SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Cardiac ablation percutaneous catheter, intended for treatment of symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation

Device Trade Name: The Boston Scientific Cardiac Cryoablation System ("Cryoablation System") consists of the following devices and components:
- POLARx™ and POLARx FIT™ Cryoablation Catheter ("Cryoablation Balloon Catheters")
- POLARMAP™ Catheter ("Cryo Mapping Catheter") (FDA Cleared via K223824)
- POLARSHEATH™ Steerable Sheath ("Cryo Steerable Sheath") (FDA Cleared via K223824)
- SMARTFREEZE™ Console ("Console")
- Diaphragm Movement Sensor (DMS)
- Related Accessories

Device Procode: OAE, Catheter, Percutaneous, Cardiac Ablation, For Treatment Of Atrial Fibrillation

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Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P220032

Date of FDA Notice of Approval: 8/08/2023

II. INDICATIONS FOR USE

Cryoablation Balloon Catheters

The Boston Scientific Cardiac Cryoablation System using the POLARx™ Cryoablation Balloon Catheters is indicated for the treatment of patients with drug refractory, recurrent symptomatic paroxysmal atrial fibrillation (PAF).

Console

The Boston Scientific Cardiac 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 drug refractory, recurrent symptomatic paroxysmal atrial fibrillation. The SMARTFREEZE™ Cryo-Console is intended to be used with POLARx™ cryoablation balloon catheters only.

III. CONTRAINDICATIONS

Use of the Boston Scientific Cardiac 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 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 POLARx™ cryoablation balloon catheters 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 any other surgical intervention in or adjacent to the intra-atrial septum.
- In patients with an interatrial baffle or path 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.
- In patients previously implanted with a percutaneous Left Atrial Appendage Occlusion device.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Cryoablation System instructions for use, and Boston Scientific Cryoablation System labeling.

V. DEVICE DESCRIPTION

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.

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 (20 mm)
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

Cryoablation Balloon 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™ Cryoablation Balloon Catheter. 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, which is a circular mapping catheter deployed within the guidewire lumen during ablation procedures.

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

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

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

Figure 1: Cryoablation Catheter Distal Tip

Figure 2: Cryoablation Catheter Handle

Table 2: Cryoablation Catheter Specifications

	POLARx™/ POLARx FIT™
Balloon diameter	28 mm/ 31 mm
Nominal Distal Tip Length	5 mm
	12 mm
Shaft diameter	4.0 mm / 11.8F
Working length	99 cm

Cyro Mapping Catheter (FDA Cleared via K223824)

The Cryo Mapping Catheter is a single-use, sterile, multi-electrode, diagnostic catheter designed to map cardiac signals during ablation procedures. The catheter is 20 mm 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 endovascular/endocardial surface. This allows for recording and interrogation of electrical conduction between the LA and the pulmonary veins. The Cryo Mapping

Catheter also allows for delivery of pacing stimuli used in the interpretation of PV isolation (PVI).

Figure 3: Mapping Catheter Assembly

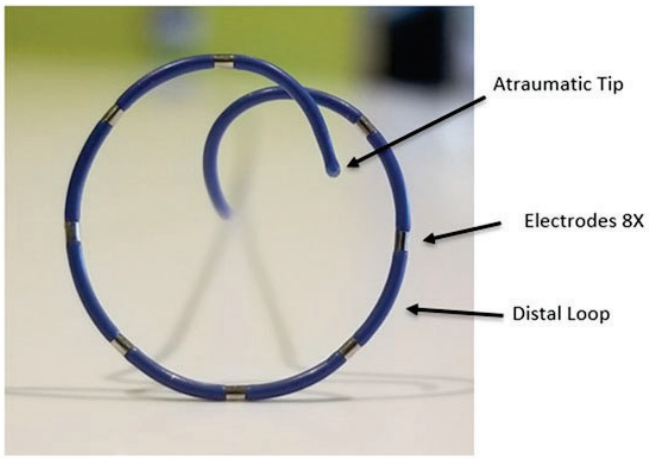

Figure 4: Cryo Mapping Catheter with Electrode Arrangements

Table 3: Cryoablation Catheter Specifications

Catheter Model Number	Catheter Diameter	Evenly Spaced Electrodes
2317	20mm	8

Cryo Steerable Sheath (FDA Cleared via K223824)

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

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

Table 4: Cryo Steerable Sheath Specifications

Inner diameter	0.165in / 12.7F
Outer diameter	0.208in / 15.9F
Working length	68 cm
Total length	82 cm
Dilator working length	85cm
Reach at 90°	4.6 cm
Guidewire compatibility	0.035 inches

Console

The Console is a device that uses N2O 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 N2O (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, N2O is delivered as a chilled liquid to the Cryoablation Catheter for a programmable time duration. The user interface also displays key information allowing the operator to focus attention on critical tasks and speed up the overall procedure.

