changes to current medication regimen
- Reportable Adverse Events, including resolution of ongoing events, if applicable
- Protocol Deviations, if applicable

If the NIH stroke scale demonstrates new abnormal findings when compared with the pre-procedure assessment, the subject will have a neurology consultation. A brain DW-MRI scan is required if neurology consultation determines possibility of new stroke. The DW MRI scan sequences required will be performed within the local guidelines associated with brain MRI scan. The following parameters for the DW-MRI are recommended in order to allow comparability of potential findings across patients:

- 1.5T MRI imaging equipment
- Diffusion-weighted imaging technique
- 5mm slice thickness

12.8. *Day 7 Follow-up Contact*

A telephone contact will occur at 7 days post-procedure (7 days±1 day). If the patient is still hospitalized the 7 days follow-up will be performed as in-hospital visits. The data collection at the day 7 follow-up includes:

- Date of visit
- New, discontinued or changes to in current medication regime
- Reportable Adverse Events, including resolution of ongoing events, if applicable
- Protocol Deviations, if applicable

In cases of in-hospital visit and phrenic nerve palsy at the index procedure, patients should be assessed by means of sniff-test or inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved.

12.9. *Month 3 Follow-Up Visit*

This visit should be completed at 3 months post-procedure (91 days±14 days). Due to the range for the visit completion and the endpoint requirement for medication, AAD medication changes made during the three-month follow-up visit will be counted as being made within the blanking period, but efforts should be made to remove subjects from AADs by eight weeks post-procedure to allow for complete washout. The data collection at the 3-month follow-up includes:

- Date of visit
- Physical assessment including weight, resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (by means of a 12-lead ECG)
- Quality of Life Instruments (AFEQT and EQ-5D-5L)
- Review of any symptomatic transmissions (arrhythmia/event monitor such as a TTM)
- Documentation of any intervention for AF/AT/AFL (e.g. Repeat Procedure, Cardioversion), if applicable

- Perform a cardiac MRI or spiral CT if planned at 3 months as part of the PV stenosis screening substudy. Use the same imaging modality used at baseline.
- For sites not participating in the PV stenosis substudy, perform a cardiac MRI or spiral CT if PV stenosis is suspected at any time throughout the follow-up period. Recommend using the same imaging modality used at baseline.
- New, discontinued or changes to current medication regimen
- Reportable Adverse Events, including resolution of ongoing events, if applicable; in particular:
    - In cases of a pre-existing and unresolved phrenic nerve palsy the patient should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Protocol Deviations, if applicable

12.10. *Month 6 Follow-Up Visit*

This visit should be completed at 6 months post-procedure (180 days±30 days). The data collection at the month 6 follow-up includes:

- Date of visit
- Physical assessment including weight, resting heart rate, systolic and diastolic blood pressure;
- Rhythm at time of visit (by means of a 12-lead ECG)
- Quality of Life Instruments (AFEQT and EQ-5D-5L)
- Review of any symptomatic or asymptomatic transmissions (arrhythmia/event monitor such as TTM)
- Documentation of any intervention for AF/AT/AFL (e.g. Repeat Procedure, Cardioversion), if applicable
- Perform a cardiac MRI or spiral CT at any point in time during the 3 to 6 months follow-up as part of the PV stenosis screening substudy. Use the same imaging modality used at baseline
- For sites which are not part of the PV stenosis screening substudy, perform a cardiac MRI or spiral CT if PV stenosis is suspected at any time throughout the follow-up period. Recommend using the same imaging modality used at baseline
- New, discontinued or changes to current medication regimen
- Reportable Adverse Events, including resolution of ongoing events, if applicable; in particular:

- In cases of phrenic nerve palsy at the index procedure, patients should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Protocol Deviations, if applicable

12.11. *Month 12 Follow-Up Visit*

Investigators will assess subject status at 12 months (365 days±30 days) post index procedure. The data collection at the month 12 follow-up includes:

- Date of visit
- Physical assessment including weight, resting heart rate, systolic and diastolic blood pressure;
- Rhythm at time of visit (by means of a 12-lead ECG)
- Quality of Life Instruments (AFEQT and EQ-5D-5L)
- Review of any symptomatic or asymptomatic transmissions (arrhythmia/event monitor such as TTM)
- 24-hour Holter monitor data recorded with the study specific TTM

Note: While wearing the Holter monitor, subjects should also make every attempt to capture the symptomatic episode with the TTM

- Documentation of any intervention for AF/AT/AFL (e.g. Repeat Procedure, Cardioversion), if applicable
- Perform a cardiac MRI or spiral CT if PV stenosis is suspected. Recommend using the same imaging modality used at baseline
- New, discontinued or changes to in current medication regime
- Reportable Adverse Events, including resolution of ongoing events, if applicable; in particular:
    - In cases of phrenic nerve palsy at the index procedure, patients should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Protocol Deviations, if applicable

12.12. *Unscheduled Visits*

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

If subjects experience symptoms associated with cardiac arrhythmias (e.g. palpitations, lightheadedness, syncope, dyspnea) during the first 12 months, they will be instructed to record the arrhythmia on the event monitor. The investigator will review the information transmitted

and will contact the subject to schedule an additional office visit if deemed necessary per investigator's decision.

In addition to determining the best course of action for the subject (repeat ablation, medication adjustment), during the visit, the following will be collected:

- Date of visit
- Physical assessment including: weight, resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (by means of a 12-lead ECG)
- Review of any symptomatic or asymptomatic transmissions (arrhythmia/event monitor, such as TTM)
- Documentation of any intervention for AF/AT/AFL (e.g. Repeat Procedure, Cardioversion), if applicable
- Perform a cardiac MRI or spiral CT at any point in time during the 3 to 6 month follow-up as part of the PV stenosis screening substudy. Use the same imaging modality used at baseline
- For sites not part of the PV stenosis screening substudy, perform a cardiac MRI or spiral CT if PV stenosis is suspected at any time throughout the follow-up period. Recommend using the same imaging modality used at baseline
- New, discontinued or changes to current medication regimen
- Reportable Adverse Events, including resolution of ongoing events, if applicable; in particular:
    - In cases of phrenic nerve palsy at the index procedure, patients should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Protocol Deviations, if applicable

12.13. *Additional/Repeat Procedure*

In case an additional procedure (including but not limited to a repeat ablation procedure for PAF) occurs during the month 12 follow-up period, the data of this procedure will be entered in the 'Additional/ Repeat Procedure' eCRF. In case this additional procedure is an ablation procedure (for the same, or different arrhythmias or for an unsuccessful ablation of the arrhythmia presented at index procedure), detailed information about this additional ablation procedure will be entered in the 'Additional/Repeat Procedure' eCRF:

- Was the additional ablation procedure performed in the LA? If yes, TEE or ICE to rule out presence of left atrial thrombus. ***
- For additional ablation procedures performed in the LA: was this additional ablation procedure performed to treat AF? If no, specify the arrhythmia type.

It is known that a repeat ablation procedure for PAF may be necessary in certain subjects after the index ablation procedure due to recurrences of PAF or other tachyarrhythmias requiring treatment. One repeat ablation procedure for PAF is allowed within the blanking period if considered medically necessary due to patient's intolerability of the PAF. If the repeated ablation procedure occurs during the blanking period (within 90 days of the Index procedure) it is recommended to use the Cryoablation system. Use of a non-study device for AF re-ablation during blanking period constitutes a failure for the effectiveness endpoint. Data for the repeat ablation procedure will be collected in the eCRF.

Subjects must follow the same anticoagulation requirements as defined for the index procedure in section 12.5.2 prior to proceeding with the repeat ablation procedure for PAF.

- If a 3D mapping system is used for this additional procedure, additional info will be collected
- Reportable Adverse Events, including resolution of ongoing events, if applicable; in particular:
    - In cases of phrenic nerve palsy at the index procedure, patients should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Protocol deviations, if applicable

The appropriate type of pre-procedure imaging (CT/MRI) is to be determined by the investigator. As available, the PV images must be reviewed against the pre-ablation imaging from the index procedure to rule out PV stenosis from the index ablation procedure.

12.14. *Study Completion*

Each Treatment subject will be followed until the month 12 follow-up. Participation in the study is considered complete upon completion of the month 12 follow-up.

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Data Collection Schedule.

In case of premature termination of the study, please refer to section 24.

Following termination/completion of the study, subjects will be managed according to local institution practice.

Sites will need to document and complete the "End of Study" CRF to signify study completion.

12.15. *Unforeseen Circumstances (Natural Disaster/Global Pandemic)*

There may be unforeseen circumstances that occur during the course of the study, such as a natural disaster or a global pandemic (e.g. COVID-19) that prevents a subject from attending study visits during the required follow-up window. While every attempt should be made to avoid disruptions in collecting study data, it is important to collect as much data as possible, by any available means and from any available resources. This may include obtaining records from an outside clinic, hospital or other healthcare facility that is not IRB/EC/REB approved.

In the event that study data must be collected remotely, every effort should be made to collect the data within the study visit window, if possible. Critical data collected during the study includes any procedure or device related adverse events, recurrence of any AF/AT/AFL, and a Cardiac CT or MRI (if PV stenosis is suspected). Event monitors and 24-hour Holter monitors can be used to detect any recurrence of AF/AT/AFL. If a Cardiac CT or MRI is required because PV stenosis is suspected, the Cardiac CT or MRI may be performed at another healthcare facility and the window to conduct this test may be extended by up to one month (30 days) following the normal study visit window.

12.16. *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 the Table below.

Table 10: Source Documentation Requirements

Requirement	Disposition
Screening and enrollment log	Retain at Center
Informed consent documentation process	Retain at Center
Medical history documents pertaining to eligibility criteria	Retain at Center
Documentation of demographics data	Retain at Center
Pregnancy, if applicable	Retain at Center
Physical assessment	Retain at Center
Cardiovascular/pulmonary examination	Retain at Center
Medication Regimen and Changes	Retain at Center
Medical history	Retain at Center
Quality of Life Instruments (AFEQT and EQ-5D-5L)	Retain at Center

Requirement	Disposition
NIH Stroke Scale Assessments	Retain original at center and submit copies and all associated source documents if a change in scale is observed from baseline
If determined necessary, neurological consultation and brain MRI (DW-MRI)	Retain originals at center and submit all source documents and copy of complete scan to BSC
Imaging	Retain at Center
12-Lead ECGs data including ongoing rhythm	Retain at Center
Imaging, per standard of care	Retain at Center
Recording System Print-Outs, showing entrance/exit block for each Pulmonary Vein	Retain at Center
Pre-ablation electrograms with baseline entrance and exit conduction for each PV	Retain at Center
Recording lab logs, showing the time of entrance/exit block	Retain at Center
Signed Technical Source Form	Retain at Center
Console Report	Retain at Center
Console Export Case Data	Retain at Center Submit one copy to BSC
Printed EP Lab Procedure Report	Retain at Center
Adverse Events	Retain at Center
In the event of a patient death: • Death narrative • Relevant medical records • Death Certificate • Autopsy report Events be adjudicated by CEC: • Relevant medical records	Submit one copy to BSC, Retain one copy at center

13. Statistical Considerations

13.1. *Endpoints*

13.1.1. Primary Safety Endpoints

The expected safety event rate for the primary safety endpoint has been estimated by performing a meta-analysis on recently completed IDE studies (see **Table 11**). Although referring to the first-generation Cryoballoon (Arctic Front™ Balloon, Medtronic®), the STOP-AF IDE study was included in the model as it is the only reported IDE study that utilizes a cryoablation balloon. Event rates and their 95% confidence intervals were estimated from

SSED, primary publications or results disclosed on *clinicaltrials.gov* and calculated based on the occurrence of the events that constitute the primary safety endpoint defined in this protocol.

Table 11: Meta-Analysis to Determine Expected rate and 95% CI for Primary Safety Endpoint

Study	Patients with events	Total patients	Proportion	95%-CI	Weight (fixed)	Weight (random)
STOP AF	9	163	5.52	[2.56; 10.22]	7.6%	7.6%
TOCCASTAR (TactiCath)	9	152	5.92	[2.74; 10.94]	7.6%	7.6%
TOCCASTAR (TC)	8	143	5.59	[2.45; 10.73]	6.8%	6.8%
Smart AF	11	161	6.83	[3.46; 11.90]	9.2%	9.2%
Heartlight (LB)	8	170	4.71	[2.05; 9.06]	6.8%	6.8%
Heartlight (TC)	13	172	7.56	[4.09; 12.58]	10.8%	10.8%
Fire and Ice (cryo)	14	374	3.74	[2.06; 6.20]	12.1%	12.1%
Fire and Ice (RF)	30	376	7.98	[5.45; 11.19]	24.7%	24.7%
Zero AF (Blazer)	10	157	6.37	[3.10; 11.40]	8.4%	8.4%
Zero AF (TC)	7	164	4.27	[1.73; 8.60]	6.0%	6.0%
Fixed effect model	**119**	**2032**	**6.05**	**[5.08; 7.19]**	**100.0%**	--
Random effects model			**6.05**	**[5.08; 7.19]**	--	**100.0%**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.50$

The overall safety event rate from this meta-analysis is 6.05%. All the studies passed their pre-specified primary safety endpoint and established that the device under study exhibited an acceptable safety profile. In conclusion, BSC proposes a primary safety endpoint expected event rate of 6% (94% event-free rate). A performance goal for the primary safety endpoint was derived using the sum of the 95% upper confidence bound of the meta-analysis rate and a margin of indifference that is 50% of the upper confidence bound (7.2% + 0.5*7.2%). This resulted in a performance goal of 11% (89% event-free rate).

13.1.1.1. Hypotheses

H_o: The primary safety endpoint event-free rate at 12 months post procedure ≤89%
Ha: The primary safety endpoint event-free rate at 12 months post procedure >89%

13.1.1.2. Sample Size

Minimum of 325 *non roll-in* TREATMENT subjects treated with the Cryoablation System. Additionally, all ATTEMPT subjects will be included in the primary safety endpoint analysis.
The sample size estimate was obtained using the normal approximation to the binomial distribution and verified through simulations based on Kaplan-Meier methodology. The following assumptions were used in the sample size calculation:

Assumptions	Primary Safety
Expected rate	94%

Performance goal	89%
Attrition (per year)	10%
Significance level (one-sided)	5%
Power	90%
Patients after attrition	325

13.1.1.3. 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 89%. 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.

13.1.2. Secondary Safety Endpoint

Reportable Adverse Events rates at 12 months.

Adverse events will be collected at all subject follow-up visits. Reportable events include:

- All Serious Adverse Events
- All Study Procedure-Related Adverse Events
- All Study Device-Related Adverse Events
- All Study Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in DFU/Investigator's Brochure

13.1.3. **Primary Effectiveness Endpoint**

An effectiveness performance goal of 50% has been chosen based on the minimum chronic acceptable success rate for paroxysmal AF at 12-month follow-up defined in 2017 HRS Consensus document (ref). When considering recurrence of AF/AT/AFL, obtained in the pivotal trials on Cryoablation (STOP AF and FIRE & ICE) the starting point for the estimate failure-free rate was set as the one obtained for the second generation cryoballoon (FIRE & ICE: 66%), Effectiveness results are not easily poolable as aggregate from recent IDE studies on AF ablation to difference in methodology and definitions found in the selected trials when evaluating the freedom from AF/AT/AFL recurrences off AADs after 3-months blanking period. Accordingly, an estimate of the failure-free rate taking into account recurrence of symptomatic and asymptomatic events has been estimated from the data of the recently concluded ZERO-AF trial from Boston Scientific, that led to the choice of 60% was based on as expected rate.

13.1.3.1. Hypotheses

H_o: The 12-month failure-free rate ≤ 50%

Ha: The 12-month failure-free rate >50%

13.1.3.2. Sample Size

Two hundred forty-nine *non roll-in* TREATMENT subjects treated with the Cryoablation System.

The sample size estimate was obtained using the normal approximation to the binomial distribution and verified through simulations based on Kaplan-Meier methodology. The following assumptions were used in the sample size calculation:

Assumptions	**Primary Effectiveness paroxysmal**
Expected rate	60%
Performance goal	50%
Attrition (per year)	10%
Significance level (one-sided)	5%
Power	90%
Patients after attrition	249

13.1.3.3. Statistical Methods

For the primary effectiveness endpoint, the Kaplan-Meier 12 month (365-day) primary effectiveness event-free rate will be calculated. 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 primary effectiveness event-free rate will be compared to the performance goal of 50%. 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.

13.1.4. Secondary Effectiveness Endpoint

Rate of Acute Procedural Success defined as the achievement of electrical isolation of all PVs by using the Cardiac Cryoablation system only. Electrical isolation of a PV is demonstrated by entrance and exit block.

13.2. ***General Statistical Methods***

13.2.1. **Analysis Sets**

Each primary endpoint analysis will use all available data from all *non roll-in* TREATMENT subjects.

13.2.2. **Control of Systematic Error/Bias**

Selection of patients will be made from the Investigator's population. All patients meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study. Control and reduction of potential bias associated with a single-arm study design have been taken into account by considering a series of measures including but not limited to:

- defining inclusion and exclusion criteria to represent a population similar to the one enrolled in recently completed trials on AF ablation;
- implementing a screening log to document reason(s) for screening failure and a pre-specified analysis on screening failures;
- employing a rhythm surveillance monitoring strategy that is equivalent to that used in recent PAF IDE studies and consistent with the relevant recommendation in the HRS consensus document;
- utilizing core lab for reviewing electrocardiographic recordings from study specific rhythm surveillance monitoring after the blanking period.

13.2.3. **Study Success and Control of Type I Error**

As this study was designed to address the safety and effectiveness of the Boston Scientific Cardiac Cryoablation System, there is one primary safety endpoint and one primary effectiveness endpoint. Both the primary endpoints must pass in order for study success to be achieved. Each primary endpoint would be tested at a significance level of 5% while still maintaining the overall Type I error level at no greater than 5%. This follows the methodology of the Intersection-Union Test (IUT). If all primary endpoints for a given study are passed, then the secondary effectiveness endpoint will be tested at alpha = 0.05.

13.2.4. **Number of Subjects per Investigative Site**

To avoid any center effect and bias, one center will not be authorized to enroll more than 48 subjects (15% of the minimum 325 enrollment total of *non roll-in* TREATMENT subjects).

13.3. ***Data Analyses***

13.3.1. **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.

13.3.2. **Missing Data Analyses**

Because endpoints will be analyzed using Kaplan-Meier methodology, all TREATMENT subjects will contribute data to the primary effectiveness endpoint and all TREATMENT and ATTEMPT subjects will contribute data to the primary safety endpoint. A tipping point analysis will be done to assess the potential impact of missing data in INTENT and ATTEMPT

subjects for the primary effectiveness endpoint and in INTENT subjects for the primary safety endpoint.
In the tipping point analysis, missing data subjects will be assigned as either having or not having an endpoint event. All possible combinations of success and failure in these subject's data will be evaluated along with the actual observed data to find the point at which the endpoint would have failed.

13.3.3. **Subgroup Analyses**

An analysis will be performed for the primary endpoints to determine whether significant differences exist in endpoint results between subgroups. The list of covariates (with applicable subgroups in parentheses) includes the following:

- Sex (Female vs. Male)
- Age at time of consent (subjects > 60 years vs subjects ≤60 years)
- Geography (International vs. United States)
- Enrollment criteria (protocol versions A-G vs. subsequent protocol versions)

Each subgroup covariate will be included as a single independent variable in a logistic regression model with the primary endpoint outcome as the dependent variable and a test for significance at the 15% level will be performed**.**

In addition to subgroup analyses, descriptive statistics of subject demographic and baseline characteristics will be presented for each subgroup listed in this section.

13.3.4. **Center 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.

13.3.5. **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,)

13.3.6. **Additional Analyses**

Additional endpoints and analyses include, but are not limited to:

- Changes in the quality of life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up
- Single procedure success, defined as freedom from primary effectiveness failure without a repeat procedure
- Duration of LA dwell time, defined as time from the Cryoablation Catheter exiting the sheath in the LA to time of final PV isolation;
- Total Cryoablation time for the index procedure;
- Total fluoroscopy time for the index procedure;
- Total index procedure time;
- Freedom from recurrence of individual types atrial arrhythmias between 91 and 365 days post index procedure: 1) AF 2) AT 3) AFL;
- Failure- free rate as defined in primary effectiveness endpoint when considering AF/AT/AFL episodes reported to the investigators by study specific (event recorder transmissions, 12 lead ECG and Holter) and non-study related devices (other commercial applications for arrhythmia monitoring and detection the subject may access during the study including telemetry, other sources of continuous recording etc.);

Freedom from primary effectiveness failure at six (6) months will be included in the final study report as a "proof-of-concept" analysis to potentially show the ability to predict 1-year effectiveness results using 6-month effectiveness data.

13.3.7. **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.

14. **Health Economics Outcomes**

A formal health economics analysis may be completed as part of this trial study, given meaningful clinical results are obtained. This will take into consideration complication rates, quality of life, and resource utilization. The EQ-5D, generic quality of life measure, will be used to assess health utilities. We may estimate costs associated with the health care utilization measures at all sites. These inputs may be used in health economics analysis performed.

15. Data Management

15.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

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(s). 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 EDC system and will be issued to the site for appropriate response. Site staff will be responsible for resolving all queries in the database.

Data transfers from other systems such as core labs and electronic questionnaires will be coordinated by Boston Scientific.

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

15.2. *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.

15.3. *Technical Source Forms*

The Technical Source Form (TSF) is the sponsor-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. If available, the console operator will provide the delegated site personnel with the study related data collected during the case directly from the console.

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

- Delegated Site Personnel completing the forms
- Delegated Investigator conducting and/or supervising the case
- Console operator supporting the case

15.4. *Core Laboratories*

15.4.1. **Event and 24-Hour Holter Monitors' Core Lab**

15.4.1.1. Event Monitors

A Core Lab will provide the center and/or subject all necessary instructions and/or materials related to the use of the event monitor. Only TREATMENT subjects will be provided with an event monitor, such as a Trans-Telephonic Monitor (TTM), either prior to discharge from the hospital or will be sent to the subject's residence immediately following discharge. All events will be analyzed by the centralized research company to determine if the episodes are associated with arrhythmia recurrence. The Core Lab will make this information accessible to the Investigator center for concurrence. If there is discordance in arrhythmia classification between the Core Lab and the investigator, a third-party cardiologist will be used for final rhythm determination.
Within the first 90 days (3 months) after the index ablation procedure (blanking period), TREATMENT subjects will be instructed to transmit all symptomatic episodes for detection and/or treatment of early recurrences. After the subject's 3-month follow-up visit, subjects will be instructed to send at least two transmissions per month (either symptomatic or asymptomatic) through the 12-month follow-up to ensure continued reporting compliance. If subjects experience symptoms associated with cardiac arrhythmias (e.g. palpitations, lightheadedness, syncope, dyspnea), they will be instructed to transmit a recording. Such recording will count towards the required transmission of that period. The Core Lab will work with the investigational site to ensure reporting compliance.

All event monitors must be returned to the centralized research company upon completion of a subject's 12-month follow-up or withdrawal from the study.

15.4.1.2. 24-Hour Holter Monitors

All TREATMENT subjects will be provided with 24-Hour Holter Monitors at the 12-month follow-up visit.

Investigational centers will be trained on the set-up of the monitors and will provide the subjects with the instructions necessary to complete the test. If a subject has a symptomatic episode while wearing the Holter Monitor, they will be strongly encouraged to report the

symptoms to their physician. Once the Holter Monitor is returned to the centralized research company, the monitor will be analyzed for all symptomatic and asymptomatic arrhythmia episodes, and investigators will be informed of the results.

15.4.2. **ECG Core Lab**

To ensure objective assessment of rhythm monitoring data, 12-lead ECG tracings obtained beyond 3 months post-procedure will be reviewed by an independent core lab.

15.4.3. **PV Imaging Core Lab**

As part of the PV Imaging sub-study, a core lab will be contracted to review the baseline and follow-up CT/MRI scans for assessment of PV diameter narrowing and determination of severe PV stenosis. The Core Lab will report the degree of narrowing (None, mild 50%, moderate 50-70%, severe ≥70%) in the follow-up scan compared to baseline. All results will be provided both to BSC and to the investigator for adverse event reporting, if applicable.

If PV stenosis is a suspected adverse event for subjects not partaking in the PV Imaging sub-study, the PV Imaging core lab will also review the pre-ablation and post-ablation PV images collected on non-sub-study subjects to assess the degree of narrowing of the PV diameter for the Primary Safety Endpoint. If it is determined that the baseline diameter of the vein of interest is not visually identifiable from the pre-ablation image, the PV Imaging core lab will measure the diameter of the vein before and after the narrowing region to determine the percentage change. The results of the analysis will be provided to the investigator for submission of an adverse event, if applicable. All necessary data will be provided to the study's independent clinical events committee (CEC) for adjudication of the submitted adverse event, with a definition of severe PV stenosis being defined as ≥70% reduction in diameter from baseline.

15.5. ***Quality of Life (QOL)***

Clinical trials increasingly recognize the value of including patient reported outcome measures in their design. To understand the impact of atrial fibrillation ablation procedures on patient's quality of life, the quality of life instruments used for the trial will be the EQ-5D-5L for a generic questionnaire and the AFEQT for disease specific. Subjects will be asked to complete the questionnaires at the Enrollment visit as well as at the three, six, and 12-month follow-ups.

The Atrial Fibrillation Effect on Quality of Life (AFEQT) was developed to evaluate disease-specific quality of life for patients with atrial fibrillation. The 20-item questionnaire is subdivided into three domains: symptoms, daily activities, and treatment concerns with responses provided on a seven-point Likert scale.

The EQ-5D, generic quality of life measure, will be used to assess health utilities. It is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.

16. 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 IRB/EC/REB, and the regulatory authority if applicable, 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 investigation. 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 eCRF. Sites may also be required to report deviations to the IRB/EC/REB, 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 IRB/FDA notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

17. Device/Equipment Accountability for Products Labelled Investigational

17.1. *Investigationally-Labelled Products*

The investigational devices/equipment shall be securely maintained, controlled, and used only in this clinical study. Investigational equipment shall be returned in the condition in which it was provided, reasonable wear and tear excepted.