Figure 5: Cryo Console

Integration between the Cryoablation Catheter and the Console includes monitoring the 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.

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 notified when the measured pacing response decreases below a pre-set value.

Phrenic nerve monitoring is essential for ensuring safety during a cryoablation procedure. It has been reported with cryoablation balloon technology that the incidence of phrenic nerve injury ranges from 1.7-11.2% in the acute setting and persists in 0.3%-1.8% of patients at one year. The 2017 HRS Expert Consensus states *monitoring of diaphragmatic excursion with abdominal palpation, fluoroscopy or intracardiac ultrasound while pacing the phrenic nerve from the SVC or subclavian vein during*

ablation is now considered standard of care when ablating the right sided PVs. The physician should stop ablating if a significant reduction in diaphragmatic excursion is detected. Currently, manually palpating the abdomen is the most common monitoring method. However, this technique is subjective and experience dependent.

The accelerometer based DMS provides an additional means to visually monitor diaphragmatic excursions during ablation. The DMS is designed to detect motion and can be used as an adjunct to palpation during phrenic nerve pacing while delivering cryo energy. 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).

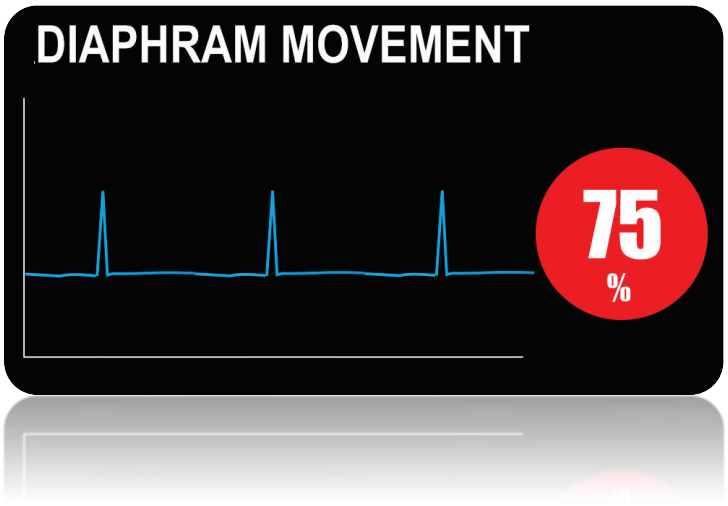

Figure 6: Diaphragm Movement Sensor (DMS) Data Cryoablation Console Display Phrenic Nerve Pacing Signal & Alert

By integrating the information into the Console, the physician can visually monitor the pacing response throughout the ablation. Additionally, the console can alert the physician with audible and visual notifications if the pacing response decreases below a pre-set value. The measured pacing response is displayed graphically and as a percentage of a baseline measurement; with the first physical excursion establishing the baseline at 100%. The default threshold for notification is 80% and can be adjusted as desired by the physician. The measurement display changes from "Blue" to "Red" if the value falls below the physician's programmed set notification value (see Figure 6 above).

The DMS is an adjunct tool designed to complement physicians' established clinical practice for phrenic nerve assessment. The DMS is not a substitute for physicians' standard of care for phrenic nerve assessment during a cryoablation.

Esophageal Temperature Sensor Cable

Esophageal ulceration may occur due to thermal damage from cryoablation in areas with close proximity to the esophagus, with a reported incidence of up to 17% of patients.

Although generally reversible, it may lead to the fatal complication of atrioesophageal fistula. Although not proven to reduce the incidence of esophageal injury, esophageal temperature monitoring is frequently used during cryoablation. 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 notification value. The default threshold for notification is 20°C and can be adjusted as desired by the physician. 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.

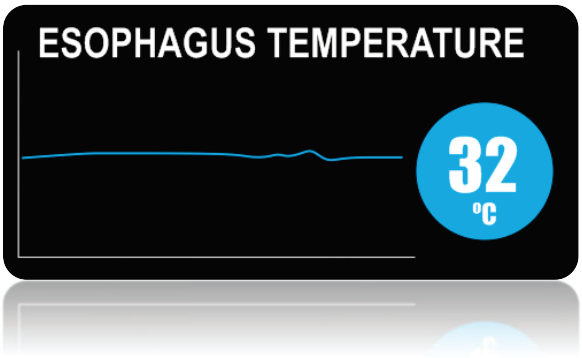

Figure 6: Esophagus Temperature Monitoring Data Display

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.