For investigationally-labelled items, the principal investigator or an authorized designee shall do the following:

- Securely maintain and control access to these items to ensure they are used only in this clinical study and only per the protocol.
- Ensure the storage environment for these items is appropriate for maintaining conditions per the items' labeling (e.g. temperature, humidity, etc., as applicable)
- Return remaining items upon Sponsor request and in the condition in which they were provided, reasonable wear and tear excepted.

The sponsor shall keep records to document the physical location of all investigationally-labelled devices/ equipment from shipment of investigational devices from BSC or designated facility/equipment to the investigation sites until return or disposal.

The principal investigator or an authorized designee shall maintain accurate and timely Device Accountability Records documenting the receipt, use, return and disposal of the investigational devices/equipment, which shall include the following

- Date of receipt
- Identification and quantity of each investigational device/piece of equipment (examples of identification: batch number, serial number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the investigational device/piece of equipment was returned/explanted from subject, if applicable
- Date of return (and number) of unused, expired, or malfunctioning investigational devices/equipment, if applicable.

17.2. *Commercially-Labelled Product*

The principal investigator or an authorized designee shall maintain accurate and timely Device Accountability Records documenting the use and out of service of the devices/equipment, which shall include the following:

- Identification and quantity of each investigational device/piece of equipment (examples of identification: batch number, serial number or unique code)
- Date or dates of use
- Subject identification
- Date on which the device/piece of equipment was out of service.

18. Compliance

18.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator.

This study will be conducted in accordance with 21 CFR 814.20 part 56, part 50 and part 812 or 813, 45 CFR part 46, ISO 14155Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice, 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 IRB and 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 IRB or regulatory authority shall be followed, if appropriate.

18.2. *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, 21 CFR 814.20 part 56, part 50 and part 812 or 813, ISO 14155 Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice, any conditions of approval imposed by the reviewing IRB/EC/REB, 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.
- Prior to beginning the study, sign the Investigator Brochure Signature Page (if applicable) and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- 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 investigation.
- 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-investigation-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 reportable events.

- Report to the IRB/EC/REB 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 IRB/EC/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event
- Maintain the device accountability records and control of the investigationnally-labelled device, ensuring that the investigationally-labelled device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use
- 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 IRB/EC/REB when performing auditing activities
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC/REB 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 investigational device when it is used/operated by the subject
- Inform the subject of any new significant findings occurring during the clinical investigation, 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, 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 investigation are provided with some means of showing their participation in the clinical investigation, 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 investigation

- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks 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.

18.2.1. **Delegation of Responsibility**

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, ensuring that the individuals 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.

18.3. ***Institutional Review Board/Ethics Committee/REB***

The investigational site will obtain the written and dated approval/favorable opinion of the IRB/EC/REB for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required.
A copy of the written IRB/EC/REB and FDA approval or local authority if applicable of the protocol (or permission to conduct the study) and ICF, must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product/equipment. 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 IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB 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 IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable local-state laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB continuance of approval must be provided to the sponsor.

18.4. ***Sponsor Responsibilities***

BSC has extensive experience conducting global clinical trials. 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.

18.4.1. **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 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 the Cryoablation System and other support equipment).

At the request of the investigator and while under investigator supervision, BSC personnel may operate equipment during ablation 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 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 clinical protocol compliance.
- Reviewing collected data and study documentation for completeness, accuracy and compliance.

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 without the approval and presence of the investigator
- Collect critical study data without review and approval of the ablating physician
- Enter data in electronic data capture systems or study medical data into paper forms

18.5. *Insurance*

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

19. 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 sponsor will put a plan in place to document the specific monitoring requirements.

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 or remote monitoring visits or audits and that sufficient time is devoted to the process.

20. Potential Risks and Benefits

20.1. *Anticipated Adverse Events*

Subjects participating in this study are subject to the same risks shared by all patients undergoing an ablation procedure for treatment of PAF. Since the handling characteristics of the Cryoablation System are designed to be similar to those of other approved catheters for AF ablation, it is anticipated that the rate of catheter-related complications in this study will be similar to those reported from catheter ablations performed with approved catheter ablation systems. The protocol-required testing for this study uses standard techniques that are routinely used for the treatment and management of subjects with drug refractory PAF.

Based upon the current literature and BSC reports on adverse events with an ablation catheter, the Table below includes an alphabetical list of the possible anticipated adverse events and possible adverse device effects associated with ablation with a cryoballoon ablation catheter for the treatment of PAF. Occurrence of any of the listed events could lead to prolonged hospitalization for the subject.

The following anticipated adverse events (AE) and adverse device effects (ADE) have been identified for this study:

Table 12: Potential Adverse Events and Adverse Device Effects for PAF Ablation and Study Device

Access site complications	Headache
Allergic reaction	Heart failure
Anemia	Hematoma
Arrhythmias	Hemothorax
Bleeding/Hemorrhage	Hemodynamic instability
Blurred vision	Hypertension/Hypotension
Cardiac perforation	Inadvertent injury to adjacent structures
Cardiac/pulmonary arrest	Infection
Catheter entrapment	Myocardial infarction
Cerebrovascular accident (CVA)	Nerve weakness/palsy/injury (i.e. phrenic/ vagus)
Chest discomfort/pain or pressure	Pericarditis
Complete heart block (transient/permanent)	Pneumothorax
Complications of sedative agents/anesthesia/medications	Pseudoaneurysm
Coronary artery spasm	Pulmonary complications (i.e. edema, pulmonary hypertension, pleuritis, pneumonia)
Cough	Pulmonary vein stenosis
Death	Radiation injury/exposure
Diaphragmatic paralysis	Renal insufficiency/failure
Dizziness or lightheadedness	Respiratory Depression
Edema	Residual atrial septal defect (ASD)
Pericardial effusion/pleural effusion	Skin burns (i.e. radiation/defibrillator/ cardioverter)
Elevated cardiac enzymes	ST segment Elevation
Embolism (venous/arterial) (i.e. air, gas, thrombo, pulmonary)	Sore Throat
Endocarditis	Tamponade
Esophageal injury	Thrombus/thrombosis
Fever	Transient ischemic attack (TIA)
Exacerbation of existing conditions	Valvular damage
Fatigue	Vasospasm
Fistula (arterial-venous, atrial-esophageal)	Visual disturbances

Gastroparesis	Vasovagal reactions
	Vessel trauma (i.e. injury/ulceration/ perforation/ dissection/rupture)

20.2. *Risks Associated with the Study Device(s)*

Benchtop studies, pre-clinical research and a CE Mark clinical study have demonstrated that the System is safe for human use. All potential risks have been evaluated and mitigation strategies have been implemented to reduce potential risks to acceptable levels.

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

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

20.4. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, using the devices in accordance with their applicable Directions for Use, performing the procedures following recommended standard practices/guidelines, performing procedures in the appropriate hospital environment, 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.

20.5. *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 PAF. Potential benefits of the Cryoablation System for the subject may include the following:

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

20.6. *Risk to Benefit Rationale*

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.

21. Safety Reporting

21.1. *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:

Reportable Events:

- All Serious Adverse Events;
- All Events Leading to Death
- All Thromboembolic Events
- All Procedure Related AEs inclusive of AEs related to the assessments (TTE, TEE, ICE or CT/MRI scan) listed in section 12.4.
- All BSC commercialized diagnostic catheter-related events
- All Cryoablation System Device Related Adverse Events;
- All Device Deficiencies related to the study device;
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in the DFU/IB and ICF.
-

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 AE but should only be reflected as an outcome of one (1) specific SAE (see **Table 13** for Safety Definitions).

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.

If the patient experiences a new arrhythmia between the index procedure and the end of study, and the investigator considers this Adverse Event to be procedure related, it needs to be

reported. Refer to Investigator's Brochure or DFU as appropriate for the known risks associated with the study device(s).

Pre-existing diseases or conditions will not be reported as adverse events unless there has been a substantial increase in severity or frequency of the problem which cannot be attributed to the expected progression of the disease or condition.

The Boston Scientific Medical Safety group will provide safety oversight by reviewing and classifying individual events that are reported to the sponsor. Routine aggregate safety reviews will be conducted to ensure subject safety.

Refer to section 20 for the known risks associated with the study device(s).

21.2. *Definitions and Classification*

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

Table 13: 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, in the context of a clinical investigation, whether or not related to the investigational medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the investigational 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 investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	Adverse event related to the use of an investigational 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 investigational medical device. **NOTE 2**: This definition includes any event resulting from use error or intentional misuse of the investigational 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 led to any of the following: a) death, b) 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, including chronic diseases or

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) 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 assessment. **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 assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. Note 1: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MEDDEV 2.7/3*	An inadequacy of an investigational medical device (defined as the study device/Cryoablation System) related to its identity, quality, durability, reliability, usability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer. NOTE 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. NOTE 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

Term	Definition
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g. medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment • admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g. subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g. procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criteria.

21.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the reportable AE to the study device and/or study procedure, see criteria in **Table 14**.

Table 14: 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, comparator 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 investigational 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 investigational 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.

Possibly Related *Ref: MEDDEV 2.7/3*	The relationship with the use of the investigational device or comparator, or the relationship with procedures 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 investigational device or comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.
Causal Relationship *Ref: MEDDEV 2.7/3*	The serious event is associated with the investigational 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 investigational device use/application or procedures; - the event involves a body-site or organ that -the investigational device or procedures are applied to; -the investigational 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 investigational 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 adverse event.

21.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in **Table 15**.

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:

FROZENAF.safety@bsci.com

Table 15: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
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, as requested by sponsor.	• Upon request of sponsor.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar 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
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Within 3 calendar 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.	• When documentation is available
		• At sponsor request.
Device Deficiencies (including but not limited to failures, malfunctions, and product nonconformities) Note: Any Investigational 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	Complete Device Deficiencies eCRF with all available new and updated information.	• Within 3 calendar 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 pre-market studies (MEDDEV 2.7/3: CLINICAL INVESTIGATIONS: SERIOUS ADVERSE EVENT REPORTING UNDER DIRECTIVES 90/385/EEC AND 93/42/EEC)
or c) if circumstances had been less fortunate is considered a reportable event.		
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 10 business days) after becoming aware of the information • Reporting required through end of study • Upon sponsor request
	Provide all relevant source documentation (de-identified/pseudonymized) for reported event, as requested by sponsor.	

* Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

21.5. *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 (Cryoablation System) will be documented and reported to BSC. If possible, the device(s) should be returned to BSC for analysis. Instructions for returning the study catheters will be provided in the Site Initiation Visit slides. 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 failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, a reportable event that results from a device failure or malfunction, would be recorded as an adverse event on the appropriate eCRF.

For Device Deficiencies, the investigator must assess and report if the device deficiency could 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.

21.6. *Reporting to Regulatory Authorities / IRBs/ ECs/ REBs/ Investigators*

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

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

21.7. ***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 IRB/EC/REB must be notified of any deaths in accordance with that site's IRB/EC/REB policies and procedures.

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 catheter, clinical investigation, procedure, or patient condition
- Whether or not the death was witnessed
- Whether the patient 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:

If the patient 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 patient 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)

The Clinical Events Committee (CEC) must review information regarding subject deaths for events listed in section 23.2.

22. **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 investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with 21 CFR 814.20 part 56, part 50 and part 812 or 813, ISO 14155: Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice and Japan Medical Device GCP, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and any applicable national regulations, IRB/EC/REB 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 IRB/EC/REB, or central IRB/EC/REB, 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 IRB/EC/REB. 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 IRB/EC/REB 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 and by the investigator and/or an authorized designee responsible for conducting the informed consent process. 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. IRB/EC/REB), 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 IRB/EC/REB. The new version of the ICF must be approved by the IRB/EC/REB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC/REB. The IRB/EC/REB will determine the subject population to be re-consented.

23. Committees

23.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Clinical Events Committee and Data Monitoring Committee will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information.

The BSC personnel from the Medical Safety and Safety Trial Operation Teams review safety data as it is reported by the sites throughout the duration of the study. The BSC Medical Safety group includes health care providers with expertise in Electrophysiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

23.2. *Clinical Events Committee*

A Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that will adjudicate events reported by study investigators and their relationship toward the primary endpoints.

- All Deaths

- All Adverse Events included in the composite primary safety endpoint per Section 8.2 of Protocol
- All Adverse Event that are potentially related to the procedure or any of the devices included in the POLARx Cardiac Cryoablation System
- All unanticipated device effects.
- Other events at the discretion of BSC

Committee members will include practitioners of Electrophysiology (EP), and/ or Cardiology, as well as other experts with the necessary therapeutic and subject matter expertise to adjudicate the event categories outlined above. A complete description of CEC responsibilities, qualifications, membership, and committee procedures will be outlined in the CEC charter.

The CEC will review a safety event dossier, prepared by BSC, which may include copies of subject source documents provided by study sites, core lab results and independent reviewer information as available for the above listed events. For purposes of determining inclusion into the primary safety endpoint, the CEC will adjudicate all the above listed events as to their level of seriousness and relation to the ablation procedure and/or catheter. The death classification system that will be used by the CEC was developed using the NASPE policy36, as well as definitions from Epstein et al. (15) and O'Connor et al. (16). All supporting source documentation provided by the center will be sent to the CEC for adjudication as defined in the CEC charter.

23.3. *Data Monitoring Committee*

A Data Monitoring Committee (DMC) is responsible for the oversight review of all AEs. The DMC will include leading experts in Electrophysiology and Biostatistics who are not participating in the study and who have no affiliation with BSC. During the course of the study, the DMC will review accumulating safety data to monitor the incidence of AEs sent to the CEC and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and DMC procedures will be included in the DMC Charter.

Any DMC recommendation for study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to BSC and the study Principal Investigator for consideration and final decision. If the DMC at any time determines that a potentially serious risk exists to subjects in this study, the DMC chairman will immediately notify both BSC and the Principal Investigator.

23.4. *Executive/ Steering Committee*

A Steering Committee composed of the sponsor's Clinical Management, the study Principal Investigator, other prominent Electrophysiologists from around the globe and a patient who underwent an electrophysiology procedure has been convened for this study. Responsibilities for the Committee include oversight of the overall conduct of the study with regards 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.

24. Suspension or Termination

24.1. *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 IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

24.1.1. Criteria for Premature Termination of the Study

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

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.
- Instructions by the IRB/EC/ REB or regulatory authorities to suspend or terminate the clinical investigation.
- 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 of the device.

24.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB Approval*

Any investigator, or associated IRB 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 IRBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

24.3. *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 IRB 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 IRB terminates participation in the study, participating investigators, associated IRB, 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 investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

24.4. *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 6 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 study 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 IRB and regulatory authorities, as applicable, will be notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

25. **Study Registration and Results Posting**

This research-study is registered on http://www.ClinicalTrials.gov, as required by U.S. Law and other jurisdictions.

25.1. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC/ REB and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable, an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

26. **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 may 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 trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

27. Reimbursement and Compensation for Subjects

27.1. *Subject Reimbursement*

Travel and other expenses incurred by subjects as a result of participation in the study may be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

27.2. *Compensation for Subject's Health Injury*

Boston Scientific will purchase an insurance policy to cover the cost of potential health injury for study subjects, if required by applicable law.

28. Bibliography

1. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A, Task Force on the Management of Valvular Hearth Disease of the European Society of Cardiology., and ESC Committee for Practice Guidelines. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J. 2007 Jan;28(2):230-68.
2. January, CT et al., 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American

Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64(21): e1-e76.

3. Lloyd-Jones, DM et al., Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010 Feb 2;121(4):586-613. doi: 10.1161/CIRCULATIONAHA.109.192703. Epub 2010 Jan 20.
4. Feinberg WM BJ, Laupacis A, et al. Prevalence, age distribution and gender in patients with atrial fibrillation; analysis and implications. Arch Intern Med. 1995;155: 469-473.
5. Friberg J BP, Scharling H. Rising rates of hospital admissions for atrial fibrillation. Epidemiology 2003;14 666-672.
6. Wolf PA BEaBA. Secular trends in the prevalence of atrial fibrillation: The framingham study. Am heart J 1996; 131:790-795.
7. Furburg CD PB, Manolio TA, et al. Prevalence of diagnosed atrial fibrillation in elderly subjects. Am J Cardiol. 1995; 74:236-241.
8. Piccini JP, Hammill BG, Sinner MF, et al. Incidence and Prevalence of Atrial Fibrillation and Associated Mortality Among Medicare Beneficiaries, 1993-2007. *Circulation Cardiovascular Quality and Outcomes*. 2012;5(1):85-93. doi:10.1161/CIRCOUTCOMES.111.962688.
9. Wann S CA, January C, et al. ACC/AHA/HRS focused update on the management of patients with atrial fibrillation (2011 writing group members) (updating the 2006 guideline): A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation. 2011; 123:104-123.
10. Fuster V RL, Cannom DS, et al. ACCF/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: Executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines and the European Society of Cardiology committee for practice guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): Developed in collaboration with the North American Society of Pacing and Electrophysiology. Circulation. 2006;114: e257-e354.
11. Wazni O, Wilkoff, B, Saliba, W. Catheter ablation for atrial fibrillation. New Engl J Med. 2011; 365:2296-2304.Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/ SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary: executive summary. Europace. 2018 Jan 1;20(1):157-208.
12. Packer D, Kowal R, Wheelan K, Irwin J, et al. Cryoballoon Ablation of Pulmonary Veins for paroxysmal Atrial Fibrillation. JACC, 2013;61:1713-23.
13. Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albeneque JP, Tondo C, for the FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial

fibrillation. N Engl J Med, 2016;374:2235–2245.Medtronic Press Release, “Clinical Trial to Evaluate Medtronic Cryoablation as First-Line Treatment for Patients with Symptomatic Paroxysmal Atrial Fibrillation”, July 11, 2017.

14. Epstein AE CM, Fogoros RN, et al. Classification of death in antiarrhythmia trials. J Am Coll Cardiol 1996; 27:433-442
15. O’Connor CM CP, Miller AB, et al. Effect of amlodipine on mode of death among patients with advanced heart failure in the praise trial. Am J Cardiol 1998; 82:881-887
16. Reference of the consensus document: Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. 2018 Europace.

29. Abbreviations and Definitions

29.1. *Abbreviations*

Abbreviations are shown in **Table 16**.

Table 16: Abbreviations

Abbreviation/Acronym	Term
AAD	Anti-Arrhythmic Drug
AF	Atrial Fibrillation
AFL	Atrial Flutter
AT	Atrial Tachycardia
CABG	Coronary artery bypass grafting
CRT	Cardiac Resynchronization Therapy
CVA	Cerebral Vascular Accident
DFU	Directions for Use
DMS	Diaphragm Movement Sensor
DVT	Deep Vein Thrombosis
EDC	Electronic Data Capture
EP	Electrophysiology
HRS	Heart Rhythm Society
IB	Investigator’s Brochure
ICB	Inter Connection Box
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
LA	Left Atrium
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
PAF	Paroxysmal Atrial Fibrillation
PE	Pulmonary Embolism

Abbreviation/Acronym	Term
PTCA	Percutaneous transluminal coronary angioplasty
PV	Pulmonary Veins
PVI	Pulmonary Vein Isolation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TEE	Trans-esophageal echocardiography
TIA	Transient Ischemic Attack

29.2. *Definitions*

Terms are defined in **Table 17**.

Table 17: 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, meets eligibility criteria 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 procedures 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 is eligible for enrollment and signs an informed consent document 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 30 days from consent signature date may not be reconsented and will be withdrawn from the study.
In-patient Hospitalization	Hospitalizations ≥24 hours in duration or <24 hours with medical intravenous therapy or surgical intervention

Term	Definition
Activated Coagulation/Clotting Time	ACT is a test that is used to monitor the effectiveness of high dose heparin therapy.
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
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 • Failure to achieve acute procedural success in the index procedure or repeat procedure during the blanking period • Use of amiodarone post index procedure • Surgical treatment for AF/AFL/AT post index procedure • Use of a non-study ablation catheter for AF targets in the index procedure or repeat procedure during the blanking period • More than one repeat procedure during the blanking period (90 days post procedure) • 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 any AAD
Acute Procedural Success	Rate of acute procedural success defined as the achievement of electrical isolation of all PVs by using the POLARx CardiacCryoablation system only. Electrical isolation of a PV is 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.

Term	Definition
Activated Coagulation/Clotting Time	ACT is a test that is used to monitor the effectiveness of high dose heparin therapy.
Pulmonary Vein Stenosis (Severe)	Severe PV stenosis is defined as ≥ 70% reduction in the diameter of the PV or PV branch from baseline measure. For this study a severe PV stenosis will count toward the primary safety endpoint.
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.
Source Data	All information in original records of clinical findings, observations, or other activities in a clinical investigation, 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

Term	Definition
Activated Coagulation/Clotting Time	ACT is a test that is used to monitor the effectiveness of high dose heparin therapy.
Treatment Subject	Any subject that signs the consent form, meets eligibility criteria 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.

30. **Appendices**

30.1. ***Indications for ablation of PAF according to 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation***

Indications	Recommendation	class	Level of Evidence
Symptomatic AF refractory or intolerant to at least one Class I or III antiarrhythmic medication	Paroxysmal: Catheter ablation is recommended.	I	A
Symptomatic AF prior to initiation of antiarrhythmic therapy with a Class I or III antiarrhythmic medication	Paroxysmal: Catheter ablation is reasonable	IIa	B-R

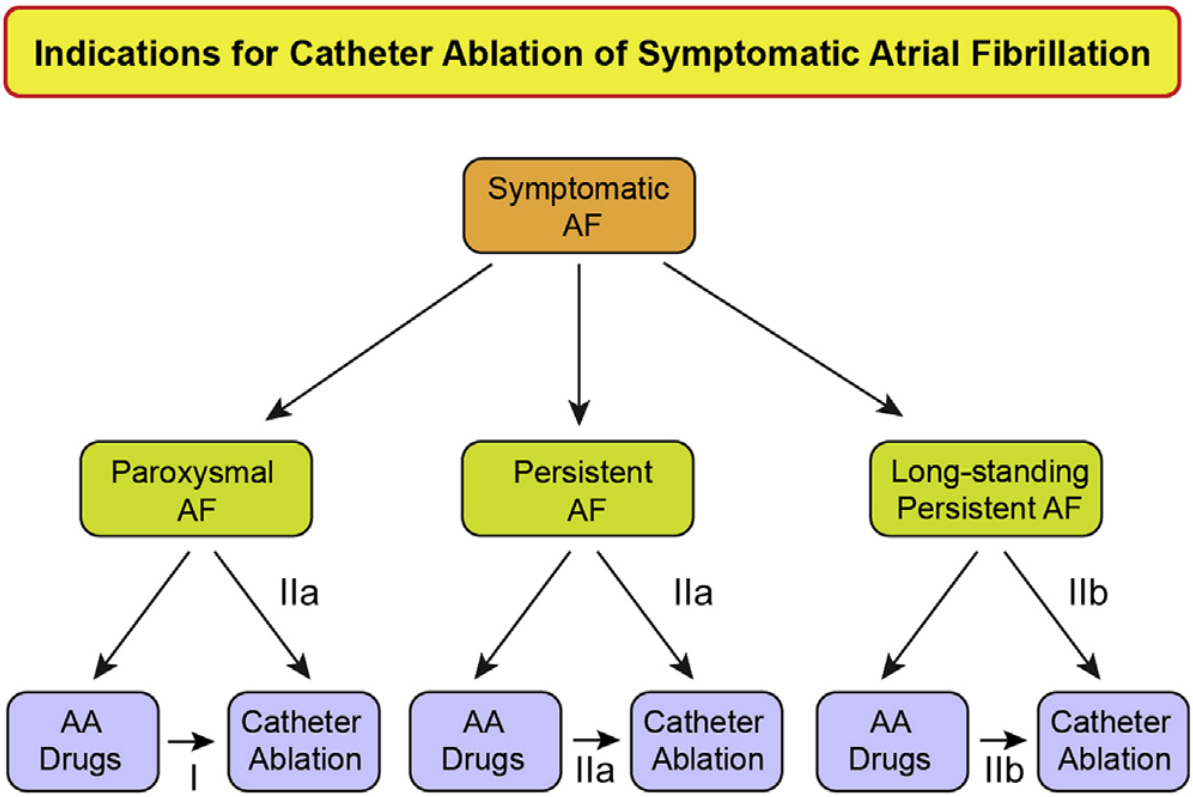


Figure 9: Indications for catheter ablation of symptomatic atrial fibrillation
Shown in this figure are the indications for catheter ablation of symptomatic paroxysmal, persistent, and long-standing persistent AF. The Class for each indication based on whether ablation is performed after failure of antiarrhythmic drug therapy or as first-line therapy is shown.

30.2. *Quality of Life Instruments*

Clinical trials increasingly recognize the value of including patient reported outcome measures in their design. To understand the impact of atrial fibrillation ablation procedures on patient's quality of life, the quality of life instruments used for the trial will be the EQ-5D-5L for a generic questionnaire and the AFEQT for disease specific. Subjects will be asked to complete the questionnaires at the Enrollment visit as well as at the three, six, and 12- month follow-ups.

The EQ-5D, generic quality of life measure, will be used to assess health utilities. It is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.

The Atrial Fibrillation Effect on Quality of Life (AFEQT) was developed to evaluate disease-specific quality of life for patients with atrial fibrillation. The 20-item questionnaire is subdivided into three domains: symptoms, daily activities, and treatment concerns with responses provided on a seven-point Likert scale.

30.3. *National Institutes of Health Stroke Assessment*

The NIH Stroke Scale (NIHSS) is an assessment tool which quantifies stroke related neurological deficit. This assessment must be conducted in person to provide valuable information on stroke severity.

An Investigator or appropriately trained and delegated site staff designee will administer NIH Stroke Scale assessment prior to the index ablation procedure (Baseline) and again at the pre-discharge visit (1-7 days post the ablation procedure). All individuals conducting the assessment will be required to become certified on administration of the assessment and provide BSC with documentation of certification prior to assessment completion with subjects.

Investigational sites will be provided with instructions for assessment completion for the test. They will be instructed to administer stroke scale items in the order listed on the form. Scores should reflect what the subject does, not what the clinician thinks the subject can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the subject should not be coached. If a worsening score is noted from the previous assessment, the Investigator must follow the additional requirements defined throughout Section 12.7.

30.4. *CHA_2DS_2-VASc Score for AF*

The CHA2DS2-VASc score is used for risk stratification of ischemic stroke in patients with nonvalvular atrial fibrillation.

	Condition	**Points**
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA or thromboembolism	2
V	Vascular disease (e.g. peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e. female sex)	1

30.5. ***POLARx FIT: FROzEN-AF Extension Study***

The Clinical Investigational Plan for the POLARx FIT: FROzEN-AF Extension Study will be provided under separate cover.

POLARx FIT: FROzEN-AF Extension Study

Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

CLINICAL INVESTIGATION PLAN

Appendix 30.5
(to Protocol 92348334 Rev I)

G190060

National Clinical Trial (NCT) Identified Number: NCT04133168

Sponsored By

Boston Scientific Corporation
4100 Hamline Ave. N.
St. Paul, MN 55112

and

Boston Scientific International S.A.
Le Val Saint-Quentin,
2 rue René Caudron,
78960 Voisins le Bretonneux, France

Contact Information

Role	Contact	
BSC Clinical Contact	**Clinical Trial Managers, Protocol Authors** Sheryl McCammon Clinical Trial Manager 4100 Hamline Ave. N. St. Paul, MN 55112 USA Tel. +1 (763) 647- 0113 Sheryl.McCammon@bsci.com Sarah Kenneweg Clinical Trial Manager 4100 Hamline Ave. N. St. Paul, MN 55112 USA Tel. +1 (510) 701- 1351 Sarah.kenneweg@bsci.com Elke Sommerijns Sr. Clinical Trial Manager Guidant Europe, a Boston Scientific Company Green Square, Lambroekstraat 5D 1831 Diegem Belgium Tel. +32 479 76 71 56 Elke.sommerijns@bsci.com	
Coordinating Principal Investigator(s)	Kenneth Ellenbogen, MD Kimmerling Professor of Cardiology Chair, Division of Cardiology VCU Pauley Heart Center Medical College of Virginia / VCU School of Medicine Gateway Building 1200E. Marshall Street 3rd Floor – Electrophysiology Division - Room 3-223 Richmond, Virginia 23219 Office (804) 828-7565 E-mail: kenneth.ellenbogen@vcuhealth.org	
Executive Steering Committee Members	Ante Anić, MD EP lab, Heart Center, University Hospital Split, Croatia	Robin Boisseau 9131 Stony Point Parkway Apt 3213 Richmond, VA 23235. Tel: (843) 860-9004 Email:

	A. Starcevica 25 D, 23000 Zadar, Croatia Telephone: +38523240605 Email: anteanic@gmail.com	Robin.Boisseau@vcuhealth.org
	Arash Aryana, MD, PhD, FACC, FHRS Medical Director, Cardiovascular Services Mercy General Hospital 3941 J Street, Suite #350 Sacramento, CA 95819 (916) 453 2684 E-mail: a_aryana@outlook.com	Nassir Marrouche, MD Tulane University School of Medicine Cardiology 1430 Tulane Avenue, Box 8548 New Orleans, LA 70112 (804) 988-2025 Email: Nmarrouche@tulane.edu
	Suneet Mittal, MD, FACC, FHRS Director, Electrophysiology Associate Chief of Cardiology Medical Director, Snyder AF Center Director, Cardiac Research 200 West 57th Street, Suite 610 New York, NY 10019 (212) HEART DR (432-7837) Email: MITTSU@Valleyhealth.com	Niraj Varma MD, PhD, FRCP Cardiac Pacing & Electrophysiology Department of Cardiovascular Medicine Cleveland Clinic 9500 Euclid Ave J2-2 Cleveland, OH 44195 (216) 444-2142 Email: varman@ccf.org
	Wilber W. Su, MD, FACC, FHRS Cardiology and Cardiac Electrophysiology Banner– University Medical Group- Heart Center 755 E. McDowell Rd, 4th Floor Phoenix, AZ 85006 (602) 521-3090 Email: wilwsu@gmail.com	This section is intentionally left blank.
Vendors/Labs/External Organizations	A list of vendors/laboratories/external organizations involved in the trial is maintained by the sponsor.	

Original Release: February 21, 2022

Current Version: February 21, 2022

Revision Version	Protocol Date	Template number and version	Protocol Section Modified	Summary of Changes	Justification for Modification
A	**February 23, 2022**	**90702637 Rev/Ver AP**	**NA-Initial Release**	**NA-Initial Release**	**NA-Initial Release**

2. Protocol Synopsis

POLARx FIT: FROzEN-AF Extension Study ***Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation*** **Appendix 30.5** **(to Protocol 92348334 Rev I)**	
Study Objective(s)	To establish the safety and effectiveness of Boston Scientific's POLARx Cryoablation System with the POLARx FIT catheter models for treatment of symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation (AF).
Planned Indication(s) for Use	The POLARx Cryoablation System is intended for cryoablation and electrical mapping of the pulmonary veins for pulmonary vein isolation (PVI) in the ablation treatment of patients with paroxysmal atrial fibrillation (PAF). Treatment will occur according to the approved indication for use within each geography and the defined inclusion/exclusion criteria within the protocol.
Test Device and sizes, if applicable	The individual devices within the Cryoablation system are as follows: • POLARx FIT™ Cryoablation Catheter (Cryoablation Catheter) • SMARTFREEZE™ Console (Console) • POLARMAP™ Catheter (Cryoablation Mapping Catheter) • POLARSHEATH™ Steerable Sheath (Cryoablation Steerable Sheath) • Diaphragm Movement Sensor (DMS) • Inter Connection Box (ICB) • Esophageal Temperature Sensor Cable • Other Cryoablation System Devices as listed in Section 7.1.7 POLARx FIT catheter models included in this trial allow treatment to be applied at either 28 mm or 31 mm balloon size per physician discretion. The POLARx Cryoablation Catheter models assessed in the FROzEN-AF study do not have the capability to increase their diameter to 31 mm balloon size.

POLARx FIT: FROzEN-AF Extension Study
Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

Appendix 30.5
(to Protocol 92348334 Rev I)

Control Device and device sizes, if applicable	There are no control devices in this extension study.
Study Design	Multi-center, open label, prospective, single arm study to document the safety and performance of Boston Scientific's Cryoablation System with the POLARx FIT catheter models. All subjects fitting the enrollment criteria, signing the consent and undergoing the index procedure with the study devices will be followed up for twelve months after the index procedure. Due to the similarities between the POLARx and POLARx FIT catheters, the safety and effectiveness data from subjects treated with POLARx ("FROZEN-AF subjects") may be pooled with the safety and effectiveness data from subjects treated with POLARx FIT catheter models ("POLARx FIT subjects"). The data will be submitted for product approvals once 3 months of follow-up data is available for POLARx FIT subjects.
Planned Number of Subjects	A maximum of 75 subjects will be enrolled and treated with the POLARx FIT balloon size at 31 or 28 mm (based on clinical judgement) to achieve 50 subjects in the 31 mm TREATMENT group (subjects who receive at least one cryoablation applied at the 31 mm configuration).
Planned Number of Investigational Sites / Countries	Up to 20 sites in North America may participate in this study. To reduce the impact of individual center bias, each site participating in the extension study will enroll and treat a maximum of 18 subjects with cryoablation applied at the 31 mm configuration.
Primary Safety Endpoint	**Primary Safety Endpoint at 3 Months** The primary safety endpoint at 3 months is defined as the safety event-free rate at 3 months post-procedure.

POLARx FIT: FROzEN-AF Extension Study
Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

Appendix 30.5
(to Protocol 92348334 Rev I)

	Primary safety events at 3 months will consist of a composite of the following procedure-related and/or device-related adverse events. Events through 7 days post index procedure or hospital discharge, whichever is later, unless denoted as events counting through 3 months post index procedure. • Death • Myocardial infarction (MI) • Major Vagal Nerve Injury/Gastroparesis • Transient ischemic attack (TIA) • Stroke/Cerebrovascular accident (CVA) • Thromboembolism • Cardiac tamponade/perforation* • Pneumothorax • Major vascular access complications • Pulmonary edema/heart failure • AV block** • Atrial esophageal fistula** • Severe pulmonary vein stenosis (≥70% reduction in the diameter of the PV or PV branch from baseline)*** • Persistent phrenic nerve palsy **** *Cardiac tamponade/perforation occurring up to 30 days post-index-procedure will count as primary safety endpoint events. **AV block not attributable to medication effect or vasovagal reaction. ***Atrial esophageal fistula and severe pulmonary vein stenosis occurring up to 3 months post-index-procedure will count as primary safety endpoint events. ****Phrenic nerve palsy not resolved at the end of the 3 months follow up will count as primary safety endpoint event.
Secondary Safety Endpoint	**Secondary Safety Endpoint at 12 Months** The secondary safety endpoint at 12 months is defined as the safety event-free rate at 12 months post-procedure. Secondary safety events at 12 months will consist of a composite of the following procedure-related and/or device-related adverse events.

POLARx FIT: FROzEN-AF Extension Study
Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

Appendix 30.5
(to Protocol 92348334 Rev I)

	The following events will be counted through 7 days post index procedure or hospital discharge, whichever is later: • Death • Myocardial infarction (MI) • Major Vagal Nerve Injury/Gastroparesis • Transient ischemic attack (TIA) • Stroke/Cerebrovascular accident (CVA) • Thromboembolism • Pneumothorax • Major vascular access complications • Pulmonary edema/heart failure • AV block* The following events will be counted through 30 days post index procedure: • Cardiac tamponade/perforation And the following events will be counted through 12 months post index procedure: • Atrial esophageal fistula • Severe pulmonary vein stenosis (≥70% reduction in the diameter of the PV or PV branch from baseline) • Persistent phrenic nerve palsy** * AV block not attributable to medication effect or vasovagal reaction. **A non-recovered phrenic nerve palsy at 12 months occurring post index procedure will count toward the endpoint. The study will collect information on phrenic nerve palsy observed before the end of the index procedure and, in case of occurrence, will track information for potential recovery during the study visits.
Tertiary Safety Endpoint	Reportable Adverse Events rates at 12 months. Adverse events will be collected at all subject follow-up visits. Reportable events include: • All Serious Adverse Events • All Study Procedure-Related Adverse Events

POLARx FIT: FROzEN-AF Extension Study
Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

Appendix 30.5
(to Protocol 92348334 Rev I)

	• All Study Device-Related Adverse Events • All Study Device Deficiencies • Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in IFU
Primary Effectiveness Endpoint	Rate of acute procedural success defined as the achievement of electrical isolation of all PVs by using the POLARx Cardiac Cryoablation System with the POLARx FIT cryoablation balloon catheter models (with treatment applied at 28 mm or 31 mm balloon size per physician discretion). Electrical isolation of a PV is demonstrated by entrance and exit block.
Secondary Effectiveness Endpoint	Failure free rate at 12 months post procedure. *Failure defined as:* • Failure to achieve acute procedural success in the index procedure or repeat procedure during the blanking period • Use of amiodarone post index procedure • Surgical treatment for AF/AFL/AT post index procedure • Use of a non-study ablation catheter for AF targets in the index procedure or repeat procedure during the blanking period • More than one repeat procedure with the Cryoablation System during the blanking period (90 days post index procedure) • Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia event [≥ 30 seconds in duration from the study specific event monitor, Holter Monitor, or from a 10 second 12-lead Electrocardiography (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 days 91 post index procedure and 365 days: • Repeat procedure • Electrical and/or pharmacological cardioversion for AF/AFL/AT • Prescribed any antiarrhythmic drug (AAD)*

POLARx FIT: FROzEN-AF Extension Study
Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

Appendix 30.5
(to Protocol 92348334 Rev I)

	*AADs for endpoint will consist of all Class I/III, including Amiodarone, and any Class II/IV medications taken for control of atrial fibrillation (AF)/Atrial tachycardia (AT)/Atrial flutter (AFL) recurrence
Additional Endpoints	Additional endpoints and analysis include, but are not limited to: • Changes in the quality-of-life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up • Single procedure success, defined as freedom from failure at 12 months post procedure as defined in the secondary effectiveness endpoint without a repeat procedure • Duration of LA dwell time, defined as time from the Cryoablation Catheter exiting the sheath in the LA to time of final PV isolation • Total Cryoablation time for the index procedure • Total fluoroscopy time for the index procedure • Total index procedure time • Freedom from recurrence of individual types of atrial arrhythmias between 91 and 365 days from index procedure: 1) AF 2) AT 3) AFL • Failure- free rate as defined in secondary effectiveness endpoint when considering AF/AT/AFL episodes reported to the investigators by study specific (event recorder transmissions, 12 lead ECG and Holter) and non-study related devices (other commercial applications for arrhythmia monitoring and detection the subject may access during the study including telemetry, other sources of continuous recording etc.)
Method of Assigning Patients to Treatment	Any subject that signs the consent form, meets eligibility criteria, has the study device inserted into the body and receives Cryoablation therapy with the Cryoablation System with the POLARx FIT cryoablation balloon catheters will be assigned to the TREATMENT group. The disposition of all subjects enrolled in the study will be described in tables and diagrams. The data will include number of subjects screened, subjects that fail screening, subjects treated and assessed at

POLARx FIT: FROzEN-AF Extension Study
Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

Appendix 30.5
(to Protocol 92348334 Rev I)

	each follow-up interval. Subjects who fail screening, or who do not complete the study will be enumerated and the reason(s) for their screening failure or discontinuation from the study will be described.
Follow-up Schedule	Visit schedule: pre-discharge, Day 7, 3 months (blanking period), 6 months, 12 months.
Study Duration	Enrollment is expected to be completed in approximately 5 months; therefore the total sub-study duration is estimated to be approximately 17 months.
Participant Duration	The study duration for each subject is expected to be approximately 12 months.
Inclusion Criteria	• History of recurrent symptomatic paroxysmal atrial fibrillation (PAF), defined as atrial fibrillation that terminates spontaneously or with intervention (either procedure or drug therapy) within seven days of onset. Minimum documentation includes the following: o a physician's note indicating recurrent self-terminating atrial fibrillation (AF) which includes at least two symptomatic AF episodes within six months prior to enrollment, and o one electrocardiographically documented AF episode within 12 months prior to enrollment. • No amiodarone use within 90 days prior to enrollment • Subjects who are indicated for an ablation procedure for paroxysmal atrial fibrillation (PAF) according to 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation • Subjects refractory or intolerant to at least one class I or III antiarrhythmic medication or contraindicated to any class I or III medications

POLARx FIT: FROzEN-AF Extension Study
Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

Appendix 30.5
(to Protocol 92348334 Rev I)

	• Subjects who are willing and capable of providing informed consent • Subjects who are willing and capable of participating in all testing associated with this clinical investigation at an approved clinical investigational center • 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	• Any known contraindication to an AF ablation or anticoagulation • Continuous AF lasting longer than seven (7) days from onset • History of previous left atrial ablation or surgical treatment for AF/ AFL/ AT • Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause • Structural heart disease or implanted devices as described below: a. Left ventricular ejection fraction (LVEF) < 40% based on most recent transthoracic echocardiogram (TTE) performed ≤180 days prior to enrollment * b. Left atrial diameter > 5.5 cm OR left atrial volume > 50 ml/m2 indexed based on the most recent TTE performed ≤ 180 days prior to enrollment * c. An implanted pacemaker, ICD, CRT device or an active arrhythmia loop recorder d. Previous cardiac surgery: i.e. ventriculotomy or atriotomy (excluding atriotomy for CABG) e. Previous cardiac valvular surgical or percutaneous procedure, or prosthetic valve, including mitral valve clips f. Interatrial baffle, closure device, patch, or patent foramen ovale (PFO) occluder

POLARx FIT: FROzEN-AF Extension Study
Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

Appendix 30.5
(to Protocol 92348334 Rev I)

	g. Presence of a left atrial appendage occlusion device h. Presence of any pulmonary vein stents i. Coronary artery bypass graft (CABG), PTCA/ PCI/ coronary stent procedures within 90 days prior to enrollment j. Unstable angina or ongoing myocardial ischemia k. Myocardial infarction within 90 days prior to enrollment l. Moderate or severe mitral stenosis [severity assessed on the most recent TTE ≤180 days prior to enrollment as pulmonary artery systolic pressure >30 mmHg (1)] m. Evidence of left atrial thrombus** • Any previous history of cryoglobulinemia • Stage 3B or higher renal disease (estimated glomerular filtration rate, eGFR <45 mL/min) • History of blood clotting or bleeding disease • Any prior history of documented cerebral infarct, TIA or systemic embolism [excluding a post-operative deep vein thrombosis (DVT)] ≤180 days prior to enrollment • Active systemic infection • Pregnant, lactating (current or anticipated during study follow up), or women of childbearing potential who are, or plan to become, pregnant during the time of the study (method of assessment upon physician's discretion) • 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

POLARx FIT: FROzEN-AF Extension Study
Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

Appendix 30.5
(to Protocol 92348334 Rev I)

	• Subjects who in the judgment of the investigator have a life expectancy of less than two years **LVEF and LA diameters obtained ≤180 days prior to enrollment will be acceptable, unless a cardiac event has occurred (e.g. MI) between the date of the exam and the enrollment date, otherwise a new echocardiogram (trans-thoracic or trans-esophageal, or intracardiac echo) must be performed to confirm eligibility prior to performing ablation. For TTE, LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used. If both LA diameter and volume are available, only one meeting eligibility criteria is required.* ***The absence of thrombus must be confirmed by means of a trans-esophageal echocardiogram (TEE) within 48 hours prior to the procedure or Intracardiac Echography (ICE) during the procedure in subjects not adequately anticoagulated (see Section 12.5.2) for at least 3 weeks prior to procedure OR with CHA_2DS_2-VASc score (see Appendix 27.4) ≥2 in men and ≥3 in women OR enlarged LA (≥4.5cm). If a thrombus is observed, the subject no longer meets eligibility criteria. When screening for thrombus prior to the index procedure, ensure that the anticoagulation approach as described in Section 12.5.2 is followed until the day of the procedure.*
Arrhythmia Monitoring Strategy	This study will employ a rhythm surveillance monitoring strategy consistent with the recommendations in the 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation. A wearable arrhythmia/event monitor (e.g. Trans-Telephonic Monitor-TTM) will be used to assess atrial arrhythmia recurrence (including unscheduled visits for symptomatic atrial arrhythmias and 24-hour Holter monitoring at 12 months follow up). Subjects will be instructed to transmit all symptomatic episodes for detection and treatment of early recurrences. At least two transmissions every month are to be made. All TREATMENT subjects will be provided with 24-Hour Holter Monitors at the 12-month follow-up visit. Core lab will be utilized for reviewing electrocardiographic recordings from the surveillance monitoring, inclusive of data from the wearable arrhythmia/event monitors and in-hospital ECGs.

POLARx FIT: FROzEN-AF Extension Study
Safety and Effectiveness IDE trial for Boston Scientific's Cryoballoon in the Treatment of Symptomatic Drug Refractory Paroxysmal Atrial Fibrillation

Appendix 30.5
(to Protocol 92348334 Rev I)

Statistical Methods	
Primary Statistical Hypothesis	Statistical considerations were not utilized in the design of this extension study and no statistical hypothesis was defined. Analysis of the primary endpoints for submission to FDA will occur after 3 months of follow-up data is available for POLARx FIT subjects. Analysis of each endpoint will be performed when all applicable data for that endpoint has been collected.
Statistical Test Method	Analysis of study data will use descriptive statistical methods.
Sample Size Parameters	No power estimates were used to drive sample size calculations.

3. Table of Contents

4. Table of Figures

5. Table of Tables

6. Introduction

6.1. *Background*

Atrial fibrillation (AF) is the most commonly encountered sustained cardiac arrhythmia in clinical practice (2). 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 (3). It currently affects approximately 2.3 million people in North America (4). 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 (5,6,7). Among Medicare beneficiaries, incident AF is common and increases as individuals age with incidence rates per 1,000 person-years reported at ages 70-74 of 18.8, increasing to 28.8 for persons 75-79 and 38.3 for persons 80-84. Similarly, the overall prevalence among Medicare beneficiaries age 70-74 is about 6% increasing to over 13% for individuals 80 years of age and older (8).

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

There are multiple therapies in current use for the treatment of AF; however, it is recognized that many of these therapies are suboptimal for most patients. Treatment options include medical management, pacing, cardioversion, implantable devices, surgery, and ablation therapy to eliminate the arrhythmia (9,10,11). 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, 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.

Two studies have been completed with the currently approved cryoablation technology (Arctic Front™/ Arctic Front Advance™ Cryoablation Balloon, Medtronic®) 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.

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 with the POLARx cryoablation system was completed in 2018 and the system obtained CE-mark in 2020. The POLARx cryoablation system is currently commercially available in Europe / Middle East, Australia / New Zealand, Japan, and other select countries.

Good occlusion of the pulmonary vein and intimate contact between the balloon and atrial tissue are critical for successful pulmonary vein isolation with cryoablation.

Despite the clinical effectiveness of the standard 28 mm diameter cryoballoon (both POLARx and Arctic Front Advance balloons are 28 mm), physicians have consistently communicated a desire for a larger diameter balloon to improve occlusion in a variety of clinical scenarios (15, 16).

BSC has developed POLARx FIT which gives users the capability to increase the balloon diameter of POLARx from 28 mm to 31 mm on demand. The FIT feature is available on POLARx FIT catheter models. This additional capability has been developed without any physical changes to the POLARx catheter or SMARTFREEZE console and without sacrificing existing capabilities of the POLARx Cryoablation System studied in FROzEN-AF.

6.2. *Study Rationale*

The data of up to 75 subjects who will undergo treatment with the Boston Scientific Cryoablation System for de-novo PAF will be evaluated in this extension study of FROzEN-AF.

This extension study is a prospective, non-randomized, multi-center, investigation being conducted to establish the safety and effectiveness of Boston Scientific's POLARx Cryoablation System with the POLARx FIT catheter models in subjects with symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation. The aim of the trial is to collect data with the POLARx Cryoablation System using the POLARx FIT catheter models with treatment applied at 28 mm or 31 mm balloon size per physician discretion. This study seeks to obtain approval for the Boston Scientific Cryoablation System with the POLARx FIT catheter models in North America.

7. Device Description

7.1. *Boston Scientific Cardiac Cryoablation System*

The Boston Scientific Cardiac Cryoablation System (henceforth "Cryoablation System") is intended for treatment of symptomatic, drug refractory, recurrent, paroxysmal AF. The individual devices within the Cryoablation system and their associated model numbers to be used in this extension study of FROzEN-AF are listed in Table 1. The individual devices listed in Table 1 must be used together and it is not allowed to combine investigational with non-investigational devices.

Treatment will occur according to the approved indication for use and the defined inclusion/exclusion criteria within the protocol. A copy of the IFU will be provided in local language as required per national regulations.

This extension study of FROzEN-AF will be conducted as a pre-market study in the US.

Table 1: Cryoablation System

Individual Devices within the System	Model Number
POLARx FIT™ Cryoablation Catheter (Cryoablation Catheter)	2315 (Short tip and long tip)
SMARTFREEZE™ Console (Console)	2314
POLARMAP™ Catheter (Cryoablation Mapping Catheter)	2317 (20mm)
POLARSHEATH™ Steerable Sheath (Cryoablation Steerable Sheath)	2316
Diaphragm Movement Sensor (DMS)	2314
Inter Connection Box (ICB)	2314
Esophageal Temperature Sensor Cable	2314
Cryoablation -Console Foot Switch	2314
Cryoablation -Cable	2318
Cryoablation -Catheter Extension Cable	2319
Cryoablation Mapping Catheter EP Electrical Cable	2320

7.1.1. POLARx FIT Cryoablation Catheters

The POLARx FIT Cryoablation Catheters are additional models (Short Tip and Long Tip) of the POLARx cryoablation balloon catheters that are part of the POLARx cryoablation system being investigated in this extension study.

The POLARx FIT catheter models are physically identical to the POLARx models (used in the FROzEN-AF study) and differ only in the model number programmed into the EEPROM (i.e. electronic identifier) of the catheter.

Identical to the POLARx Cryoablation Catheter, the POLARx FIT catheter is a single use, flexible, over-the-wire balloon catheter used to ablate cardiac tissue. The POLARx FIT 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 FIT. The Cryoablation catheter connects to the Console with a Cryoablation Cable (for N2O delivery and removal) and an Extension Cable (for electrical connection via the Interconnection Box). The Cryoablation catheter is designed to be used with a Cryoablation Mapping Catheter circular mapping catheter deployed within the guidewire lumen during ablation procedures.

During an electrophysiology (EP) ablation procedure, the Cryoablation catheter (including the Cryoablation Mapping Catheter) is inserted through the Cryoablation Steerable Sheath 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 Cryoablation 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: POLARx FIT Cryoablation Catheter Distal Tip

Figure 2: POLARx FIT Cryoablation Catheter Handle

Table 2: POLARx FIT Cryoablation Catheter Specifications

Catheter Shaft Size	11.8 Fr	
Catheter Overall Length	134 cm	
Catheter Tip Outer Diameter (OD)	9 Fr	
Compatible Introducer Sheath	Compatible with POLARSHEATH Sheath 12F Steerable Sheath	
Guidewire Lumen Inner Diameter (ID)	Compatible with POLARMAP Mapping Catheter and guidewires ≤ 0.035	
Inflated Balloon Dimensions	Diameter	28/31 mm
	Catheter Effective Length	99 cm
	Short Tip	5 mm
	Long Tip	12 mm
Thermocouples	Internal to Balloon	
Environmental Parameters	Storage	15°C to 25°C (59°F to 77°F)
	Transit	-30°C to 60°C (-22°F to 140°F) 15% to 90% relative humidity
	Operation	15°C to 30°C (59°F to 86°F)

*The POLARx Cryoablation Catheter models assessed in the FROzEN-AF study do not have the capability to increase their diameter to 31 mm balloon size.

7.1.2. POLARMAP Cryoablation Mapping Catheter

This section identically matches the Cryoablation Mapping Catheter Section (Section 5.1.2) of the FROzEN-AF protocol (92348334).

The POLARMAP Cryoablation Mapping Catheter is a single-use, sterile, multi-electrode, diagnostic catheter designed to map cardiac signals during ablation procedures. The catheter is 20mm in 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 Cryoablation Mapping Catheter also allows for delivery of pacing stimuli used in the interpretation of PV isolation (PVI).

Figure 3: POLARMAP Cryoablation Mapping Catheter Assembly

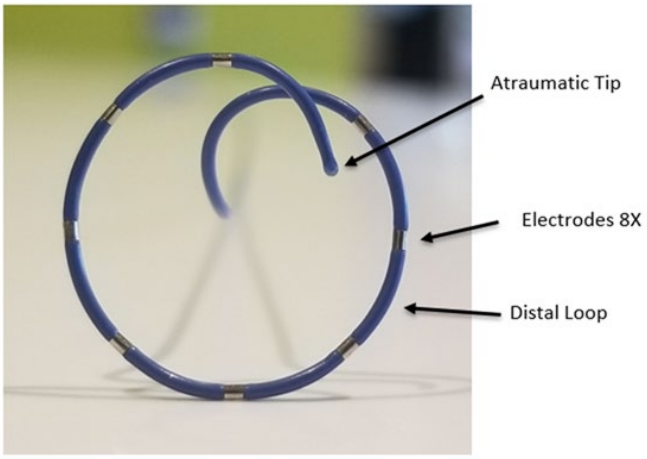


Figure 4: POLARMAP Cryoablation Mapping Catheter with Electrode Arrangements

Table 3: POLARMAP Cryoablation Mapping Catheter Specifications

POLARMAP Shaft Size	3.3 Fr (1.1 mm or 0.043 inches)	
Compatible Mating Device Minimum Internal Diameter	3.4 Fr. (1.2 mm or 0.044 inches)	
Loop Diameter	20 mm (0.79 inches)	
POLAR Shaft Length	Overall 166: cm	
	Effective: 149 cm	
Electrodes	8 electrodes	
Electrode Size	1 mm	
Electrode Spacing	6 mm	
Environmental Parameters	Storage	15°C to 25°C (59°F to 77°F)
	Transit	-30°C to 60°C (-22°F to 140°F) 15% to 90% relative humidity
	Operation	15°C to 30°C (59°F to 86°F)

7.1.3. POLARSHEATH Cryoablation Steerable Sheath

This section identically matches the Cryoablation Steerable Sheath Section (Section 5.1.3) of the FROzEN-AF protocol (92348334).

The POLARSHEATH Cryoablation 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 Cryoablation 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 4: POLARSHEATH Cryoablation Steerable Sheath Specifications

Sheath Overall Length	82 cm (32.3 in)	
Sheath Usable Length	68 cm (26.8 in)	
Sheath Inner Diameter	12.7 Fr	
Sheath Outer Diameter	15.9 Fr	
Usable Dilator Length	85 cm (33.5 in)	
Radiopaque Markers	2.5mm proximal to sheath tip	
Guidewire Compatibility	0.81 mm (0.032 in) and 0.89 mm (0.035 in)	
Environmental Parameters	Storage	15° C to 25° C (59° F to 77° F)
	Transit	-30° C to 60° C (-22° F to 140° F) 15% to 90% relative humidity
	Operation	15° C to 30° C (59° F to 86° F)

7.1.4. SMARTFREEZE Cryoablation System Console

The SMARTFREEZE Cryoablation System 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 and 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: SMARTFREEZE Cryoablation System Console

Integration between the Cryoablation Catheter and the Console includes monitoring catheter as well as console functionality, aided by a number of accessory devices that make up the overall system such as: power cords, extension cables, connection box, foot switch, diaphragmatic movement sensor, esophageal temperature sensor cable. In addition, the system incorporates a number of non-medical device items such as a scavenging hose, wrench, and nitrous oxide tank.

When connected to a SMARTFREEZE Cryoablation System Console the new EEPROM number in the POLARx FIT catheter makes the "FIT" feature button available in the user interface. This feature lets users increase the balloon diameter from 28 mm to 31 mm if desired. The FIT feature has been incorporated as an optional-use tool within the existing POLARx workflow. The system always first inflates the balloon to the standard diameter of 28 mm. Following inflation, the system will increase the balloon diameter to 31 mm when the FIT button is pressed. During the cryoablation application, the SMARTFREEZE system delivers the same freezing power to both the standard and larger diameter balloons (as demonstrated by equivalent temperature on the balloon surface). The balloon diameter will return to the standard 28 mm upon the next inflation. For ablations using the POLARx FIT catheter with the balloon inflated to the standard diameter, the POLARx Cryoablation System is physically, functionally, and operationally identical to that currently used in the FROzEN-AF study.

7.1.5. Diaphragm Movement Sensor

This section identically matches the Diaphragm Movement Sensor Section (Section 5.1.5) of the FROzEN-AF protocol (92348334).

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 Cryoablation 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 patient's chest and assess the patient'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 phrenic nerve injury ranges from 2.7% - 11.2% 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 Cryoablation Console and sends data to be displayed on the Cryoablation Console's user interface (see Figure 6).

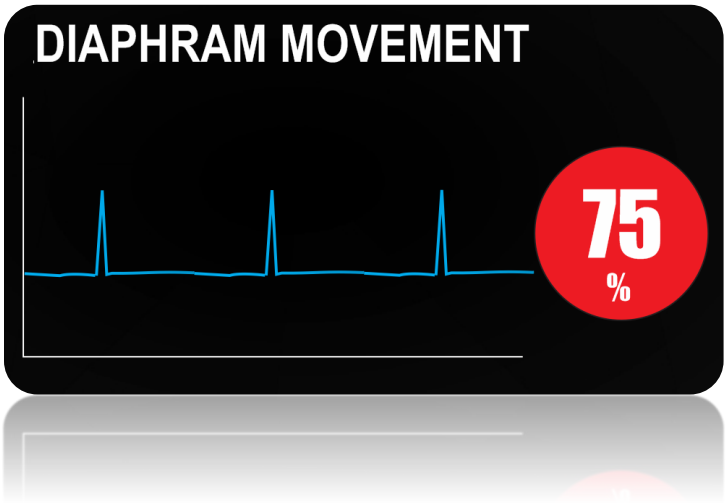


Figure 6: Diaphragm Movement Sensor (DMS) Data Cryoablation Console Display Phrenic Nerve Pacing Signal & Alert

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 a 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.

7.1.6. Esophageal Temperature Sensor Cable

Esophageal temperature monitoring is a frequently used technique; used more so 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 incidence of esophageal ulceration is generally reversible, with a reported incidence of 17% of patients.

As noted above, 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 **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. Multisensor

probes and CIRCA S-CATH™ esophageal temperature probes are not compatible with the POLARx Cryoablation System and are therefore not permitted under this protocol.

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 (see Figure 7 below). This feature potentially reduces adverse events such as esophageal ulcerations and fistulas. This is a redundant safety alert system to the measurement systems used today although the alert is now displayed on the Console.

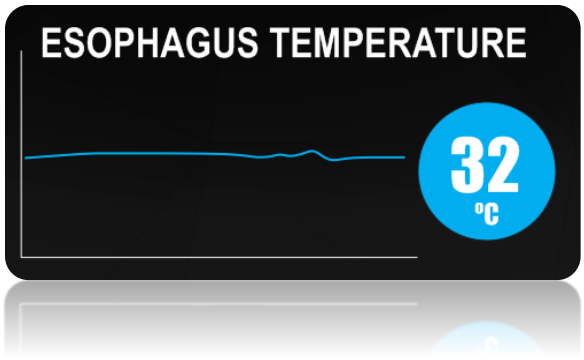


Figure 7: Esophagus Temperature Monitoring Data Display

7.1.7. Other Cryoablation System Devices

This section identically matches the Other Cryoablation System Devices Section (Section 5.1.7) of the FROzEN-AF protocol (92348334).

3.1.1.1.Inter Connection Box

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.

3.1.1.2.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.

3.1.1.3.Cryoablation Cable

The Cryoablation 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.

3.1.1.4.Cryoablation Catheter Extension Cable

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

3.1.1.5.Cryoablation Mapping Catheter EP Electrical Cable

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

7.2. *Intended Use and Contraindications*

This section identically matches the Intended Use and Contraindications Section (Section 5.2) of the FROzEN-AF protocol (92348334), with the exception that the Cryoablation Catheter referenced in this protocol is the POLARx FIT Cryoablation Catheter.

The Cryoablation System is intended for treatment of symptomatic, drug refractory, recurrent, paroxysmal AF.

7.2.1. POLARx FIT Cryoablation Catheter

The POLARx FIT Cryoablation Catheter is a single use, flexible, over-the wire balloon catheter intended to ablate cardiac tissue.

Use of the Cryoablation Catheter is contraindicated as follows:

- In patients with an active systemic infection, as this may increase the risk for endocarditis and sepsis.
- In patients with a myxoma or an intracardiac thrombus, as the catheter could precipitate an embolic event.
- In patients with a prosthetic valve (mechanical or tissue)
- In the ventricle of the heart where the device may become entrapped in a valve or chordae structures.
- In patients with a recent ventriculotomy or atriotomy, as this may increase the risk of cardiac perforation or embolic event.
- In patients with pulmonary vein stents, as the catheter may dislodge or damage the stent.
- In patients with cryoglobulinemia, as the cryoablation application may lead to vascular injury.
- In conditions where insertion into or manipulation in the atrium is unsafe, as this may increase the risk of perforation or systemic embolic event.

- In patients with intra-atrial septal patch or surgical intervention in or adjacent to the intra-atrial septum.
- In patients with an interatrial baffle or patch, as the transseptal puncture could fail to close.
- In patients with hypercoagulopathy or an inability to tolerate anticoagulation therapy during an electrophysiology procedure
- In patients with a contraindication to an invasive electrophysiology procedure where insertion or manipulation of a catheter in the cardiac chambers is deemed unsafe.

7.2.2. POLARMAP Cryoablation Mapping Catheter

This section identically matches the Cryoablation Mapping Catheter Section (Section 5.2.2) of the FROzEN-AF protocol (92348334).

During an ablation procedure when PVs are isolated, the Cryoablation Mapping Catheter is intended to obtain electrograms and provide pacing in cardiac structures in the atrial regions of the heart.

Use of the POLARMAP Mapping Catheter is contraindicated as follows:

- In patients with an active systemic infection as this may increase the risk for endocarditis and sepsis.
- In patients with a myxoma or an intracardiac thrombus as the catheter could precipitate an embolic event.
- In patients with a prosthetic heart valve (mechanical or tissue).
- In the ventricle of the heart where the device may become entrapped in a valve or chordae structures.
- In patients with a recent ventriculotomy or atriotomy as this may increase the risk of cardiac perforation or embolic event.
- In patients with pulmonary vein stents as the catheter may dislodge or damage the stent.
- In patients with cryoglobulinemia as the cryoablation application may lead to vascular injury.
- In conditions where insertion into or manipulation in the atrium is unsafe as this may increase the risk of perforation or systemic embolic event.
- In patients with intra-atrial septal patch or other surgical intervention in or adjacent to the intra-atrial septum.
- In patients with a contraindication to an invasive EP procedure where insertion or manipulation of a catheter in the cardiac chambers is deemed unsafe.

7.2.3. POLARSHEATH Cryoablation Steerable Sheath

This section identically matches the Cryoablation Steerable Sheath Section (Section 5.2.3) of the FROzEN-AF protocol (92348334).

The Cryoablation Steerable Sheath is intended to facilitate the placement of diagnostic and/ or therapeutic intracardiac devices during percutaneous catheter ablation procedures. The sheath deflection facilitates catheter positioning.
Use of the POLARSHEATH is contraindicated as follows:

- In patients with an active systemic infection as this may increase the risk for endocarditis and sepsis.
- In patients where vascular access is unobtainable, or the femoral vein is known to be obstructed.
- In conditions where insertion into or manipulation in the atrium is unsafe as this may increase the risk of perforation or systemic embolic event.
- In the ventricle of the heart where the device may become entrapped in a valve or chordae structures.
- In patients with a prosthetic heart valve (mechanical or tissue)
- In patients with a recent ventriculotomy or atriotomy as this may increase the risk of cardiac perforation or embolic event.
- In patients with pulmonary vein stents as the sheath may dislodge or damage the stent.
- In patients with an interatrial baffle or patch as the transseptal puncture could fail to close.
- In patients with hypercoagulopathy or an inability to tolerate anticoagulation therapy during an electrophysiology procedure.
- In patients with a contraindication to an invasive electrophysiology procedure where insertion or manipulation of a catheter in the cardiac chambers is deemed unsafe.

7.2.4. SMARTFREEZE Cryoablation System Console

This section identically matches the Console Section (Section 5.2.4) of the FROzEN-AF protocol (92348334).

The SMARTFREEZE Cryoablation System Console is a component of the Cryoablation System which is intended for cryoablation and electrical mapping of the pulmonary veins for pulmonary vein isolation (PVI) in the ablation treatment of paroxysmal atrial fibrillation.

Use of the SMARTFREEZE Cryoablation System is contraindicated as follows:

- In patients with an active systemic infection as this may increase the risk for endocarditis and sepsis.
- In patients with a prosthetic valve (mechanical or tissue)
- In patients with a myxoma or an intracardiac thrombus as the catheter could precipitate an embolic event.
- In the ventricle of the heart where the device may become entrapped in the valve or chordae structures.
- In patients with a recent ventriculostomy or atriotomy because this may increase the risk of cardiac perforation or embolic event.
- In patients with pulmonary vein stents as the catheter may dislodge or damage the stent.

- In patients with cryoglobulinemia as the application of cryogenic energy may lead to vascular injury.
- In conditions where insertion into or manipulation in the atria is unsafe as this may increase the risk of perforation or systemic embolic event.
- In patients with an interatrial baffle or patch as the transseptal puncture could fail to close.
- In patients with hyper-coagulopathy or an inability to tolerate anticoagulation therapy during an electrophysiology procedure.
- In patients with a contraindication to an invasive electrophysiology procedure where insertion or manipulation of a catheter in the cardiac chambers is deemed unsafe.

8. Study Objectives and Endpoints

A complete overview of objectives and endpoints is provided in Table 6.

8.1. *Study Objective*

To establish the safety and effectiveness of Boston Scientific's Cryoablation System with the POLARx FIT catheter models for treatment of symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation (AF).

8.2. *Primary Safety Endpoint*

The primary safety endpoint at 3 months is defined as the safety event-free rate at 3 months post-procedure.

Primary safety events at 3 months will consist of a composite of the following procedure-related and/or device-related adverse events.

Events will be counted through 7 days post index procedure or hospital discharge, whichever is later, unless denoted as events counting through 3 months post index procedure.

- Death
- Myocardial infarction (MI)
- Major Vagal Nerve Injury/Gastroparesis
- Transient ischemic attack (TIA)
- Stroke/Cerebrovascular accident (CVA)
- Thromboembolism
- Cardiac tamponade/perforation*
- Pneumothorax
- Major vascular access complications
- Pulmonary edema/heart failure
- AV block**
- Atrial esophageal fistula***
- Severe pulmonary vein stenosis (≥70% reduction in the diameter of the PV or PV branch from baseline)***
- Persistent phrenic nerve palsy ****

*Cardiac tamponade/perforation occurring up to 30 days post-index-procedure will count as primary safety endpoint events
**AV block not attributable to medication effect or vasovagal reaction.
***Atrial esophageal fistula, and severe pulmonary vein stenosis occurring up to 3 months post-index-procedure will count as primary safety endpoint events

**** Phrenic nerve palsy not resolved at the end of the 3 months follow up will count as primary safety endpoint event.

Table 5: Safety Endpoint Components Definitions

Term	Definition
Atrioesophageal Fistula	An atrioesophageal fistula is defined as a connection between the atrium and the lumen of the esophagus. Evidence supporting this diagnosis includes documentation of esophageal erosion combined with evidence of a fistulous connection to the atrium, such as air emboli, an embolic event, or direct observation at the time of surgical repair. A CT scan or MRI scan is the most common method of documentation of an atrioesophageal fistula.
AV block	A conduction disturbance that results in the partial inability of an electrical impulse generated in the atria to reach the ventricles.
Cardiac tamponade/perforation	Cardiac tamponade/perforation is defined as 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.
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 left bundle branch block, 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.
Pericardial Effusion	A collection of fluid or blood in the pericardial space around the heart or in pleural space around the lungs.
Phrenic nerve palsy	Phrenic nerve palsy is defined as absent phrenic nerve function as assessed by a sniff test. A phrenic nerve palsy is considered to be permanent when it is documented to be present 12 months or longer following ablation.
Pneumothorax	Collapse of the lung due to an abrupt change in the intrapleural pressure within the chest cavity.
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.
Pulmonary Vein Stenosis (Severe)	Pulmonary vein stenosis is defined as a reduction of the diameter of a PV or PV branch. PV stenosis can be categorized as mild <50%, moderate 50%–70%, and severe ≥70% reduction in the diameter of the PV or PV branch. A severe PV stenosis will count toward the primary safety endpoint.

Term	Definition
Stroke/Cerebrovascular accident (CVA)	Stroke diagnostic criteria: • 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) • Stroke: (diagnosis as above, preferably with positive neuroimaging study); o Minor–Modified Rankin score <2 at 30 and 90 days† o Major–Modified Rankin score ≥2 at 30 and 90 days
Thromboembolism	The blockage of a blood vessel lumen by 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. Transient ischemic attack: new focal neurological deficit with rapid symptom resolution (usually 1 to 2 hours), always within 24 hours; neuroimaging without tissue injury
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*	Vascular access complications include the 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.

**Events of vascular access complications and gastroparesis/ injury to vagus nerve will only be considered primary safety endpoint events if they meet the criteria for a major complication, per protocol Table 5. Non-major events of this type will not be considered primary safety endpoint events. This is consistent with the methods used in the meta-analysis performed to determine expected rates and an appropriate performance goal for the primary safety endpoint (Section 8.2).*

8.3. *Primary Effectiveness Endpoint*

Rate of acute procedural success defined as the achievement of electrical isolation of all PVs by using the POLARx Cardiac Cryoablation System with the POLARx FIT cryoablation balloon catheter models (with treatment applied at 28 mm or 31 mm balloon size per physician discretion). Electrical isolation of a PV is demonstrated by entrance and exit block.

8.4. *Secondary Safety Endpoints:*

The secondary safety endpoint at 12 months is defined as the safety event-free rate at 12 months post-procedure.

Secondary safety events at 12 months will consist of a composite of the following procedure-related and/or device-related adverse events.

The following events will be counted through 7 days post index procedure or hospital discharge, whichever is later:

- Death
- Myocardial infarction (MI)
- Major Vagal Nerve Injury/Gastroparesis
- Transient ischemic attack (TIA)
- Stroke/Cerebrovascular accident (CVA)
- Thromboembolism
- Pneumothorax
- Major vascular access complications
- Pulmonary edema/heart failure
- AV block*

The following events will be counted through 30 days post index procedure:

- Cardiac tamponade/perforation

And the following events will be counted through 12 months post index procedure:

- Atrial esophageal fistula
- Severe pulmonary vein stenosis (≥70% reduction in the diameter of the PV or PV branch from baseline)
- Persistent phrenic nerve palsy**

* AV block not attributable to medication effect or vasovagal reaction.

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

8.5. *Secondary Effectiveness Endpoints:*

Failure free rate at 12 months post procedure.

Failure defined as:

- Failure to achieve acute procedural success in the index procedure or repeat procedure during the blanking period
- Use of amiodarone post index procedure
- Surgical treatment for AF/AFL/AT post index procedure
- Use of a non-study ablation catheter for AF targets in the index procedure or repeat procedure during the blanking period
- More than one repeat procedure with the Cryoablation System during the blanking period (90 days post index procedure)
- Documented atrial fibrillation, or new onset of atrial flutter or atrial tachycardia event [≥ 30 seconds in duration from the study specific event monitor, Holter Monitor, or from a 10 second 12-lead Electrocardiography (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 days 91 post index procedure and 365 days:
    - Repeat procedure
    - Electrical and/or pharmacological cardioversion for AF/AFL/AT
    - Prescribed any antiarrhythmic drug (AAD)*

    *AADs for endpoint will consist of all Class I/III, including Amiodarone, and any Class II/IV medications taken for control of atrial fibrillation (AF)/Atrial tachycardia (AT)/Atrial flutter (AFL) recurrence.

8.6. *Tertiary Safety Endpoints:*

Reportable Adverse Events rates at 12 months.

Adverse events will be collected at all subject follow-up visits. Reportable events include:

- All Serious Adverse Events
- All Study Procedure-Related Adverse Events
- All Study Device-Related Adverse Events
- All Study Device Deficiencies

- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in IFU.

8.7. *Additional Endpoints*

Additional endpoints and analysis include, but are not limited to:

- Changes in the quality-of-life measures (AFEQT and EQ-5D- 5L) between baseline and 12 months follow up
- Single procedure success, defined as freedom from failure at 12 months post procedure as defined in the secondary effectiveness endpoint without a repeat procedure
- Duration of LA dwell time, defined as time from the Cryoablation Catheter exiting the sheath in the LA to time of final PV isolation
- Total Cryoablation time for the index procedure
- Total fluoroscopy time for the index procedure
- Total index procedure time
- Freedom from recurrence of individual types of atrial arrhythmias between 91 and 365 days from index procedure: 1) AF 2) AT 3) AFL
- Failure- free rate as defined in secondary effectiveness endpoint when considering AF/AT/AFL episodes reported to the investigators by study specific (event recorder transmissions, 12 lead ECG and Holter) and non-study related devices (other commercial applications for arrhythmia monitoring and detection the subject may access during the study including telemetry, other sources of continuous recording etc.)

Table 6: Overview of Objectives and Endpoints

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
Establish the safety of the Cryoablation System	Composite of acute and 3-month study specific adverse events	List of events were selected from those typically associated with catheter ablation of AF.
Establish the acute procedural effectiveness of the Cryoablation System	Rate of acute procedural success defined as the achievement of electrical isolation of all PVs by using the POLARx Cardiac Cryoablation System with the POLARx FIT cryoablation balloon catheter models only. Electrical isolation of a PV is demonstrated by entrance and exit block.	Component of the secondary effectiveness endpoint
Secondary		
Establish the chronic effectiveness of the Cryoablation System	Failure- free rate at 12 months including failure to achieve success at index or repeated procedure in blanking period, amiodarone post procedure, documented AF/AT/AFL or interventions to treat these arrhythmias after blanking period, including repeated procedures cardioversion or pharmacologic treatment	Performance goal and expected rates calculated from a meta-analysis of pivotal and IDE studies on AF ablation
Tertiary		
Adverse events reporting	Reportable Adverse Events rates at 12 months	Complete overview of the safety events collected in the study
Additional		
Recurrence of individual arrhythmia types	Freedom from recurrence of AF/AT/AFL	Component of the primary effectiveness endpoint
Quality of life assessment	Changes in the quality-of-life measures (AFEQT and EQ-5D-5L) between baseline and 12 months follow up	Consistent with the objective of AF ablation to improve quality of life and reduce AF-associated symptoms
Single procedure success	Freedom from failure at 12 months post procedure as defined in the secondary effectiveness endpoint without repeat procedure	To assess success rate after a single procedure
Procedure-related times	LA dwell time, ablation time, fluoroscopy time, index procedure time	To relate with published data on other AF ablation devices

9. Study Design

This extension study of FROzEN-AF is a prospective, non-randomized, multi-center, investigation being conducted to establish the safety and effectiveness of Boston Scientific's POLARx Cryoablation System with the POLARx FIT catheter models in subjects with symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation.

9.1. *Scale and Duration*

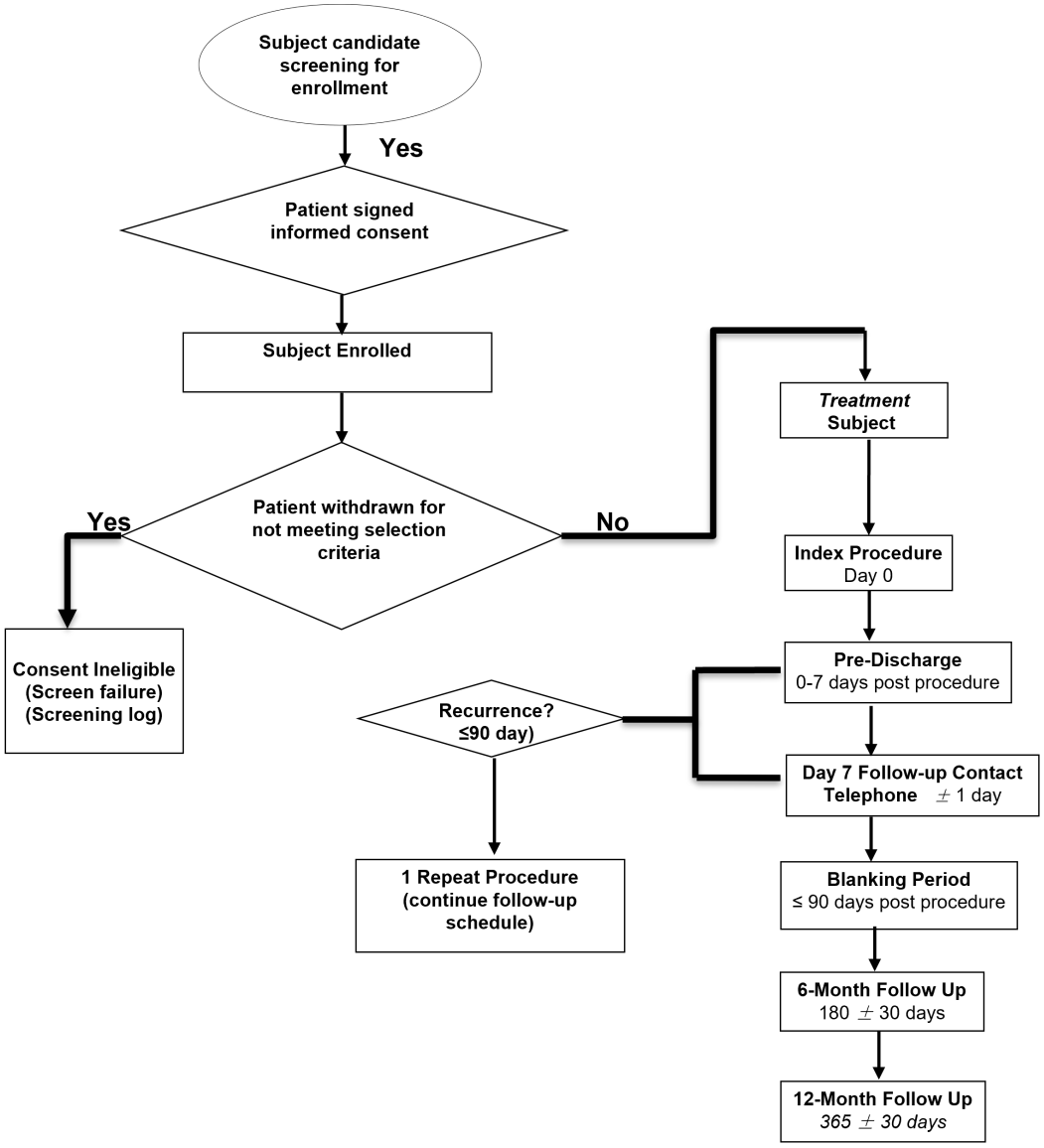
A maximum of 75 subjects will be enrolled and treated with the investigational system in the study. Subject enrollment will stop once 50 evaluable

31 mm TREATMENT subjects are accrued (per subject status classification, Section 11.5).

Up to 20 sites in North America may participate in this study. All sites will be selected from the FROzEN-AF study. To reduce the impact of individual center bias, each site participating in the extension study will enroll and treat a maximum of 18 subjects with cryoablation applied at the 31 mm configuration.

The enrollment period for this study is expected to last approximately 5 months. Each subject will be followed at specified time points after the ablation procedure (index procedure), with a follow-up duration of 12 months. A study subject's participation will be considered complete when all protocol required visits have been completed as indicated in Figure 8. The total sub-study duration is estimated to be approximately 17 months. Subjects may be requested to consent to provide long term follow-up data, if needed for post-approval requirements.

Figure 8: Extension Study of FROzEN-AF: Study Design



9.2. *Treatment Assignment*

All screened subjects who sign the informed consent will be considered enrolled. Data will be collected during the baseline visit, the ablation (index) procedure, the pre-discharge visit, the Day 7 telephone contact/follow up, month 3 follow up, the month 6 follow up and during the month 12 follow up. In case unscheduled visits or additional ablation procedures take place, this data will also be collected. Please refer to Section 12 for an overview of data to be collected during these visits.

Subjects will be classified based on Subject Status and Classification as per Section 11.5.

9.2.1. Treatment

All enrolled subjects who undergo the ablation procedure will be treated with Boston Scientific's POLARx Cryoablation System (with the POLARx FIT catheter models as Cryoablation catheters). The physician will apply treatment at 28 mm or 31 mm balloon size per clinical judgement as outlined in Section 12.6.

It is recommended that each investigational center will be limited to 2 ablating investigators. Additional investigators may participate for completion of subject follow-up visits if appropriately delegated (Section 12.6.1) and trained to complete the assigned tasks.

9.3. *Justification for the Study Design*

9.3.1. Extension Study

Boston Scientific proposes a prospective non-randomized IDE extension study with the POLARx Cryoablation System (and the POLARx FIT catheter models as Cryoablation catheters) as treatment device in order to seek approval of the POLARx Cryoablation System. The rationale for a non-randomized extension study can be justified as follows:

- All aspects of usage, including preparation, introduction, occlusion and ablation with the POLARx FIT catheters are identical to POLARx Cryoablation System. The POLARx FIT catheter models are physically identical to POLARx models and differ only in the model number programmed into the EEPROM (i.e., electronic identifier) of the catheter. When connected to a SMARTFREEZE Cryoablation Console the new EEPROM number makes the "FIT" feature available. This feature gives users the ability to increase the balloon diameter from 28 mm to 31 mm following inflation, when desired. By design, the SMARTFREEZE console will always inflate the cryoballoon to the standard size of 28 mm diameter on the initial inflation. If a physician prefers to apply the 31 mm diameter size, the FIT size must be selected on the Console to increase the balloon diameter from 28 mm to 31 mm. Size selection may vary within patients for each pulmonary vein, allowing the physician to select the desired balloon size per treatment. The POLARx FIT catheter model leverages the materials and manufacturing assembly processes as the POLARx catheter.

- The POLARx FIT catheter models and POLARx catheters are intended to be used in the same patient population. BSC's POLARx FIT capability gives users both the standard 28 mm balloon and an option to increase to a larger, 31 mm balloon on demand. The added choice of a 31 mm balloon size for the POLARx FIT Catheter will allow physicians to provide cryoablation for PV isolation in a larger variety of pulmonary vein geometries (i.e., those that might not have been as good a fit using a 28 mm balloon size).
- The POLARx FIT catheter models and POLARx catheters have been tested to ensure that both balloon diameters provide the same therapeutic cooling. This was tested in a bench model that allowed measurement and comparison of the balloon surface temperature of the POLARx FIT catheter models and POLARx catheters. The comparison study showed no statistical difference in the average surface temperature between POLARx FIT at 31 mm balloon diameter and POLARx at 28 mm.
- The POLARx FIT catheter models and POLARx catheters are introduced into the body the same way and have the same mechanism of deployment-inflation via low pressure N2O refrigerant, with the only difference being the pressure and flow rate applied by the SMARTFREEZE Console when using the larger diameter balloon. By maintaining the same therapeutic cooling for both 28 mm and 31 mm diameters, the safety and effectiveness of POLARx FIT to alter cardiac tissue is not expected to differ.

Due to the similarities between the POLARx and POLARx FIT catheters, the safety and effectiveness data from subjects treated with POLARx ("FROZEN-AF subjects") may be pooled with the safety and effectiveness data from subjects treated with POLARx FIT catheter models ("POLARx FIT subjects"). The data will be submitted for product approvals once 3 months of follow-up data is available for POLARx FIT subjects.

9.3.2. Treatment Subjects

Sites participating in the POLARx FIT extension study will be selected from the FROzEN-AF study. Only ablating physicians who contributed a roll-in subject during the FROzEN-AF study will be selected. No roll-in subjects will be included in this extension study as the ablating physicians will already have significant experience with the Boston Scientific Cryoablation System from the FROzEN-AF study.

All subjects treated with the investigational system will be considered as non-roll-in TREATMENT subjects. All safety and effectiveness data will be collected and reported for these subjects and will be included in the endpoint analyses.

To reduce the impact of individual center bias, each site participating in the extension study will enroll and treat a maximum of 18 subjects with cryoablation applied at the 31 mm configuration.

10. Subject Selection

10.1. *Study Population and Eligibility*

Subjects enrolled in the POLARx FIT extension study of FROzEN-AF study will be clinically indicated for an ablation procedure for the treatment of symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation. Subjects should meet the study inclusion/exclusion criteria as outlined below in Sections 10.2 and 10.3.

The subjects selected for participation will be from the investigator's general patient population. The investigator or its designee has the responsibility for screening all potential subjects and selecting those who meet study inclusion/exclusion.

The Inclusion/Exclusion Criteria outlined below in Section 8.2 and 8.3 identically match the Inclusion/Exclusion Criteria listed in Section 8.2 and 8.3 of the FROzEN-AF protocol (92348334).

10.2. *Inclusion Criteria*

Subjects who meet the following criteria (Table 7) may be given consideration for inclusion in this clinical investigation, provided no exclusion criterion (see Section 10.3) is met.

Table 7: Inclusion Criteria

Inclusion Criteria	• History of recurrent symptomatic paroxysmal atrial fibrillation (PAF), defined as atrial fibrillation that terminates spontaneously or with intervention (either procedure or drug therapy) within seven days of onset. Minimum documentation includes the following: o a physician's note indicating recurrent self-terminating atrial fibrillation (AF) which includes at least two symptomatic AF episodes within six months prior to enrollment, and o one electrocardiographically documented AF episode within 12 months prior to enrollment. • Subjects who are indicated for an ablation procedure for paroxysmal atrial fibrillation (PAF) according to 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation • No amiodarone use within 90 days prior to enrollment • Subjects refractory or intolerant to at least one class I or III antiarrhythmic medication or contraindicated to any class I or III medications • Subjects who are willing and capable of providing informed consent • Subjects who are willing and capable of participating in all testing associated with this clinical investigation at an approved clinical investigation center • Subjects whose age is 18 years or above, or who are of legal age to give informed consent specific to state and national law

10.3. *Exclusion Criteria*

Subjects who meet any one of the following criteria (Table 8) cannot be included in this study or will be excluded from this clinical study.

Table 8: Exclusion Criteria

Exclusion Criteria	• Any known contraindication to an AF ablation or anticoagulation • Continuous AF lasting longer than seven (7) days from onset • History of previous left atrial ablation or surgical treatment for AF/ AFL/ AT • Atrial fibrillation secondary to electrolyte imbalance, thyroid disease, or any other reversible or non-cardiac cause

	• Structural heart disease or implanted devices as described below: a. Left ventricular ejection fraction (LVEF) < 40% based on the most recent TTE performed ≤180 days prior to enrollment* b. Left atrial diameter > 5.5 cm OR left atrial volume > 50 ml/m2 indexed based on the most recent TTE performed ≤ 180 days prior to enrollment* c. An implanted pacemaker, ICD, CRT device or an active arrhythmia loop recorder d. Previous cardiac surgery: i.e., ventriculotomy or atriotomy (excluding atriotomy for CABG) e. Previous cardiac valvular surgical or percutaneous procedure, or prosthetic valve, including mitral valve clips f. Interatrial baffle, closure device, patch, or PFO occluder g. Presence of a left atrial appendage occlusion device h. Presence of any pulmonary vein stents i. Coronary artery bypass graft (CABG), PTCA/ PCI/ coronary stent procedures within 90 days prior to enrollment j. Unstable angina or ongoing myocardial ischemia k. Myocardial infarction within 90 days prior to enrollment l. Moderate or severe mitral stenosis [severity assessed on the most recent TTE ≤180 days prior to enrollment as Pulmonary artery systolic pressure >30 mm Hg (1)] m. Evidence of left atrial thrombus** • Any previous history of cryoglobulinemia • Stage 3B or higher renal disease (estimated glomerular filtration rate, eGFR <45 mL/min) • History of blood clotting or bleeding disease • Any prior history of documented cerebral infarct, TIA or systemic embolism (excluding a post-operative DVT) ≤180 days prior to enrollment • Active systemic infection • Pregnant, lactating (current or anticipated during study follow up), or women of childbearing potential who are, or plan to become, pregnant

	during the time of the study (method of assessment upon physician's discretion) • 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 • Subjects who in the judgment of the investigator have a life expectancy of less than two years **LVEF and LA diameters obtained ≤180 days prior to enrollment will be acceptable, unless a cardiac event has occurred (e.g., MI) between the date of the exam and the enrollment date, otherwise a new echocardiogram (trans-thoracic or trans-esophageal, or intracardiac echo) must be performed to confirm eligibility prior to performing ablation. For TTE, the LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used. If both LA diameter and volume are available, only one meeting eligibility criteria is required.* ***The absence of thrombus must be confirmed by means of a TEE within 48 hours prior to the procedure or ICE during procedure in subjects not adequately anticoagulated (see Section 12.5.2) for at least 3 weeks prior to the procedure OR with CHA_2DS_2-VASc score (see Appendix 27.4) ≥2 in men and ≥3 in women OR enlarged LA (≥4.5cm). If a thrombus is observed, the subject no longer meets eligibility criteria. When screening for thrombus prior to the index procedure, ensure that the anticoagulation approach as described in Section 12.5.2 is followed until the day of the procedure.*

11. Subject Accountability

11.1. *Point of Enrollment*

A maximum of 75 subjects will be enrolled and treated with the POLARx FIT balloon size at 31 or 28 mm (based on clinical judgement) to ensure a minimum of 50 31 mm TREATMENT subjects (subjects who receive at least one cryoablation applied at the 31 mm configuration.) are enrolled.

Subjects who have signed and dated the Informed Consent Form are considered enrolled in the study. 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 SOC can be used to determine pre-eligibility. Study 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.

11.2. *Enrollment Controls*

Study-specific subject IDs will be generated through the Electronic Data Capture (EDC) system used for this study. This database will also be utilized to provide the sites with subject classification assignments once a subject has provided written informed consent. Enrollment controls will be put in place to ensure that each site participating in the extension study will enroll and treat a maximum of 18 subjects with cryoablation applied at the 31 mm configuration.

11.3. *Withdrawals*

This section identically matches the Withdrawals Section (Section 9.3) of the FROzEN-AF protocol (92348334).

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 investigation, the reason(s) shall be reported. If such withdrawal is due to problems related to investigational device safety or performance, the investigator shall ask for the subject's documented permission to follow his/her status/condition outside of the clinical study.

Reasons for withdrawal may include physician discretion, subject choice to withdraw, 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. In the event a subject does decide to withdraw from the study, every effort should be made to obtain full information on any on-going reportable Adverse Events up to the point of withdrawal. 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. Data collected up to the point of subject withdrawal may be used, unless any local regulations apply which require removal of the data.

If the withdrawal is due to the investigator's discretion, the investigator is obligated to follow all open reportable Adverse Events until they can be considered as closed or chronic.

All open reportable adverse events should be closed or documented as chronic. If the withdrawal is due to problems related to device safety or performance, the investigator shall ask for the subject's documented permission to follow his/her status/condition.

Withdrawn subjects will not be replaced.

All applicable electronic case report forms (eCRFs) up to the point of subject withdrawal/lost to follow up and an "End of Study" eCRF must be completed.

11.4. *Lost to Follow-Up*

This section identically matches the Lost to Follow-Up Section (Section 9.4) of the FROzEN-AF protocol (92348334).

A participant will be considered lost to follow-up if he or she fails to return after documented attempts to attend a scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant 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 participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (at minimum 3 telephone calls and a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record or study file.
- Should the participant continue to be unreachable, he or she will be considered lost to follow-up from the study.

All applicable electronic case report forms (eCRFs) up to the point of subject withdrawal/lost to follow up and an "End of Study" eCRF must be completed.

11.5. *Subject Status and Classification*

As subjects are evaluated, enrolled and treated in the study, they will be grouped into one of the following categories. Categorization will help determine how data gathered from them will be stored and evaluated. Subjects previously enrolled in the FROZEN-AF study cannot be re-enrolled in the POLARx FIT extension study.

Consent Ineligible (Screening Failures)

A subject who has signed informed consent but is found not to meet eligibility criteria will be classified as "Consent Ineligible". There are no Follow Up reporting requirements for consent ineligible subjects. Subjects determined to be Consent Ineligible do not count towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the center's patient file. A subject Identification Number (ID) will be assigned in the EDC system.

For consent ineligible subjects the following forms must be completed:

- Enrollment and End of Study
- Adverse Event forms for any reportable event, as defined in Section 21 that occurs after signing the Informed Consent, up to the point of subject withdrawal

INTENT

A subject who signs informed consent, meets eligibility criteria, but does not have any study investigational devices inserted into the body will be classified as "INTENT". Subjects that are enrolled in the study but do not undergo ablation procedure within 30 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 not count towards the enrollment ceiling and will not be used for analysis of the endpoints. The original signed Informed Consent must be maintained in the center's patient file. A subject ID will be assigned in the EDC system.

- For intent subjects, at the miniumum the following forms must be completed: Enrollment and baseline forms such as, but not limited to, informed consent, enrollment information and other related forms
- End of Study form
- Adverse Event forms for any reportable event, as defined in Section 21, that occurs after signing the Informed Consent, up to the point of subject withdrawal

ATTEMPT

A subject who signs informed consent, meets eligibility criteria, and has any study device inserted into the body but does not receive any POLARx FIT Cryoablation application will be classified as "ATTEMPT." Attempt subjects do not count towards the enrollment ceiling. Attempt subjects will be used for analysis of the primary and secondary safety endpoint and additional analyses of safety data but will not be used for analysis of the primary and secondary effectiveness endpoints or additional analyses of effectiveness data (additional analysis include subgroup, multivariable, and center pooling analyses). The original signed Informed Consent must be maintained in the center's patient 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 through the 12 month visit. All applicable case report forms per the protocol will be completed. The original signed Informed Consent and any relevant documentation must be maintained in the center's patient file.

TREATMENT

Any subject that signs the consent form, meets eligibility criteria and has the specified study device inserted into the body and received at least one POLARx FIT Cryoablation application, regardless of the balloon size configuration, will be classified as "TREATMENT". These subjects are followed in accordance with the follow-up schedule 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 75 subject 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 patient file.

31 mm TREATMENT

Any subject that signs the consent form, meets eligibility criteria and has the specified study device inserted into the body and received at least one POLARx FIT Cryoablation performed using the 31 mm balloon size configuration, will be further classified as "31 mm TREATMENT". A minimum of 50 31mm TREATMENT subjects will be enrolled.

11.6. *End-of-Study Definition*

This section identically matches the End-of-Study Definition Section (Section 9.6) of the FROzEN-AF protocol (92348334).

A clinical trial is considered completed when participants are no longer being examined or the last participant's last study visit has occurred. The end of the study is defined as completion of the last visit or procedure shown in the Data Collection Schedule.

12. Study Methods

12.1. *Data Collection*

Each Treatment subject will be followed at index procedure, at pre-discharge visit, at the month 3 follow up, at the month 6 follow up and at 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. If the subject needs to undergo an additional ablation procedure in the LA during the follow-up period, then this additional ablation procedure will need to be captured in the EDC database. The data collection schedule is shown in Table 9.

Table 9: Data Collection Schedule

Procedure/Assessment	**Enrollment** *(up to 30 days before Index procedure)*	**Baseline** *(up to 30 days before Index procedure)*	**Index Procedure** *(Day 0)*	**Blanking Period**		**Repeat Procedure**	**Effectiveness Evaluation Period**			
				Pre-Discharge *(0-7 days post procedure)*	**Day 7 Follow-up Contact** (+/-1 day)	**Repeat Procedure for PAF**	**Month 3 Follow Up** *(91±14 days)*	**Month 6 Follow Up** *(180± 30 days)*	**Month 12 Follow Up** *(365±30 days)*	**Unscheduled Visit**
Informed Consent Process, including informed consent signature date	X									
Eligibility Criteria	X	X	X							
Demographics		X								
Medical History		X								
Blood Tests		X[1]								

Procedure/Assessment	Enrollment *(up to 30 days before Index procedure)*	Baseline *(up to 30 days before Index procedure)*	Index Procedure *(Day 0)*	Blanking Period		Repeat Procedure	Effectiveness Evaluation Period			
				Pre-Discharge *(0-7 days post procedure)*	**Day 7 Follow-up Contact** *(+/-1 day)*	**Repeat Procedure for PAF**	**Month 3 Follow Up** *(91±14 days)*	**Month 6 Follow Up** *(180± 30 days)*	**Month 12 Follow Up** *(365±30 days)*	**Unscheduled Visit**
TTE (medical history)		X[2]								
NIH Stroke Scale (NIHSS)		X[3]		X[3]						
Neurology Consultation[4]				(X)[4]						
Brain MRI Scan[5]				(X)[5]						
Physical Assessment		X					X	X	X	X
Physical Assessment with Cardiovascular/Pulmonary Examination				X[6]						
Quality of Life (AFEQT and EQ-5D-5L)		X					X	X	X	
PV Anatomical Assessment (CT/MRI)		X[7]								
Screening for LA Thrombus (TEE or ICE)		X [8]				X[8]				
PV Stenosis Assessment (CT/MRI)				(X)[9]			(X)[9]	(X)[9]	(X)[9]	(X)[9]
Procedural Data			X			X				
12-Lead ECG		X	X	X		X	X	X	X	X
Phrenic Nerve Palsy Assessment			X[10]	(X)[10]		(X)[10]	(X)[10]	(X)[10]	(X)[10]	X[10]
Holter Monitor (24 hours)									X	
Arrhythmia/Event Monitor				X			X	X	X	X
Documentation of Intervention for AF/AT/AFL (if any)						X	X	X	X	X
Medications	Prior and current AAD medications and Anticoagulant therapy regimen from Enrollment through End of Study Visit									
Protocol Deviations	From Enrollment through End of Study Visit									
Adverse Event Assessment	Continuous from Enrollment through End of Study Visit									

[1] Blood tests up to 90 days prior to enrollment, if applicable.
[2] TTE either new or from medical file, ⩽180 days prior to enrollment.
[3] NIH Stroke Scale (NIHSS) performed at baseline and the pre-discharge visit.
[4] Neurology consult is only required if NIH scale worsens from the previous assessment
[5] Brain DW-MRI scan required if neurology consultation determines possibility of new stroke
[6] Physical assessment at discharge will also include a cardiovascular/pulmonary examination: resting heart rate, systolic and diastolic blood pressure, O2 saturation, lung auscultation (includes respiratory rate and respiratory rhythm), and temperature

[7] Performed up to 180 days prior to the index procedure (CT/MRI).
[8] TEE 48 hours prior to the procedure or ICE during the procedure
[9] Assessed in case of suspected PV stenosis.
[10] Screening for phrenic nerve palsy will be performed during ablation, and prior to leaving the EP lab at the completion of the ablation procedure in all subjects. Assessment at discharge and at follow-up visits is only applicable for subjects who had phrenic nerve palsy detected at the index procedure.

Abbreviations:
IP = index procedure, NIH = National Institutes of Health, ECG = electrocardiogram, ICE = Intracardiac Echography; PV = pulmonary veins, TTM = trans-telephonic monitor, TTE = trans-thoracic echocardiogram, TEE = trans-esophageal echocardiogram, CT = Computed Tomography, MRI = Magnetic Resonance Imaging, FU = follow-up.

12.2. *Study Candidate Screening*

Investigators are responsible for screening all subjects and selecting those who are appropriate for study inclusion. The subjects selected for participation should be from the investigator's general patient population. The investigator is expected to follow standard of care testing to diagnose and screen subjects for inclusion in the study.

12.3. *Enrollment and Informed Consent*

This section identically matches the Enrollment and Informed Consent Section (Section 10.3) of the FROzEN-AF protocol (92348334).

Subjects who provide consent are considered enrolled in the study. To determine eligibility of a subject, the investigator or designee needs to implement the consent process and verify/document the subject meets the inclusion/exclusion criteria. Informed consent is required for all subjects prior to their participation in the study. No study-specific procedures should 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 personally signed and dated by the subject. 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 30 days post ICF signature. In case the index procedure has not been performed within this period, the subject will be classified as Intent (see Section 11.5). 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 will be made available for review at Interim Monitoring Visits (IMVs).

For additional information regarding the informed consent process, refer to Section 22.

12.4. *Baseline Visit*

This section identically matches the Baseline Visit Section (Section 10.4) of the FROzEN-AF protocol (92348334).

Enrolled subjects will have baseline data collected. The data collection at baseline includes:

- Visit date
- Documentation of Informed Consent process, including Informed Consent Form signature date
- Check of Eligibility Criteria*
- Demographic data, including age at time of consent, gender, race, and ethnicity

- Physical assessment including weight, height, resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (by means of a 12-lead ECG)
- Medical history, including, but not limited to:
  - Evidence of PAF in the medical history should be documented as per the inclusion criteria. Treatment history (drug, cardioversion, etc.) should be documented.
  - Underlying cardiovascular disease, if any; including but not limited to hypertension, dyslipidemia, coronary artery disease
  - Prior history of cardiac events including acute myocardial infarction, CVA, or TIA
  - Prior surgical interventions and/or cardiac procedures including: Percutaneous Trans Catheter Angioplasty (PTCA), Coronary Artery Bypass Graft (CABG), pacemaker (PM) implantation, implantable cardioverter-defibrillator (ICD) implant, Cardiac Resynchronization Therapy (CRT) implant, cardiac valve interventions, left atrial appendage closure (LAAC), patent foramen ovale (PFO) intervention, heart transplant or procedures for implantation of other intracardiac devices
  - Detailed history of all arrhythmias
  - Non-cardiac comorbidities, including but not limited to: Chronic Obstructive Pulmonary Disease, Diabetes, Hepatic Disease, Neurologic Disease, Renal Disease, Bleeding Disorders/Clot disorders, Sleep Disordered Breathing
- The following instrumental assessments will be performed or data from existing information will be collected:
  - TTE (most recent, either assessed at baseline visit or from medical file if date if not > 180 days prior to enrollment). Data will include: LVEF, left atrial diameter or left atrial volume**, pulmonary artery pressure**
  - Cardiac MRI or spiral CT scan, to assess PV anatomy and PV dimension.
  - TEE or ICE to rule out presence of left atrial thrombus. See Section 12.5.2 Anticoagulation, Thrombus Screening.

  In the event a subject has an adverse event related to the TTE, TEE, ICE or CT/MRI scan, they shall remain in the study until the event is resolved.
- Pregnancy test (urine or blood), if applicable***
- Blood tests****
- Quality of Life assessment through AFEQT and EQ-5D-5L questionnaires
- Conduct a baseline National Institute of Health Stroke Scale (NIHSS), see Appendix 27.3.
- AAD history and most recent dose prior to enrollment; stop date of amiodarone (if applicable)
- Current AAD and anticoagulation medication regimen
- Reportable Adverse Events, if applicable
- Protocol Deviations, if applicable

* LVEF and LA diameters obtained ≤ 180 days prior to enrollment will be acceptable, unless a cardiac event has occurred (e.g., MI) between the date of the exam and the enrollment date, otherwise a new echocardiogram (trans-thoracic or trans-esophageal, or intracardiac echo) must be performed to confirm eligibility prior to performing ablation. LA anteroposterior diameter measured by M-mode from the parasternal long-axis view will be used. If both LA diameter and volume are available, only one meeting eligibility criteria is required.

**Moderate to Severe mitral stenosis (severity will be assessed as pulmonary artery systolic pressure > 30 mmHg).

***A pregnancy test (method of assessment per investigators' discretion) must be performed for women of childbearing potential. Women of childbearing potential will be required to verify entrance criteria prior to the procedure by providing documentation of a negative pregnancy test. A negative pregnancy test conducted as standard of care *within 7 days prior to enrollment* will be acceptable.

****Laboratory blood tests (other than a pregnancy blood test) obtained ≤ 90 days prior to enrollment will be acceptable.

12.5. *Medications*

This section identically matches the Medications Section (Section 10.5) of the FROzEN-AF protocol (92348334).

12.5.1. Anti-Arrhythmic Drugs

12.5.1.1. AADs prior to index procedure

Inclusion criteria require the subject to be refractory or intolerant to at least one class I or III antiarrhythmic medication and amiodarone to be stopped three months before enrollment. Prior and current AAD therapy will be collected in the EDC system.
If applicable, administration of amiodarone and stop date will be entered in EDC.

12.5.1.2. AADs post index procedure during the 90-day blanking period

Blanking period is defined as the time between Index procedure and 90 days post Index procedure. Post-procedure AADs are allowed per physician's discretion during the blanking period. New AADs should not be prescribed unless considered medically necessary. If treatment with AAD is prescribed during the blanking period, it is recommended that a Class I or III AAD be selected according to the ACC/AHA/ESC 2014 Guidelines for the Management of Patients with AF. No amiodarone use is permitted post procedure. After the index procedure, the investigator should remove subjects from AADs to appropriately assess the subject for early arrhythmia recurrence that may require a repeat ablation procedure within the blanking period (on or before day 90).

12.5.1.3. AADs post 90 days blanking period

Investigators must stop administration of AADs for any atrial tachyarrhythmia after the blanking period. If the investigator determines that the subject must be prescribed any dose of 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/AT/AFL recurrence.*

Treatment with Class II/IV medications for conditions other than control of atrial arrhythmia recurrence is also permitted and will be documented. Every effort should be made to keep those drugs at a stable dose over the entire course of the study.

12.5.2. Anticoagulation

The following anticoagulation protocol is required for this study. An *adequate anticoagulation regimen* is represented by one of the 4 approaches listed in the paragraph titled "Pre-ablation".

Pre-ablation.

Physicians can follow either an uninterrupted anticoagulation approach (Recommended), based on uninterrupted warfarin or NOAC, or minimally interrupted NOAC or an interrupted anticoagulation approach with adequate bridge with LMWH (Low Molecular Weight Heparin).

- Uninterrupted anticoagulation approach (recommended) includes one of the following options:
    1) Uninterrupted treatment with warfarin or NOAC*, requiring continued treatment including the day of the index procedure
    2) Minimally interrupted NOAC, requiring continued treatment but allowing to stop NOAC 12 to 24 hours before the index procedure (e.g., holding the morning dose the day of the procedure)
- Interrupted anticoagulation approach includes one of the following options.

    3) If patient is on Warfarin, this should be stopped 5 days prior to the ablation procedure and bridged with LMWH. LMWH should be stopped 12 hours prior ablation.
    4) If patient is on NOAC, this should be stopped 5 days prior to the ablation procedure and bridged to Warfarin or bridged with LMWH. LMWH should be stopped 12 hours prior ablation. At the time NOAC is stopped, INR value should be checked, if applicable, to ensure the Time of Therapeutic Range (TTR) are achieved with normalized ratio (INR) between 2.0 and 3.0.

* Includes any of the FDA approved NOAC (dabigatran, edoxaban, apixaban or rivaroxaban)
Anticoagulation guidelines that pertain to cardioversion of AF should be adhered.

If at the time of enrollment, a patient has not been anticoagulated as defined above in the pre-ablation anticoagulation, anticoagulation must be initiated and maintained from point of enrollment to the time of the index procedure. If the patient has not been anticoagulated for at least

3 weeks prior to the index procedure, thrombus screening must be conducted as outlined in Section 12.5.3.

Intra ablation:

- Heparin should be administered prior to transseptal puncture during AF catheter ablation procedures and adjusted to achieve and maintain an ACT of at least 300 seconds. The ACT level should be checked at 10 to 15-minute intervals until therapeutic anticoagulation is achieved, and then at 15 to 30-minute intervals for the duration of the procedure.

After ablation:

- Systemic anticoagulation with warfarin or a NOAC is recommended for at least 2 months post catheter ablation of AF.
- Adherence to AF anticoagulation guidelines is recommended for patients who have undergone an AF ablation procedure, regardless of the apparent success or failure of the procedure.

Decisions regarding continuation of systemic anticoagulation more than 2 months post ablation should be based on the patient's stroke risk profile and not on the perceived success or failure of the ablation procedure.

12.5.3. Thrombus Screening

The absence of thrombus must be confirmed by means of a TEE within 48 hours prior to the procedure or ICE during the procedure in subjects not adequately anticoagulated (see section 10.5.2) for at least 3 weeks prior to procedure *OR with CHA_2DS_2-VASc score (see Appendix 27.4) ≥2 in men and ≥3 in women OR enlarged LA (≥4.5cm)*. When screening for thrombus prior to the index procedure, ensure that the anticoagulation approach as described in Section 12.5.2 is followed until the day of the procedure.

12.6. *Index (Ablation) Procedure*

12.6.1. General Info

- Authorized ablating physicians

The study-related ablation procedure, from transseptal access in the left atrium until end of the ablation procedure must be performed by investigators trained in Electrophysiology (EP), trained to the POLARx FIT extension study protocol, and authorized by BSC to handle investigational devices. The index ablation procedure must be performed within 30 days of a subject's enrollment into the study. To avoid potential bias, it is recommended the number of

active ablating physicians performing the index procedure per investigational site is restricted to 2.

- De novo procedures

For the purposes of this protocol, de novo procedures are defined as AF procedures in which there has been no prior ablation in the Left Atrium (LA). According to subject selection criteria, all Index procedures in this study are de-novo as history of previous left atrial ablation or surgical treatment for AF/ AFL/ AT constitute an exclusion criterion.

- Esophagus management

Esophagus management must be performed by means of temperature monitoring via the Console using commercially available products. A commercially available temperature probe compatible with the Cryoablation system, will be used with measurements acquired and displayed through the Console. Only temperature measurements displayed on the Console will be used for esophageal temperature management. If the esophageal temperature falls below 20°C during cryoablation applications, the ablation will be stopped until esophageal temperature returns to baseline.

- Phrenic nerve activity monitoring
    - Index Procedure:
        - During ablation phrenic nerve activity monitoring will be performed via the Console. The phrenic nerve will be paced with a focal or circular catheter, higher than the ablation position during all right sided vein ablations. 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
        - After ablation, prior to leaving the EP lab, fluoroscopy of diaphragm movement will be performed at the completion of the ablation procedure
    - Discharge:
        - All patients presenting with phrenic nerve palsy at the end of the index procedure will be re-assessed at the discharge visit for phrenic nerve palsy via sniff test or an inhalation-exhalation chest radiography of the diaphragm
    - At Follow-up Visits:
        - Patients with unresolved phrenic nerve palsy detected at discharge visit, should be assessed by means of sniff test or an inhalation -exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Three-dimensional electroanatomic mapping

3D electro-anatomical mapping is not recommended in this study. If 3D mapping is performed, a commercially available device will be used, and the following information will be collected: mapping catheter, 3D mapping system and mapping times.

3.1.1.6.Pulmonary Vein Isolation

The goal of the ablation procedure is electrical isolation of all clinically relevant PVs. Electrical isolation of the veins must be demonstrated by entrance and exit block.

If the subject is in AF prior to the ablation, it will be up to the physician'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.

3.1.1.7.Cryoablation System Preparation

The individual devices listed in Table 1 must be used together and it is not allowed to combine investigational with non-investigational devices.

The remainder of this section identically matches the Cryoablation System Preparation Section (Section 10.6.1.2) of the FROzEN-AF protocol (92348334).

The Console will create a record for each ablation attempted, including Ablation Duration, Cryoballoon Temperature, Esophagus Temperature (if connected) and DMS activity data. To accurately capture information relevant to the study, the following information must be input into the Console at each index procedure:

Prior to Ablation:

- On the subject information screen, enter the subject's identification (code provided by the EDC system when enrolling the patient) and the operating physician name.
- For this study, the DMS must 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.
    1. Place a disposable ECG electrode just below the right-side costal cartilage.
    2. Snap the DMS onto the electrode.
    3. Ask the patient to cough and verify that signal is visible on the console screen. Adjust the position of the electrode if necessary.

       Prior to performing the ablation, pace the phrenic nerve with a focal or circular catheter positioned superior to the ablation location (e.g., superior vena cava). Adjust the pacing settings and catheter location as necessary to attain phrenic nerve capture. Typically, high output at 20 mA and 800 – 1000 milliseconds (ms) may be needed.

NOTE: Avoid or minimize use of paralytics if general anesthesia is used as paralytics may interfere with pacing capture of the phrenic nerve.

4. While pacing the phrenic nerve, adjust the DMS gain and sensitivity levels within the Settings screen to maximize the DMS signal level in the display window. Reduce the gain if the DMS signal appears saturated. Stop pacing until needed for the ablation.
5. Set the DMS threshold (within the Settings screen) for which the DMS notification will be displayed. The suggested DMS threshold setting is 65%, but the threshold can be adjusted per physician discretion.
    - The movement amplitude measured by the DMS at the initiation of cryoablation is used as the baseline value and is displayed as 100%.
    - If the phrenic nerve pacing response decreases during cryoablation, the DMS amplitude will correspondingly decrease. The console will display the DMS amplitude as a percentage of the baseline value. For example, 80% displayed on the console indicates the DMS amplitude is 80% of the baseline valve and that movement amplitude is reduced by 20%.
6. In case of a DMS notification, continue to closely monitor phrenic nerve activity and pacing capture, and consider immediately interrupting cryoablation.

Balloon Size Selection:

Usage of the 31 mm balloon size will be determined by the investigator's medical judgement, for each individual cryotherapy application. It is anticipated that individual study subjects may receive cryotherapy applications from both 28 mm and 31 mm balloon diameters during their PVI procedure.

Specifically, investigators must choose which balloon size to utilize for each ablation application. Investigators should use their medical judgement to select the balloon diameter that may be effective for treating each individual PV. In determining balloon size selection, Investigators should consider the anatomic factors including PV size, geometry, and LA size as well as other procedural factors that could affect balloon placement, occlusion quality, and tissue contact.

The SMARTFREEZE console will always inflate the cryoballoon to the current POLARx diameter of 28 mm first. For each energy application that the physician chooses to use the 31 mm balloon, the balloon diameter must be increased from 28 mm to 31 mm by pressing the FIT size selection button on the Console. The balloon diameter can only be changed when the system is in the "INFLATION" state, prior to initiating "ABLATION". After increasing the balloon diameter to 31 mm, investigators should follow their standard preparation steps, including the use of intra-procedure imaging, to ensure appropriate balloon placement and occlusion prior to starting cryotherapy.

During Each Ablation Application:

- Annotate the ablation site, mark the Time-To-Isolation, and set the Ablation Duration.

3.1.1.8.Cryoablation protocol

This section identically matches the Cryoablation Protocol Section (Section 10.6.1.3) of the FROzEN-AF protocol (92348334), except for step 9.

All aspects of usage of the POLARx Cryoablation System with POLARx FIT catheters are the same as with POLARx catheters (including preparation, introduction, occlusion, and ablation) with exception for the optional step of increasing the balloon diameter.

The ablation procedure should follow this recommended sequence: Prepare patient with conscious sedation or general anaesthesia. Prepare the vascular access sites per physician preference. Follow anticoagulation protocol in Section 12.5.2.

1. Intracardiac echo (ICE) may be performed to support the procedure. Record any observation of cardiac structural damage, any evidence of pericardial effusion, or any visible anomalies on the CRF.
2. Place additional diagnostic catheters, for example in the coronary sinus or for pacing the phrenic nerve, at the discretion of the physician.
3. Per institutional protocol, complete transseptal access (single or double).
4. Baseline the fluoroscopy exposure time.
5. Per the IFU, prepare the steerable sheath. Insert the steerable sheath over the guidewire and advance the sheath across the atrial septum.
6. Per the IFU, prepare the cryoablation catheter and the mapping catheter. Insert the mapping catheter into the cryoablation catheter. Insert the POLARx FIT Cryoablation Catheter into the steerable sheath and advance it into the left atrium.
7. Baseline the LA dwell time.
8. Advance the mapping catheter into the targeted PV and attain baseline electrograms, including confirming conduction between LA and PV. Electrocardiographic documentation of the subject's rhythm prior to ablation will be collected. If entrance/exit conduction cannot be recorded due to the subject being in AF, no Protocol Deviation will be required.
9. Per the IFU, inflate the cryoballoon in the left atrium, expand the balloon diameter after inflation (per physician discretion), and advance the cryoballoon to occlude the targeted PV.

a. Verify the balloon is at an appropriate position for inflation within the left atrium. This may be performed using imaging such as fluoroscopy or echocardiography. Do not inflate the balloon while it is positioned inside the PV.

b. Inflate the cryoballoon in the LA while remaining outside the target PV. The cryoballoon will always first inflate to a diameter of 28 mm.

c. Once inflated in the LA, the balloon may be expanded to the 31 mm diameter with the FIT size selection button on the SMARTFREEZE Console. Investigators shall use their clinical judgement to determine which balloon diameter (28 mm or 31 mm) to use for the treatment of each individual PV.

d. Advance the inflated cryoballoon to occlude the targeted PV. Remain in the atrium outside the tubular portion of the PV. For best results, maneuver the sheath and/or catheter to position the distal portion of the balloon at the PV ostium.

e. Verify PV occlusion. Verification may be performed with fluoroscopy and contrast/saline injection or with other appropriate visualization / assessment techniques such as ICE. If the balloon needs to be deflated for repositioning, use the slider switch on the POLARx FIT Catheter handle to simultaneously deflate and extend the balloon.

f. Document the occlusion score prior to starting the ablation. Ensure the occlusion score was attained for the balloon diameter used for the cryoablation application.

10. Position the esophagus temperature probe as directly posterior to the cryoballoon as possible.
11. If the selected vessel is a right PV, start phrenic nerve pacing prior to starting the cryoablation.
12. Start the cryoablation and observe the electrograms for changes in conduction. Identify Time-To-Isolation and set ablation duration as required by the dosing strategy document (document 92355401 provided separately). Investigators may apply a different dosing than the one provided in this document for reasons including technical difficulties, anatomical challenges, or concerns for subject welfare.
13. Upon completing the ablation, determine if entrance and exit block were achieved. If entrance and exit block are not confirmed, ablate the PV again as required by the dosing strategy document (document 92355401). Investigators may apply a different dosing than the one provided in this document for reasons including technical difficulties, anatomical challenges, or concerns for subject welfare. If entrance and exit block are confirmed, reposition the system to target another PV.

3.1.1.9.PV isolation verification

This section identically matches the PV isolation verification Section (Section 10.6.1.4) of the FROzEN-AF protocol (92348334).

Electrograms from the POLARMAP mapping catheter will be used to assess entrance and exit block into/from the PVs. The PV will only be considered isolated if entrance and exit block are confirmed. Electrogram data must be documented.

3.1.1.10. Additional ablation(s)

Additional ablation of non-PV foci that initiate AF (including locations in the LA, RA, or SVC), targeting complex fractionated electrograms or ganglionated plexi or performing left atrial mitral isthmus or roof lines are not allowed in this protocol.

Additional ablation of the cavo-tricuspid isthmus (CTI) with a conventional market approved RF catheter is allowed only in case a typical atrial flutter is documented in prior patient history or occurs during the case (either spontaneously or inducible).

The Cryoablation System cannot be used for the ablation of other arrhythmia(s)/additional line(s) or applications outside the PVs.

It is not allowed to perform concomitant procedures during the ablation procedure (e.g., ICD implant, PM, LAAC, arrhythmia loop recorder).

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.

If at any time during the ablation procedure the investigator is unable to continue the ablation with the designated investigational catheter (for the PV isolation), the investigator may consider the case a procedural failure and complete the case with a device determined best for the subject. The point at which failure was determined as well as the rationale must be documented. A protocol deviation will be documented in the EDC system.

12.6.2. Index procedure collected data

This section identically matches the Index procedure collected data Section (Section 10.6.2) of the FROzEN-AF protocol (92348334), with the exception that the balloon size for each cryoablation application will be collected in this extension study.

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

- Date of procedure
- Identification of all investigational study devices:
    - Cryoablation Catheter
    - Cryoablation Mapping Catheter
    - Cryoablation Steerable Sheath
    - Console and all investigational accessory devices

- Identification of non-study devices if applicable:
    - Additional sheaths/introducers used during the procedure including manufacturer, model, and type
    - Additional catheter(s) used during the case other than Cryoablation Catheter including manufacturer, model, and type (e.g., mapping catheter and CS catheter)
    - Mapping system and mapping catheter (manufacturer and model); if RHYTHMIA HDx™ is used (manufacturer, model, and software version)
- 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 access to left atrium single or double transseptal
- Method of evaluating phrenic nerve function and determining when intervention is needed
- Collection of ACT levels

Specific to the ***PVI ablation*** the following information will be collected:

- Pre-ablation electrograms with baseline entrance and exit conduction for each PV
- Balloon size for each cryoablation application
- Occlusion score for each cryoablation application
- Time-to-Isolation (if achieved), minimum balloon temperature, and duration of each cryoablation application.
- Total number and total duration of cryoablation applications per PV
- Post-ablation electrograms of entrance/exit block for each PV

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
- Total Cryoablation time (duration of all cryoablation applications)
- Duration of LA dwell time defined as time from the Cryoablation Catheter exiting the sheath in the LA to time of final PV isolation.
- 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 through fluoroscopy of diaphragm movement.
- Protocol Deviations, if applicable

After removal from the subject, all investigational catheters should be inspected by the investigational site staff, and if any abnormalities are noted on the catheter, it must be documented. All investigational catheters, steerable sheaths and extension cables opened and/or used during the procedure must be returned to the sponsor. Failure to return an investigational device will result in a protocol deviation. All other control ablation or diagnostic catheters may be disposed of per standard EP practice. All adverse experiences with a BSC product, including those commercially available, during the ablation procedure must be promptly reported to BSC and documented on the eCRF.

- The Export Case Data (the data collected through the Console) will be saved and stored to external media, as provided by the sponsor
- Console Report
- The EP Lab Procedure Report will be printed and stored in the center's patient file. Please refer to Table 10 for an overview of source document requirements.

12.7. *Pre-Discharge Visit*

This section identically matches the Pre-Discharge Visit Section (Section 10.7) of the FROzEN-AF protocol (92348334), with the exception that weight does not need to be collected as part of the physical assessment.

The pre-discharge follow-up visit (0 to 7 days post procedure) should be done before hospital discharge, but 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.

The data collection at Pre-Discharge includes:

- Date of visit
- Physical assessment with cardiovascular/pulmonary examination including:
    - Resting heart rate
    - Systolic and diastolic blood pressure
    - O_2 saturation
    - Lung auscultation (includes respiratory rate and respiratory rhythm)
    - Temperature
- Rhythm at time of visit (by means of a 12-lead ECG)

- Conduct an NIH Stroke Scale (NIHSS) (see Appendix 29.3)
- In cases of phrenic nerve palsy at the index procedure, patients should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Provide subjects with arrhythmia/event monitor and operating instructions (subjects known as procedural failures do not need to be assigned an event monitor)
- Perform a cardiac MRI or spiral CT if PV stenosis is suspected at any time throughout the follow-up period. Recommend using the same imaging modality used at baseline
- New, discontinued or changes to current medication regimen
- Reportable Adverse Events, including resolution of ongoing events, if applicable
- Protocol Deviations, if applicable

If the NIH stroke scale demonstrates new abnormal findings when compared with the pre-procedure assessment, the subject will have a neurology consultation. A brain DW-MRI scan is required if neurology consultation determines possibility of new stroke. The DW MRI scan sequences required will be performed within the local guidelines associated with brain MRI scan. The following parameters for the DW-MRI are recommended to allow comparability of potential findings across patients:

- 1.5T MRI imaging equipment
- Diffusion-weighted imaging technique
- 5 mm slice thickness

12.8. *Day 7 Follow-Up Contact*

This section identically matches the Day 7 Follow-Up Contact Section (Section 10.8) of the FROzEN-AF protocol (92348334).

A telephone contact will occur at 7 days post-procedure (7 days±1 day). If the patient is still hospitalized the 7 days follow-up will be performed as in-hospital visits. The data collection at the day 7 follow-up includes:

- Date of visit
- New, discontinued or changes to in current medication regime
- Reportable Adverse Events, including resolution of ongoing events, if applicable
- Protocol Deviations, if applicable

In cases of in-hospital visit and phrenic nerve palsy at the index procedure, patients should be assessed by means of sniff-test or inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved.

12.9. *Month 3 Follow-Up Visit*

This section identically matches the Month 3 Follow-Up Visit Section (Section 10.9) of the FROzEN-AF protocol (92348334) with the exception that weight does not need to be collected as part of the physical assessment.

This visit should be completed at 3 months post-procedure (91 days±14 days). Due to the range for the visit completion and the endpoint requirement for medication, AAD medication changes made during the three-month follow-up visit will be counted as being made within the blanking period, but efforts should be made to remove subjects from AADs by eight weeks post-procedure to allow for complete washout. The data collection at the 3-month follow-up includes:

- Date of visit
- Physical assessment including resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (by means of a 12-lead ECG)
- In cases of phrenic nerve palsy at the index procedure, patients should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Quality of Life Instruments (AFEQT and EQ-5D-5L)
- Review of any symptomatic transmissions (arrhythmia/event monitor such as a TTM)
- Documentation of any intervention for AF/AT/AFL (e.g., Repeat Procedure, Cardioversion), if applicable
- Perform a cardiac MRI or spiral CT if PV stenosis is suspected at any time throughout the follow-up period. Recommend using the same imaging modality used at baseline.
- New, discontinued or changes to current medication regimen
    - *Reminder: AADs must be stopped for any atrial tachyarrhythmia after the blanking period, please refer to Section 12.5.1.3*
- Reportable Adverse Events, including resolution of ongoing events, if applicable; in particular:
    - In cases of a pre-existing and unresolved phrenic nerve palsy the patient should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Protocol Deviations, if applicable

12.10. *Month 6 Follow-Up Visit*

This section identically matches the Month 6 Follow-Up Visit Section (Section 10.10) of the FROzEN-AF protocol (92348334) with the exception that weight does not need to be collected as part of the physical assessment.

This visit should be completed at 6 months post-procedure (180 days±30 days). The data collection at the month 6 follow-up includes:

- Date of visit
- Physical assessment including resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (by means of a 12-lead ECG)
- Quality of Life Instruments (AFEQT and EQ-5D-5L)
- Review of any symptomatic or asymptomatic transmissions (arrhythmia/event monitor such as TTM)
- Documentation of any intervention for AF/AT/AFL (e.g., Repeat Procedure, Cardioversion), if applicable
- Perform a cardiac MRI or spiral CT if PV stenosis is suspected at any time throughout the follow-up period. Recommend using the same imaging modality used at baseline
- New, discontinued or changes to current medication regimen
- Reportable Adverse Events, including resolution of ongoing events, if applicable; in particular:
    - In cases of phrenic nerve palsy at the index procedure, patients should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Protocol Deviations, if applicable

12.11. *Month 12 Follow-Up Visit*

This section identically matches the Month 12 Follow-Up Visit Section (Section 10.11) of the FROzEN-AF protocol (92348334) with the exception that weight does not need to be collected as part of the physical assessment.

Investigators will assess subject status at 12 months (365 days±30 days) post index procedure. The data collection at the month 12 follow-up includes:

- Date of visit
- Physical assessment including resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (by means of a 12-lead ECG)
- Quality of Life Instruments (AFEQT and EQ-5D-5L)
- Review of any symptomatic or asymptomatic transmissions (arrhythmia/event monitor such as TTM)
- 24-hour Holter monitor data recorded with the study specific TTM

Note: While wearing the Holter monitor, subjects should also make every attempt to capture the symptomatic episode with the TTM

- Documentation of any intervention for AF/AT/AFL (e.g., Repeat Procedure, Cardioversion), if applicable
- Perform a cardiac MRI or spiral CT if PV stenosis is suspected. Recommend using the same imaging modality used at baseline
- New, discontinued or changes to in current medication regime
- Reportable Adverse Events, including resolution of ongoing events, if applicable; in particular:
    - In cases of phrenic nerve palsy at the index procedure, patients should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Protocol Deviations, if applicable

12.12. *Unscheduled Visits*

This section identically matches the Unscheduled Visits Section (Section 10.12) of the FROzEN-AF protocol (92348334).

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

If subjects experience symptoms associated with cardiac arrhythmias (e.g., palpitations, light-headedness, syncope, dyspnea) during the first 12 months, they will be instructed to record the arrhythmia on the event monitor. The investigator will review the information transmitted and will contact the subject to schedule an additional office visit if deemed necessary per investigator's decision.

In addition to determining the best course of action for the subject (repeat ablation, medication adjustment), during the visit, the following will be collected:

- Date of visit
- Physical assessment including resting heart rate, systolic and diastolic blood pressure
- Rhythm at time of visit (by means of a 12-lead ECG)
- Review of any symptomatic or asymptomatic transmissions (arrhythmia/event monitor, such as TTM)
- Documentation of any intervention for AF/AT/AFL (e.g., Repeat Procedure, Cardioversion), if applicable
- Perform a cardiac MRI or spiral CT if PV stenosis is suspected at any time throughout the follow-up period. Recommend using the same imaging modality used at baseline

- New, discontinued or changes to current medication regimen
- Reportable Adverse Events, including resolution of ongoing events, if applicable; in particular:
    - In cases of phrenic nerve palsy at the index procedure, patients should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved
- Protocol Deviations, if applicable

12.13. *Additional/Repeat Procedure*

It is recommended to use the Cryoablation system for repeated ablation procedures to treat AF (during the blanking period and during the effectiveness evaluation period).

In case an additional procedure (including but not limited to a repeat ablation procedure for PAF) occurs during the month 12 follow-up period, the data of this procedure will be entered in the 'Additional/ Repeat Procedure' eCRF. In case this additional procedure is an ablation procedure (for the same, or different arrhythmias or for an unsuccessful ablation of the arrhythmia presented at index procedure), detailed information about this additional ablation procedure will be entered in the 'Additional/Repeat Procedure' eCRF:

- Was the additional ablation procedure performed in the LA? If yes, TEE or ICE to rule out presence of left atrial thrombus.
- For additional ablation procedures performed in the LA: was this additional ablation procedure performed to treat AF? If no, specify the arrhythmia type.

  It is known that a repeat ablation procedure for PAF may be necessary in certain subjects after the index ablation procedure due to recurrences of PAF or other tachyarrhythmias requiring treatment. One repeat ablation procedure for PAF is allowed within the blanking period if considered medically necessary due to patient's intolerability of the PAF. Use of a non-study device for AF re-ablation during blanking period constitutes a failure for the effectiveness endpoint. Data for the repeat ablation procedure will be collected in the eCRF.

  Subjects must follow the same anticoagulation requirements as defined for the index procedure in Section 12.6 prior to proceeding with the repeat ablation procedure for PAF.
- If a 3D mapping system is used for this additional procedure, additional info will be collected
- Reportable Adverse Events, including resolution of ongoing events, if applicable; in particular:
    - In cases of phrenic nerve palsy at the index procedure, patients should be assessed by means of a sniff test or an inhalation-exhalation chest radiography of the diaphragm to evaluate if the event resolved

- Protocol deviations, if applicable

The appropriate type of pre-procedure imaging (CT/MRI) is to be determined by the investigator. As available, the PV images must be reviewed against the pre-ablation imaging from the index procedure to rule out PV stenosis from the index ablation procedure.

12.14. *Study Completion*

This section identically matches the Study Completion Section (Section 10.14) of the FROzEN-AF protocol (92348334).

Each Treatment subject will be followed until the month 12 follow-up. Participation in the study is considered complete upon completion of the month 12 follow-up.

A participant is considered to have completed the study if he or she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Data Collection Schedule, Table 9.

In case of premature termination of the study, please refer to Section 22.1.

Following termination/completion of the study, subjects will be managed according to local institution practice.

Sites will need to document and complete the “End of Study” CRF to signify study completion.

12.15. *Unforeseen Circumstances (Natural Disaster/Global Pandemic)*

This section identically matches the Unforeseen Circumstances Section (Section 10.15) of the FROzEN-AF protocol (92348334).

There may be unforeseen circumstances that occur during the study, such as a natural disaster or a global pandemic (e.g., COVID-19) that prevents a subject from attending study visits during the required follow-up window. While every attempt should be made to avoid disruptions in collecting study data, it is important to collect as much data as possible, by any available means and from any available resources. This may include obtaining records from an outside clinic, hospital or other healthcare facility that is not IRB/EC/REB approved.

If study data must be collected remotely, every effort should be made to collect the data within the study visit window, if possible. Critical data collected during the study includes any procedure or device related adverse events, recurrence of any AF/AT/AFL, and a Cardiac CT or MRI (if PV stenosis is suspected). Event monitors and 24- hour Holter monitors can be used to detect any recurrence of AF/AT/AFL. If a Cardiac CT or MRI is required because PV stenosis is suspected, the Cardiac CT or MRI may be performed at another healthcare facility and the window to conduct this test may be extended by up to one month (30 days) following the normal study visit window.

12.16. *Source Documents*

This section identically matches the Source Documents Section (Section 10.16) of the FROzEN-AF protocol (92348334).

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.

Table 10: 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
Pregnancy, if applicable	Retain at Center
Physical assessment	Retain at Center
Cardiovascular/pulmonary examination	Retain at Center
Medication Regimen and Changes	Retain at Center
Medical history	Retain at Center
Quality of Life Instruments (AFEQT and EQ-5D-5L)	Retain at Center
NIH Stroke Scale Assessments	Retain original at center and submit copies and all associated source documents if a change in scale is observed from baseline
If determined necessary, neurological consultation and brain MRI (DW-MRI)	Retain originals at center and submit all source documents and copy of complete scan to BSC
Imaging	Retain at Center
12-Lead ECGs data including ongoing rhythm	Retain at Center
Imaging, per standard of care	Retain at Center
Recording System Printouts, showing entrance/exit block for each Pulmonary Vein	Retain at Center
Pre-ablation electrograms with baseline entrance and exit conduction for each PV	Retain at Center
Recording lab logs, showing the time of entrance/exit block	Retain at Center
Signed Technical Source Form	Retain at Center

Requirement	Disposition
Console Report	Retain at Center
Console Export Case Data	Retain at Center Submit one copy to BSC
Printed EP Lab Procedure Report	Retain at Center
Adverse Events	Retain at Center
In the event of a patient death: • Death narrative • Relevant medical records • Death Certificate • Autopsy report Events be adjudicated by CEC: • Relevant medical records	Submit one copy to BSC, Retain one copy at center

13. Statistical Considerations

13.1. *Endpoints*

13.1.1. Primary Safety Endpoint

The primary safety endpoint at 3 months is defined as the safety event-free rate at 3 months post-procedure.

Primary safety events at 3 months will consist of a composite of the following procedure-related and/or device-related adverse events.

Events will be counted through 7 days post index procedure or hospital discharge, whichever is later, unless denoted as events counting through 3 months post index procedure.

- Death
- Myocardial infarction (MI)
- Major Vagal Nerve Injury/Gastroparesis
- Transient ischemic attack (TIA)
- Stroke/Cerebrovascular accident (CVA)
- Thromboembolism
- Cardiac tamponade/perforation*
- Pneumothorax
- Major vascular access complications
- Pulmonary edema/heart failure
- AV block**
- Atrial esophageal fistula***

- Severe pulmonary vein stenosis (≥70% reduction in the diameter of the PV or PV branch from baseline)***
- Persistent phrenic nerve palsy****

*Cardiac tamponade/perforation occurring up to 30 days post-index-procedure will count as primary safety endpoint events
**AV block not attributable to medication effect or vasovagal reaction.
***Atrial esophageal fistula and severe pulmonary vein stenosis occurring up to 3 months post-index-procedure will count as primary safety endpoint events
**** Phrenic nerve palsy not resolved at the end of the 3 months follow up will count as primary safety endpoint event.

13.1.1.1. Hypotheses

Statistical considerations were not utilized in the design of this extension study and there are no formal hypotheses to be tested for the primary safety endpoint.

13.1.1.2. Sample Size

Due to a lack of hypotheses for the objective, the sample size cannot be determined through traditional statistical powering techiniques. The chosen sample size of 50 31 mm TREATMENT subjects is intended to be a reasonable number to assess the endpoint with a sufficient degree of precision.

13.1.1.3. Statistical Methods

Analysis of study data will use descriptive statistical methods. For the primary safety endpoint, the Kaplan-Meier 3-month primary safety event free rate will be calculated. Subjects who withdraw from the study prior to 3-month or have a repeat procedure performed with a non-study catheter without experiencing an event will be censored on the date of withdrawal or repeat procedure. The observed primary safety event free rate and its 95% confidence limits (calculated as the pointwise confidence limit using the log-log methodology) will be provided.

13.1.2. Primary Effectiveness Endpoint

The primary effectiveness endpoint is the rate of acute procedural success where acute procedural success is defined as the achievement of electrical isolation of all PVs by using the Cardiac Cryoablation System with the POLARx FIT cryoablation balloon catheter models (with treatment applied at 28 mm or 31 mm balloon size per physician discretion). Electrical isolation of a PV is demonstrated by entrance and exit block.

13.1.2.1. Hypotheses

Statistical considerations were not utilized in the design of this extension study and there are no formal hypotheses to be tested for the primary effectiveness endpoint.

13.1.2.2. Sample Size

Due to a lack of hypotheses for the objective, the sample size cannot be determined through traditional statistical powering techiniques. The chosen sample size of 50 31 mm TREATMENT subjects is intended to be a reasonable number to assess the endpoint with a sufficient degree of precision.

13.1.2.3. Statistical Methods

Analysis of study data will use descriptive statistical methods. For the primary effectiveness endpoint, the binomial acute procedural success rate and Clopper-Pearson 95% confidence limits will be presented.

13.2. *General Statistical Methods*

13.2.1. Analysis Sets

The primary and secondary safety endpoints and additional analyses of safety data will use all available data from ATTEMPT and TREATMENT subjects enrolled in POLARx FIT: FROZEN-AF Extension study. The primary and secondary effectiveness endpoints and additional analyses of effectiveness data will use all available data from TREATMENT subjects.

Additionally, in order to further evaluate the safety and effectiveness of the POLARx FIT catheter when used at its larger size, an analysis will be performed of each primary and secondary endpoint including all available data from 31 mm TREATMENT subjects only.

13.2.2. Control of Systematic Error/Bias

Selection of patients will be made from the Investigator's population. All patients meeting the eligibility criteria and having signed the ICF will be eligible for enrollment in the study. Control and reduction of potential bias associated with a single-arm study design have been taken into account by considering a series of measures including but not limited to:

- defining inclusion and exclusion criteria to represent a population like the one enrolled in recently completed trials on AF ablation
- implementing a screening log to document reason(s) for screening failure and a pre-specified analysis on screening failures
- employing a rhythm surveillance monitoring strategy that is equivalent to that used in recent PAF IDE studies and consistent with the relevant recommendation in the HRS consensus document
- utilizing core lab for reviewing electrocardiographic recordings from study specific rhythm surveillance monitoring after the blanking period

13.2.3. Number of Subjects per Investigative Site

To avoid any center effect and bias, one center will not be authorized to enroll more than 18 subjects.

13.3. *Data Analyses*

13.3.1. Interim Analyses

No formal interim analyses are planned for the purpose of stopping the study early for declaring effectiveness or for futility.

An interim report on the 31 mm TREATMENT group is planned for submission to FDA. Procedural data on both a per subject and a per pulmonary vein basis, acute procedural success data, and 7-day serious adverse events data will be submitted for a sub-set of these subjects as well as a summary of the study status and safety for all POLARx FIT: FROZEN-AF Extension study subjects available at the time of the report.

Final analysis of each endpoint will be performed when all applicable data for that endpoint has been collected. Analysis of the primary endpoints for submission to FDA occur after all 3-month data has been collected on all subjects.

13.3.2. Justification of Pooling

Poolability of the FROzEN-AF Extension Study data with the data from the main FROzEN-AF study will be assessed for the primary and secondary endpoints of the FROzEN-AF Extension Study. The endpoints from the FROzEN-AF Extension study will be evaluated in the FROzEN-AF study and data from the two studies will be deemed to be poolable if the absolute difference in the endpoint rates is found to be less than a clinically meaningful delta. This analysis will occur for the FROzEN-AF Extension Study primary endpoints when 3-month data on all subjects has been collected and on the FROzEN-AF Extension Study secondary endpoints when 12-month data on all subjects has been collected.

13.3.3. 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.

14. Health Economics Outcomes

This section identically matches the Health Economics Outcomes Section (Section 12) of the FROzEN-AF protocol (92348334).

A formal health economics analysis may be completed as part of this trial study, given meaningful clinical results are obtained. This will take into consideration complication rates, quality of life, and resource utilization. The EQ-5D, generic quality of life measure, will be used to assess health utilities. We may estimate costs associated with the health care utilization measures at all sites. These inputs may be used in health economics analysis performed.

15. Data Management

Sections 13.1-13.3 identically match sections 13.1-13.3 of the FROzEN-AF protocol (92348334).

15.1. *Data Collection, Processing, and Review*

Subject data will be recorded in a limited access secure electronic data capture (EDC) system.

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.

All access to the clinical database will be changed to “Read only” after all data is either “Hard Locked” or “Entry Locked”. Once acceptance of the final report or finalization of publications (as applicable) is received, final database storage and archiving activities can begin. Once all the closeout activities are completed a request to IT is submitted to have the “Database Locked” or Decommissioned and all database access revoked.

Data transfers from other systems such as core labs and electronic questionnaires will be coordinated by Boston Scientific.

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

15.2. *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.

15.3. *Technical Source Forms*

The Technical Source Form (TSF) is the sponsor-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. If available, the console operator will provide the delegated site personnel with the study related data collected during the case directly from the console.

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

- Delegated Site Personnel completing the forms
- Delegated Investigator conducting and/or supervising the case
- Console operator supporting the case

15.4. *Core Laboratories*

15.4.1. Event and 24-Hour Holter Monitors' Core Lab

15.4.1.1. Event Monitors

A Core Lab will provide the center and/or subject all necessary instructions and/or materials related to the use of the event monitor. Only TREATMENT subjects will be provided with an event monitor, such as a Trans-Telephonic Monitor (TTM), either prior to discharge from the hospital or will be sent to the subject's residence immediately following discharge. All events will be analyzed by the centralized research company to determine if the episodes are associated with arrhythmia recurrence. The Core Lab will make this information accessible to the Investigator center for concurrence. If there is discordance in arrhythmia classification between

the Core Lab and the investigator, a third-party cardiologist will be used for final rhythm determination.

Within the first 90 days (3 months) after the index ablation procedure (blanking period), TREATMENT subjects will be instructed to transmit all symptomatic episodes for detection and/or treatment of early recurrences. After the subject's 3-month follow-up visit, subjects will be instructed to send at least two transmissions per month (either symptomatic or asymptomatic) through the 12-month follow-up to ensure continued reporting compliance. If subjects experience symptoms associated with cardiac arrhythmias (e.g., palpitations, lightheadedness, syncope, dyspnea), they will be instructed to transmit a recording. Such recording will count towards the required transmission of that period. The Core Lab will work with the investigational site to ensure reporting compliance.

All event monitors must be returned to the centralized research company upon completion of a subject's 12-month follow-up or withdrawal from the study.

15.4.1.2. 24-Hour Holter Monitors

Each TREATMENT subject will be provided with a 24-Hour Holter Monitor at the 12-month follow-up visit.

Investigational centers will be trained on the set-up of the monitors and will provide the subjects with the instructions necessary to complete the test. If a subject has a symptomatic episode while wearing the Holter Monitor, they will be strongly encouraged to report the symptoms to their physician. Once the Holter Monitor is returned to the centralized research company, the monitor will be analyzed for all symptomatic and asymptomatic arrhythmia episodes, and investigators will be informed of the results.

15.4.2. ECG Core Lab

To ensure objective assessment of rhythm monitoring data, 12-lead ECG tracings obtained beyond 3 months post-procedure will be reviewed by an independent core lab.

15.4.3. PV Stenosis Imaging

Images (CT/MRI) collected to assess adverse events associated with symptomatic pulmonary vein (PV) stenosis will be assessed by an independent core lab.

15.5. *Quality of Life (QOL)*

Clinical trials increasingly recognize the value of including patient reported outcome measures in their design. To understand the impact of atrial fibrillation ablation procedures on patient's quality of life, the quality-of-life instruments used for the trial will be the EQ-5D-5L for a generic questionnaire and the AFEQT for disease specific. Subjects will be asked to complete the questionnaires at the Enrollment visit as well as at the three, six, and 12-month follow-ups.

The Atrial Fibrillation Effect on Quality of Life (AFEQT) was developed to evaluate disease-specific quality of life for patients with atrial fibrillation. The 20-item questionnaire is subdivided into three domains: symptoms, daily activities, and treatment concerns with responses provided on a seven-point Likert scale.

The EQ-5D, generic quality of life measure, will be used to assess health utilities. It is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.

16. Deviations

This section identically matches the Deviations Section (Section 14) of the FROzEN-AF protocol (92348334).

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 IRB/EC/REB, and the regulatory authority if applicable, 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 investigation. 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 eCRF. Sites may also be required to report deviations to the IRB/EC/REB, 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 IRB/FDA notification, site re-training, or site discontinuation/termination) will be put into place by the sponsor.

17. Accountability for Study Products

17.1. *Investigationally-Labelled Products*

The investigationally-labelled devices/equipment shall be securely maintained, controlled, and used only in this clinical study.

For investigationally-labelled items, the principal investigator or an authorized designee shall do the following:

- Securely maintain and control access to these items to ensure they are used only in this clinical study and only per the protocol.
- Ensure the storage environment for these items is appropriate for maintaining conditions per the items' labeling (e.g., temperature, humidity, etc., as applicable)
- Return remaining items and equipment upon Sponsor request and in the condition in which they were provided, reasonable wear and tear excepted.

The sponsor shall keep records to document the physical location of all investigationally-labelled devices/equipment from shipment of investigational devices from BSC or designated facility to the investigation sites until return or disposal.

The principal investigator or an authorized designee shall keep records documenting the receipt, use, return and disposal of the investigationally-labeled devices/equipment, which shall include the following:

- Names of person(s) who received, used, returned or disposed of each item
- Date of receipt
- Identification and quantity of each investigational device/piece of equipment (examples of identification: batch number, serial number or unique code)
- Expiry date, as applicable
- Date or dates of use
- Subject identification
- Date on which the investigational device/piece of equipment was returned/explanted from subject, if applicable
- Date of return (and number) of unused, expired, no longer needed, and/or or malfunctioning investigational devices/equipment, if applicable
- Date and documentation of item disposal, as directed by sponsor, if applicable
- Physical location and conditions of storage

17.2. *Commercially Labelled Products*

As directed by the study case report form, the principal investigator or an authorized designee shall keep records documenting the use of commercially labeled devices/equipment in the study, which shall include the following:

- Identification and quantity of each investigational device/piece of equipment (examples of identification: batch number, serial number, or unique code)
- Date or dates of use
- Subject identification

18. Compliance

18.1. *Statement of Compliance*

This clinical investigation is financed by the study sponsor. Before the investigational site can be "Authorized to Enroll," the investigational site must enter into a Clinical Study Agreement with the sponsor that details the financing of the study as well as the rights and obligations of the investigational site and the investigator.

This study will be conducted in accordance with 21 CFR 814.20 part 56, part 50, part 54 and part 812 or 814.82, ISO 14155 Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice, 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 IRB and 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 IRB or regulatory authority shall be followed, if appropriate.

18.2. *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, ISO 14155 Clinical Investigation of Medical Devices for Human Subjects, ethical principles that have their origin in the Declaration of Helsinki, any conditions of approval imposed by the reviewing IRB/EC/REB, and prevailing local and/or country laws and/or regulations, whichever affords the greater protection to the subject.

- Prior to beginning the study, sign the Clinical Study Agreement and comply with the Investigator responsibilities as described in such Agreement.
- Prior to beginning the study, sign the Investigator Brochure Signature Page (if applicable) and Protocol Signature page documenting his/her agreement to conduct the study in accordance with the protocol.
- 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 clinical investigation.

- 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-investigation-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 reportable events.
- Report to the IRB/EC/REB 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 IRB/EC/REB, and supply BSC with any additional requested information related to the safety reporting of a particular event
- Maintain the device accountability records and control of the investigationally-labelled device, ensuring that the investigationally-labelled device is used only by authorized/designated users and in accordance with this protocol and instructions/directions for use.
- Allow the sponsor to perform monitoring and auditing activities, 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 IRB/EC/REB when performing auditing activities.
- Ensure that informed consent is obtained in accordance with applicable laws, this protocol and local IRB/EC/REB 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 investigational device when it is used/operated by the subject.
- Inform the subject of any new significant findings occurring during the clinical investigation, 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, 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 investigation are provided with some means of showing their participation in the clinical investigation, 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 investigation.
- Make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from clinical investigation while fully respecting the subject's rights.
- Ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation.

All investigators will provide their qualifications and experience to assume responsibility for their delegated tasks 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.

18.2.1. Delegation of Responsibility

When specific tasks are delegated by an investigator, including but not limited to conducting the informed consent process, the Principal Investigator is responsible for providing appropriate training, ensuring delegated personnel are competent to perform the tasks they have been delegated and provide 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.

18.3. *Institutional Review Board/ Ethics Committee*

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

A copy of the written IRB/EC/REB 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 and shipment of investigational product/equipment. 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 IRB/EC/REB before the changes are implemented to the study. All changes to the ICF will be IRB/EC/REB 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 IRB/EC/REB approval and renewals will be obtained throughout the duration of the study as required by applicable

local/country laws or regulations or IRB/EC/REB requirements. Copies of the study reports and the IRB/EC/REB continuance of approval must be provided to the sponsor.

18.4. *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.

18.4.1. 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 implant, 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 implant or follow-up, 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:

- Provide instructions for the safe return of investigational products. For potentially hazardous items, provide specialized instructions and materials, as applicable.
- Interrogating the device or programming device parameters to investigator-requested settings as well as operating investigational equipment
- Performing lead diagnostic testing using a Pacing System Analyzer or programmer to obtain pacing and sensing thresholds and impedance measurements
- Clarifying device behavior, operation or diagnostic output as requested by the investigator or other health care personnel
- Assisting with the collection of study data from Pacing System Analyzers, programmers, and other equipment

- Entering technical data on technical source form if the responsible investigator verifies and signs the completed form
- Print out programming reports directly from the programmer and provide original 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
- 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

18.5. *Insurance*

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

19. Monitoring

This section identically matches the Monitoring Section (Section 17) of the FROzEN-AF protocol (92348334).

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 sponsor will put a plan in place to document the specific monitoring requirements.

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 or remote monitoring visits or audits and that sufficient time is devoted to the process.

20. Potential Risks and Benefits

This section identically matches the Potential Risks and Benefits Section (Section 18) of the FROzEN-AF protocol (92348334).

20.1. *Anticipated Adverse Events*

Subjects participating in this study are subject to the same risks shared by all patients undergoing an ablation procedure for treatment of PAF. Since the handling characteristics of the Cryoablation System are designed to be similar to those of other approved catheters for AF ablation, it is anticipated that the rate of catheter-related complications in this study will be similar to those reported from catheter ablations performed with approved catheter ablation systems. The protocol-required testing for this study uses standard techniques that are routinely used for the treatment and management of subjects with drug refractory PAF.

Based upon the current literature and BSC reports on adverse events with an ablation catheter, Table 11 includes an alphabetical list of the possible anticipated adverse events and possible adverse device effects associated with ablation with a cryoballoon ablation catheter for the treatment of PAF. Occurrence of any of the listed events could lead to prolonged hospitalization for the subject.

The following anticipated adverse events (AE) and adverse device effects (ADE) have been identified for this study:

Table 11: Potential Adverse Events and Adverse Device Effects for PAF Ablation and Study Device

Access site complications	Headache
Allergic reaction	Heart failure
Anemia	Hematoma
Arrhythmias	Hemothorax
Bleeding/Hemorrhage	Hemodynamic instability
Blurred vision	Hypertension/Hypotension
Cardiac perforation	Inadvertent injury to adjacent structures
Cardiac/pulmonary arrest	Infection
Catheter entrapment	Myocardial infarction
Cerebrovascular accident (CVA)	Nerve weakness/palsy/injury (i.e., phrenic/ vagus)
Chest discomfort/pain or pressure	Pericarditis

Complete heart block (transient/permanent)	Pneumothorax
Complications of sedative agents/anesthesia/medications	Pseudoaneurysm
Coronary artery spasm	Pulmonary complications (i.e., edema, pulmonary hypertension, pleuritis, pneumonia)
Cough	Pulmonary vein stenosis
Death	Radiation injury/exposure
Diaphragmatic paralysis	Renal insufficiency/failure
Dizziness or lightheadedness	Respiratory Depression
Edema	Residual atrial septal defect (ASD)
Pericardial effusion/pleural effusion	Skin burns (i.e., radiation/defibrillator/ cardioverter)
Elevated cardiac enzymes	ST segment Elevation
Embolism (venous/arterial) (i.e. air, gas, thrombo, pulmonary)	Sore Throat
Endocarditis	Tamponade
Esophageal injury	Thrombus/thrombosis
Fever	Transient ischemic attack (TIA)
Exacerbation of existing conditions	Valvular damage
Fatigue	Vasospasm
Fistula (arterial-venous, atrial-esophageal)	Visual disturbances
Gastroparesis	Vasovagal reactions
	Vessel trauma (i.e., injury/ulceration/ perforation/ dissection/rupture)

20.2. *Risks Associated with the Study Device(s)*

Benchtop studies, pre-clinical research and a CE Mark clinical study have demonstrated that the System is safe for human use. All potential risks have been evaluated and mitigation strategies have been implemented to reduce potential risks to acceptable levels.

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

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

20.4. *Risk Minimization Actions*

Additional risks may exist. Risks can be minimized through compliance with this protocol, using the devices in accordance with their applicable Directions for Use, performing the procedures following recommended standard practices/guidelines, performing procedures in the appropriate hospital environment, 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.

20.5. *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 PAF. Potential benefits of the Cryoablation System for the subject may include the following:

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

20.6. *Risk to Benefit Rationale*

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.

21. Safety Reporting

21.1. *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:

Reportable Events:

- All Serious Adverse Events
- All Events Leading to Death
- All Thromboembolic Events

- All Procedure Related AEs inclusive of AEs related to the assessments (TTE, TEE, ICE or CT/MRI scan) listed in Section 12.4.
- All BSC commercialized diagnostic catheter-related events
- All Cryoablation System Device Related Adverse Events
- All Device Deficiencies
- Unanticipated Adverse Device Effects/Unanticipated Serious Adverse Device Effects previously not defined in the IFU/IB and ICF
- New findings/updates in relation to already reported events

Whenever possible, the medical diagnosis should be reported as the Event Term instead of individual symptoms.

If it is unclear whether 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 AE but should only be reflected as an outcome of one specific SAE (see Table 12 for Safety Definitions).

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.

If the patient experiences a new arrhythmia between the index procedure and the end of study, and the investigator considers this Adverse Event to be procedure related, it needs to be reported. Refer to Investigator's Brochure or IFU as appropriate for the known risks associated with the study device(s).

Pre-existing diseases or conditions will not be reported as adverse events unless there has been a substantial increase in severity or frequency of the problem which cannot be attributed to the expected progression of the disease or condition.

The Boston Scientific Medical Safety group will provide safety oversight by reviewing and classifying individual events that are reported to the sponsor. Routine aggregate safety reviews will be conducted to ensure subject safety.

Refer to Section 20 for the known risks associated with the study device(s).

21.2. *Definitions and Classification*

Adverse event definitions are provided in Table 12. Administrative edits were made on the safety definitions from applicable regulations and guidance including (but not limited to) 21 CFR

Part 812, ISO 14155, and EU MDR 2017/745/MDCG 2020-10/1 Guidance on Safety Reporting in Clinical Investigations for clarification purposes.

Table 12: Safety Definitions

Term	Definition
Adverse Event (AE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Any untoward medical occurrence, unintended disease or injury, or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device and whether anticipated or unanticipated. **NOTE 1**: This includes events related to the investigational 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 investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event related to the use of an investigational 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 investigational medical device. **NOTE 2**: This definition includes any event resulting from use error or intentional misuse of the investigational medical device. **NOTE 3**: This includes 'comparator' if the comparator is a medical device.
Serious Adverse Event (SAE) *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	Adverse event that led to any of the following: a) death, b) serious deterioration in the health of the subject, users or other persons as defined by either: 1) a life-threatening illness or injury, or 2) a permanent impairment of a body structure or a body function, including chronic diseases or 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) fetal distress, fetal death, or a congenital abnormality or birth defect including physical or mental impairment. **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*	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Term	Definition
Ref: MDCG 2020-10/1	
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: MDCG 2020-10/1*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk assessment. **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 assessment.
Serious Health Threat *Ref: ISO 14155*	Signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons. **NOTE 1**: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.
Device Deficiency *Ref: ISO 14155* *Ref: MDCG 2020-10/1*	An inadequacy of an investigational medical device (defined as the study device/Cryoablation System) related to its identity, quality, durability, reliability, usability, safety or performance. NOTE 1: Device deficiencies include malfunctions, use errors, and inadequacy in the information supplied by the manufacturer including labelling. NOTE 2: This definition includes device deficiencies related to the investigational medical device or the comparator.
The following definitions will be used for defining hospitalization or prolongation of hospitalization for SAE classification purposes:	
Hospitalizations	Hospitalization does not include: • emergency room visit that does not result in in-patient admission Note: although an emergency room visit does not itself meet the definition for hospitalization, it may meet other serious criteria (e.g., medical or surgical intervention to prevent permanent impairment or damage) • elective and pre-planned treatment/surgery for a pre-existing condition that is documented in the subject's record at the time of consent/enrollment

Term	Definition
	• admission for social reasons and/or respite care in the absence of any deterioration in the subject's general condition (e.g., subject is homeless, caregiver relief) • pre-planned, protocol-specified admission related to the clinical study (e.g., procedure required by protocol)
Prolongation of hospitalization	In-patient admission to the hospital that is prolonged beyond the expected standard duration for the condition under treatment. Note: new adverse events occurring during the hospitalization are evaluated to determine if they prolonged hospitalization or meet another SAE criterion.

21.3. *Relationship to Study Device(s)*

The Investigator must assess the relationship of the reportable AE to the study device(s) and/or study procedure, see criteria in Table 13.

Table 13: Criteria for Assessing Relationship of Study Device or Procedure to Adverse Event

Classification	Description
Not Related *Ref:* *MDCG 2020-10/1*	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the investigational device, or the procedures related to the use of the investigational device - 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 that cannot 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 investigational device used for diagnosis, when applicable. 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.

Possibly Related *Ref:* *MDCG 2020-10/1*	The relationship with the use of the investigational device or comparator, or the relationship with procedures 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 where relatedness cannot be assessed, or no information has been obtained, should also be classified as possible.
Probably Related *Ref:* *MDCG 2020-10/1*	The relationship with the use of the investigational device or comparator, or the relationship with procedures seems relevant and/or the event cannot be reasonably explained by another cause.
Causal Relationship *Ref:* *MDCG 2020-10/1*	The serious event is associated with the investigational 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 investigational device use/application or procedures - the event involves a body-site or organ that -the investigational device or procedures are applied to -the investigational 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 investigational 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 adverse event

21.4. *Investigator Reporting Requirements*

The communication requirements for reporting to BSC are as shown in Table 14.

Adverse events and device deficiencies must always be reported through the eCRF system. If 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:

FROZENAF.safety@bsci.com

Table 14: Investigator Reporting Requirements

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (21 CFR Part 812, MDCG 2020-10/1)
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, as requested by sponsor.	• Upon request of sponsor.
Serious Adverse Event	Complete AE eCRF page with all available new and updated information.	• Immediately, but not later than 3 calendar 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
Serious Adverse Device Effects	Complete AE eCRF page with all available new and updated information.	• Immediately, but not later than 3 calendar 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.	• When documentation is available
		• Upon request of sponsor
Device Deficiencies (including but not limited to, malfunctions, use errors and inadequacy in information	Complete Device Deficiencies eCRF with all available new and updated information.	• Immediately, but not later than 3 calendar days of first becoming aware of the event. • Reporting required through the end of the study

Event Classification	**Communication Method**	**Communication Timeline pre-market studies** (21 CFR Part 812, MDCG 2020-10/1)
supplied by the manufacturer, including labeling) Note: Any Device Deficiency that might have led to a serious adverse event if appropriate action had not been taken, intervention had not occurred, circumstances had been less fortunate is considered a reportable event.	Provide all relevant source documentation (de-identified/ pseudonymized) for reported event.	• Upon request of sponsor
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. Provide all relevant source documentation (de-identified/pseudonymized) for reported event, as requested by sponsor.	• Adverse Device Effects: In a timely manner but not later than 10 business days after becoming aware of the information • Adverse Events: In a timely manner but recommend within 10 business days after becoming aware of the information • Reporting required through end of study • Upon sponsor request

* Please note that pre-market studies are clinical studies with investigational devices or with medical devices that bear the regulatory approval and are not being used for the same approved indications.

21.5. *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 (Cryoablation System) will be documented and reported to BSC. If possible, the study device(s) should be returned to BSC for analysis. Instructions for returning the study catheters will be provided in the Site Initiation Visit slides. 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 failures and malfunctions should also be documented in the subject's medical record.

Device deficiencies (including but not limited to failures, malfunctions, and product nonconformities) are not adverse events. However, a reportable event that results from a device failure or malfunction, would be recorded as an adverse event on the appropriate eCRF.

For Device Deficiencies, the investigator must assess and report if the device deficiency could 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.

21.6. *Reporting to Regulatory Authorities / IRBs / ECs / REBs/ Investigators*

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

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

21.7. *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 IRB/EC/REB must be notified of any deaths in accordance with that site's IRB/EC/REB policies and procedures.

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, 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 catheter, clinical investigation, procedure, or patient condition
- Whether or not the death was witnessed
- Whether the patient 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:

- If the patient 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 patient 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)

The Clinical Events Committee (CEC) must review information regarding subject deaths for events listed in Section 23.2.

22. Informed Consent

This section identically matches the Informed Consent Section (Section 20) of the FROzEN-AF protocol (92348334).

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 investigational devices, study-required procedures and/or testing, or data collection.

The obtaining and documentation of Informed Consent must be in accordance with 21 CFR 814.20 part 56, part 50 and part 812 or 813, ISO 14155: Clinical Investigation of Medical Devices for Human Subjects - Good Clinical Practice and Japan Medical Device GCP, ethical principles that have their origins in the Declaration of Helsinki, and applicable individual country laws and any applicable national regulations, IRB/EC/REB 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 IRB/EC/REB, or central IRB/EC/REB, 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 IRB/EC/REB. 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 IRB/EC/REB 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 and by the investigator and/or an authorized designee responsible for conducting the informed consent process. 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., IRB/EC/REB), 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 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 IRB/EC/REB. The new version of the ICF must be approved by the IRB/EC/REB. Acceptance by Boston Scientific is required if changes to the revised ICF are requested by the site's IRB/EC/REB. The IRB/EC/REB will determine the subject population to be re-consented.

23. Committees

This section identically matches the Committees Section (Section 21) of the FROzEN-AF protocol (92348334).

23.1. *Safety Monitoring Process*

To promote early detection of safety issues, the Clinical Events Committee and Data Monitoring Committee will provide evaluations of safety events. Success of this program requires dynamic collection of unmonitored data as soon as the event is reported. During regularly scheduled

monitoring activities, clinical research monitors will support the dynamic reporting process through their review of source document and other data information.

BSC personnel, from the Medical Safety and Safety Trial Operation Teams, review safety data as it is reported by the sites throughout the duration of the study. The BSC Medical Safety group includes health care providers with expertise in Electrophysiology and with the necessary therapeutic and subject matter expertise to evaluate and classify the events into the categories outlined above.

23.2. *Clinical Events Committee*

A Clinical Events Committee (CEC) is an independent group of individuals with pertinent expertise that will adjudicate events reported by study investigators and their relationship toward the primary endpoints.

- All Deaths
- All Adverse Events included in the composite primary safety endpoint per Section 8.2 of Protocol
- All Adverse Event that are potentially related to the procedure or any of the devices included in the Cryoablation System, as defined in Table 1.
- All unanticipated device effects.
- Other events at the discretion of BSC

Committee members will include practitioners of Electrophysiology (EP), and/ or Cardiology, as well as other experts with the necessary therapeutic and subject matter expertise to adjudicate the event categories outlined above. A complete description of CEC responsibilities, qualifications, membership, and committee procedures will be outlined in the CEC charter.

The CEC will review a safety event dossier, prepared by BSC, which may include copies of subject source documents provided by study sites, core lab results and independent reviewer information as available for the above listed events. For purposes of determining inclusion into the primary safety endpoint, the CEC will adjudicate all the above listed events as to their level of seriousness and relation to the ablation procedure and/or catheter. The death classification system that will be used by the CEC was developed using the NASPE policy 36, as well as definitions from Epstein et al. (16) and O'Connor et al. (17). All supporting source documentation provided by the center will be sent to the CEC for adjudication as defined in the CEC charter.

23.3. *Data Monitoring Committee*

A Data Monitoring Committee (DMC) is responsible for the oversight review of all AEs. The DMC will include leading experts in Electrophysiology and Biostatistics who are not

participating in the study and who have no affiliation with BSC. During the study, the DMC will review accumulating safety data to monitor the incidence of AEs sent to the CEC and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and DMC procedures will be included in the DMC Charter.

Any DMC recommendation for study modification or termination because of concerns over subject safety or issues relating to data monitoring or quality control will be submitted in writing to BSC and the study Principal Investigator for consideration and final decision. If the DMC at any time determines that a potentially serious risk exists to subjects in this study, the DMC chairman will immediately notify both BSC and the Principal Investigator.

23.4. *Executive/ Steering Committee*

A Steering Committee composed of the sponsor's Clinical Management, the study Principal Investigator, other prominent Electrophysiologists from around the globe and a patient who underwent an electrophysiology procedure has been convened for this study. Responsibilities for the Committee include oversight of the overall conduct of the study with regards 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.

24. Suspension or Termination

This section identically matches the Suspension or Termination Section (Section 22) of the FROzEN-AF protocol (92348334).

24.1. *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 IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination.

24.1.1. Criteria for Premature Termination of the Study

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

- Suspicion of an unacceptable risk, including serious health threat. In this case, the sponsor shall suspend the clinical investigation while the risk is assessed. The sponsor shall terminate the clinical investigation if an unacceptable risk which cannot be controlled is confirmed.

- Instructions by the IRB/EC/REB or regulatory authorities to suspend or terminate the clinical investigation.
- 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 of the device.

24.2. *Termination of Study Participation by the Investigator or Withdrawal of IRB/ EC /REB Approval*

Any investigator, or associated IRB/EC/REB 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 IRBs/ECs/REBs, and regulatory authorities, as applicable, will be notified in writing in the event of these occurrences.

24.3. *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 IRB, EC/REB 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 IRB, EC/REB terminates participation in the study, participating investigators, associated IRB, EC/REB, 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 investigational product to Boston Scientific, unless this action would jeopardize the rights, safety, or welfare of the subjects.

24.4. *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 6 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 study 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 IRB/EC/REB and regulatory authorities, as applicable, will be

notified. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

25. Study Registration and Results

This section identically matches the Study Registration and Results Section (Section 23) of the FROzEN-AF protocol (92348334).

25.1. *Study Registration*

This research-study is registered on http://www.ClinicalTrials.gov, as required by U.S. Law and other jurisdictions.

25.2. *Clinical Investigation Report*

Study results will be made available in accordance with the legal requirements and the recognized ethical principles, in accordance with the Boston Scientific Policy. A Clinical Investigation Report will be made available to all investigators, IRB/EC/REB and regulatory authorities, as applicable in accordance with the Boston Scientific Policy and local requirements. As applicable an abbreviated Clinical Investigation Report will be made available on a publicly accessible database.

25.3. *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 may 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). 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 trial may be made available to other researchers in accordance with the Boston Scientific Data Sharing Policy (https://www.bostonscientific.com/).

26. Reimbursement and Compensation for Subjects

This section identically matches the Reimbursement and Compensation for Subjects Section (Section 24) of the FROzEN-AF protocol (92348334).

26.1. *Subject Reimbursement*

Travel and other expenses incurred by subjects because of participation in the study will be reimbursed in accordance with pertinent country laws and regulations and per the study site's regulations.

26.2. *Compensation for Subject's Health Injury*

Boston Scientific will purchase an insurance policy to cover the cost of potential health injury for study subjects, if required by applicable law.

27. Bibliography

This section identically matches the Bibliography Section (Section 25) of the FROzEN-AF protocol (92348334).

1. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A, Task Force on the Management of Valvular Hearth Disease of the European Society of Cardiology., and ESC Committee for Practice Guidelines. Guidelines on the management of valvular heart disease: The Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J. 2007 Jan;28(2):230-68.
2. January, CT et al., 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol 2014; 64(21): e1-e76.
3. Lloyd-Jones, DM et al., Defining and setting national goals for cardiovascular health promotion and disease reduction: the American Heart Association's strategic Impact Goal through 2020 and beyond. Circulation. 2010 Feb 2;121(4):586-613. doi: 10.1161/CIRCULATIONAHA.109.192703. Epub 2010 Jan 20.
4. Feinberg WM BJ, Laupacis A, et al. Prevalence, age distribution and gender in patients with atrial fibrillation; analysis and implications. Arch Intern Med. 1995;155: 469-473.
5. Friberg J BP, Scharling H. Rising rates of hospital admissions for atrial fibrillation. Epidemiology 2003;14 666-672.
6. Wolf PA BEaBA. Secular trends in the prevalence of atrial fibrillation: The framingham study. Am heart J 1996; 131:790-795.

7. Furburg CD PB, Manolio TA, et al. Prevalence of diagnosed atrial fibrillation in elderly subjects. Am J Cardiol. 1995; 74:236-241.
8. Piccini JP, Hammill BG, Sinner MF, et al. Incidence and Prevalence of Atrial Fibrillation and Associated Mortality Among Medicare Beneficiaries, 1993-2007. *Circulation Cardiovascular Quality and Outcomes*. 2012;5(1):85-93. doi:10.1161/CIRCOUTCOMES.111.962688.
9. Wann S CA, January C, et al. ACC/AHA/HRS focused update on the management of patients with atrial fibrillation (2011 writing group members) (updating the 2006 guideline): A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation. 2011; 123:104-123.
10. Fuster V RL, Cannom DS, et al. ACCF/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: Executive summary. A report of the American College of Cardiology/American Heart Association task force on practice guidelines and the European Society of Cardiology committee for practice guidelines (writing committee to revise the 2001 guidelines for the management of patients with atrial fibrillation): Developed in collaboration with the North American Society of Pacing and Electrophysiology. Circulation. 2006;114: e257-e354.
11. Wazni O, Wilkoff, B, Saliba, W. Catheter ablation for atrial fibrillation. New Engl J Med. 2011; 365:2296-2304.Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/ SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary: executive summary. Europace. 2018 Jan 1;20(1):157-208.
12. Packer D, Kowal R, Wheelan K, Irwin J, et al. Cryoballoon Ablation of Pulmonary Veins for paroxysmal Atrial Fibrillation. JACC, 2013;61:1713-23.
13. Kuck KH, Brugada J, Furnkranz A, Metzner A, Ouyang F, Chun KR, Elvan A, Arentz T, Bestehorn K, Pocock SJ, Albeneque JP, Tondo C, for the FIRE AND ICE Investigators. Cryoballoon or radiofrequency ablation for paroxysmal atrial fibrillation. N Engl J Med, 2016;374:2235–2245.Medtronic Press Release, “Clinical Trial to Evaluate Medtronic Cryoablation as First-Line Treatment for Patients with Symptomatic Paroxysmal Atrial Fibrillation”, July 11, 2017.
14. Rahul Bhardwaj, Petr Neuzil , Vivek Y Reddy et al. Balloon-Based Ablation Technologies. Card Electrophysiol Clin 2020;12(2):175-185.
15. Stefan Hartl, Uwe Dorwarth, Benedikt Bunz et al Lessons from individualized cryoballoon sizing. Is there a role for the small balloon? J Cardiol. 2017 Oct;70(4):374-381.
16. Epstein AE CM, Fogoros RN, et al. Classification of death in antiarrhythmia trials. J Am Coll Cardiol 1996; 27:433-442
17. O’Connor CM CP, Miller AB, et al. Effect of amlodipine on mode of death among patients with advanced heart failure in the praise trial. Am J Cardiol 1998; 82:881-887

18. Reference of the consensus document: Calkins H, Hindricks G, Cappato R, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation: Executive summary. 2018 Europace.

28. Abbreviations and Definitions

This section identically matches the Abbreviations and Definitions Section (Section 26) of the FROzEN-AF protocol (92348334).

28.1. *Abbreviations*

Abbreviations are shown in Table **15**.

Table 15: Abbreviations

Abbreviation/Acronym	Term
AAD	Anti-Arrhythmic Drug
AF	Atrial Fibrillation
AFL	Atrial Flutter
AT	Atrial Tachycardia
CABG	Coronary artery bypass grafting
CRT	Cardiac Resynchronization Therapy
DMS	Diaphragm Movement Sensor
DVT	Deep Vein Thrombosis
EDC	Electronic Data Capture
EP	Electrophysiology
HRS	Heart Rhythm Society
IB	Investigator's Brochure
ICB	Inter Connection Box
ICD	Implantable Cardioverter Defibrillator
ICF	Informed Consent Form
IFU	Instructions for Use
LA	Left Atrium
LVEF	Left Ventricular Ejection Fraction
MRI	Magnetic Resonance Imaging
PAF	Paroxysmal Atrial Fibrillation
PE	Pulmonary Embolism
PTCA	Percutaneous transluminal coronary angioplasty
PV	Pulmonary Veins
PVI	Pulmonary Vein Isolation
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
TEE	Trans-esophageal echocardiography

Abbreviation/Acronym	Term
TIA	Transient Ischemic Attack

28.2. *Definitions*

Terms are defined in Table **16**.

Table 16: 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, meets eligibility criteria 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 procedures 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 is eligible for enrollment and signs an informed consent document 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 30 days from consent signature date may not be reconsented and will be withdrawn from the study.
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
Paroxysmal Atrial Fibrillation (PAF)	Recurrent symptomatic Atrial Fibrillation that terminates spontaneously or with intervention within seven days of onset.

Term	Definition
Activated Coagulation/Clotting Time	ACT is a test that is used to monitor the effectiveness of high dose heparin therapy.
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 • Failure to achieve acute procedural success in the index procedure or repeat procedure during the blanking period • Use of amiodarone post index procedure • Surgical treatment for AF/AFL/AT post index procedure • Use of a non-study ablation catheter for AF targets in the index procedure or repeat procedure during the blanking period • More than one repeat procedure during the blanking period (90 days post procedure) • 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 any AAD
Acute Procedural Success	Rate of acute procedural success defined as the achievement of electrical isolation of all PVs by using the POLARx Cardiac Cryoablation System with the POLARx FIT cryoablation balloon catheter models only. Electrical isolation of a PV is 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 (Severe)	Severe PV stenosis is defined as ≥ 70% reduction in the diameter of the PV or PV branch from baseline measure. For this study a severe PV stenosis will count toward the primary safety endpoint.
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
Activated Coagulation/Clotting Time	ACT is a test that is used to monitor the effectiveness of high dose heparin therapy.
Source Data	All information in original records of clinical findings, observations, or other activities in a clinical investigation, 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, meets eligibility criteria and has the specified study devices inserted into the body and undergoes protocol specific treatment for the intended disease.

Term	Definition
Activated Coagulation/Clotting Time	ACT is a test that is used to monitor the effectiveness of high dose heparin therapy.
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 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.

29. Appendices

29.1. *Indications for ablation of PAF according to 2017 HRS expert consensus statement on catheter and surgical ablation of atrial fibrillation*

This section identically matches Section 27.2 of the FROzEN-AF protocol (92348334).

Indications	Recommendation	class	Level of Evidence
Symptomatic AF refractory or intolerant to at least one Class I or III antiarrhythmic medication	Paroxysmal: Catheter ablation is recommended.	I	A
Symptomatic AF prior to initiation of antiarrhythmic therapy with a Class I or III antiarrhythmic medication	Paroxysmal: Catheter ablation is reasonable	IIa	B-R

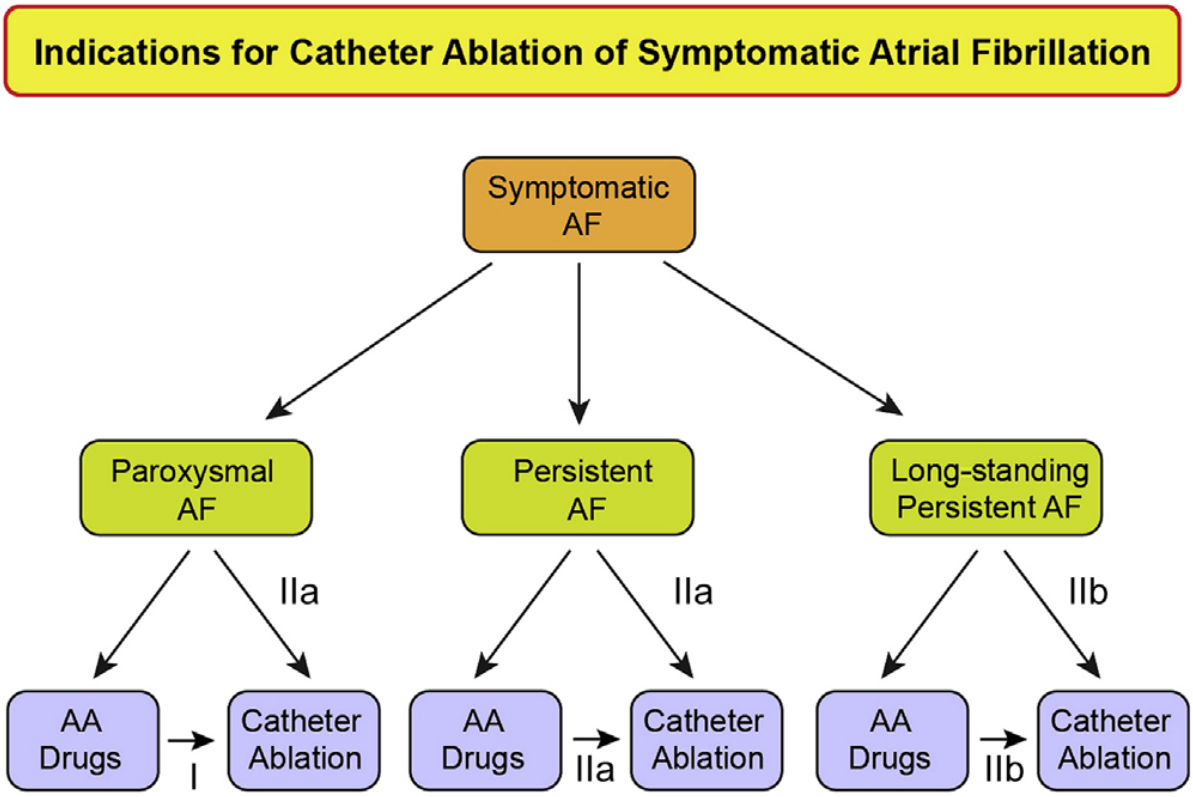


Figure 9: Indications for catheter ablation of symptomatic atrial fibrillation

Shown in Figure 9 are the indications for catheter ablation of symptomatic paroxysmal, persistent, and long-standing persistent AF. The Class for each indication based on whether ablation is performed after failure of antiarrhythmic drug therapy or as first-line therapy is shown.

29.2. *Quality of Life Instruments*

This section identically matches Section 27.3 of the FROzEN-AF protocol (92348334).

Clinical trials increasingly recognize the value of including patient reported outcome measures in their design. To understand the impact of atrial fibrillation ablation procedures on patient's quality of life, the quality-of-life instruments used for the trial will be the EQ-5D-5L for a generic questionnaire and the AFEQT for disease specific. Subjects will be asked to complete the questionnaires at the Enrollment visit as well as at the three, six, and 12-month follow-ups.

The EQ-5D, generic quality of life measure, will be used to assess health utilities. It is a descriptive system of health-related quality of life states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) each of which can take one of five responses. The responses record five levels of severity (no problems/slight

problems/moderate problems/severe problems/extreme problems) within a particular EQ-5D dimension.

The Atrial Fibrillation Effect on Quality of Life (AFEQT) was developed to evaluate disease-specific quality of life for patients with atrial fibrillation. The 20-item questionnaire is subdivided into three domains: symptoms, daily activities, and treatment concerns with responses provided on a seven-point Likert scale.

29.3. *National Institutes of Health Stroke Assessment*

This section identically matches Section 27.4 of the FROzEN-AF protocol (92348334).

The NIH Stroke Scale (NIHSS) is an assessment tool which quantifies stroke related neurological deficit. This assessment must be conducted in-person to provide valuable information on stroke severity.

An Investigator or appropriately trained and delegated site staff designee will administer NIH Stroke Scale assessment prior to the index ablation procedure (Baseline) and again at the pre-discharge visit (0-7 days post the ablation procedure). All individuals conducting the assessment will be required to become certified on administration of the assessment and provide BSC with documentation of certification prior to assessment completion with subjects.

Investigational sites will be provided with instructions for administering the assessment. They will be instructed to administer stroke scale items in the order listed on the form. Scores should reflect what the subject does, not what the clinician thinks the subject can do. The clinician should record answers while administering the exam and work quickly. Except where indicated, the subject should not be coached. If a worsening score is noted from the previous assessment, the Investigator must follow the additional requirements defined throughout Section 12.7.

29.4. *CHA2DS2-VASc Score for AF*

This section identically matches Section 27.5 of the FROzEN-AF protocol (92348334).

The CHA2DS2-VASc score is used for risk stratification of ischemic stroke in patients with nonvalvular atrial fibrillation.

	Condition	Points
C	Congestive heart failure (or Left ventricular systolic dysfunction)	1
H	Hypertension: blood pressure consistently above 140/90 mmHg (or treated hypertension on medication)	1
A_2	Age ≥75 years	2
D	Diabetes Mellitus	1
S_2	Prior Stroke or TIA or thromboembolism	2

V	Vascular disease (e.g., peripheral artery disease, myocardial infarction, aortic plaque)	1
A	Age 65–74 years	1
Sc	Sex category (i.e., female sex)	1