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 N2O (cryoablation) as well as deflate the Cryoablation Catheter at the conclusion of the ablation.

Cryo Cable

The Cryo Cable is a sterile, single-use cable that provides the connectivity between the Cryoablation Catheter to the Console to support the delivery of liquid refrigerant and the evacuation of remaining N2O gas.

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 to support the delivery of liquid refrigerant and the evacuation of remaining N2O gas.

Cryo 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 Cryo Mapping Catheter with standard EP recording systems.

This medical device product has functions subject to FDA premarket review as well as functions that are not subject to FDA premarket review. For this application, if the product has functions that are not subject to FDA premarket review, FDA assessed those functions only to the extent that they either could adversely impact the safety and effectiveness of the functions subject to FDA premarket review or they are included as a labeled positive impact that was considered in the assessment of the functions subject to FDA premarket review.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of symptomatic, drug refractory, recurrent, paroxysmal atrial fibrillation, including:

- Commercially available PMA-approved ablation devices
- Pharmacological therapy for rate and/or rhythm control
- Electrical or pharmacological cardioversion
- Surgical intervention to create atrial lesions
- Implantable devices to control heart rate

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Cryoablation System is commercially available in the following countries: Andorra, Unit. Arab Emir., Dutch Antilles, Austria, Australia, Azerbaijan, Belgium, Bulgaria, Belarus, Switzerland, Chile, Costa Rica, Cyprus, Czech Republic, Germany, Denmark, Algeria, Estonia, Spain, Finland, France, Great Britain, Georgia, Greece, Hong Kong, Croatia, Hungary, Ireland, Israel, Iraq, Iran, Iceland, Italy, Japan, South Korea, Kuwait, Kazakhstan, Liechtenstein, Lithuania, Luxembourg, Latvia, Macau, Malta, Malaysia, Netherlands, Norway, New Zealand, Oman, Poland, W. Bank Gaza Strip, Portugal,

Qatar, Romania, Serbia, Russian Fed., Saudi Arabia, Sweden, Singapore, Slovenia, Slovakia, Thailand, Turkey, Ukraine, Kosovo and South Africa.

There are no countries from which the Cryoablation System has been withdrawn from marketing for any reason related to safety and effectiveness. The Cryoablation System has not been marketed in the United States.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Table 5: 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)

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

Testing of the Boston Scientific Cardiac Cryoablation System included verification and validation testing (device, system and software), device electrical safety testing, biocompatibility of patient-contacting materials, sterilization, packaging testing, and animal studies. Performance testing was conducted to demonstrate design integrity. Tests that were identified in standards or guidance documents were performed based on product specification requirements. Test results confirm that the POLARx™, POLARx FIT™, POLARMAP™, POLARSHEATH™ and SMARTFREEZE™ devices met product specifications. In all cases, specifications must be met with a capability appropriate to the patient risk relevant to the specification being tested, as determined by a risk assessment. Test results for POLARx™ and POLARx FIT™, POLARSHEATH™, POLARMAP™ and SMARTFREEZE™ are summarized in Table 6, Table 7, Table 8, and Table 9 respectively. There have been no major changes to the design or materials for these devices.

Table 6: Summary of POLARx™ and POLARx FIT™ Bench Testing

Test	Purpose	Acceptance Criteria	Results
Catheter and balloon dimensions	Ensure the catheter shaft and balloon dimensions are consistent and enable compatibility with other devices	All 7 dimensions measured must meet specified tolerances.	Passed
Balloon surface temperature	Ensure the balloon surface temperature during ablation is consistent	Balloon surface temperature during the last 2 minutes of a 4 minute ablation, as measured in an *in vitro* model, must meet specified tolerances.	Passed
Balloon pressure control	Ensure the internal balloon pressure is consistent whenever it is	Average internal balloon pressure during all inflated states must meet specified tolerances.	Passed

	inflated, including during ablation		
Simulated use cycling (including balloon inflation/deflation cycling, temperature cycling, catheter articulation cycling, insertion/ withdrawal cycling into/out of POLARSHEATH ™)	Ensure the catheter appropriately communicates with the console, responds to the console's commands and user articulation, and is compatible with other single-use devices over 16 cycles of cryoablation, and is free of mechanical defects or leaks after cycling	All specifications for communication with the console, response to console commands and user articulation, compatibility with other single-use devices, and freedom from mechanical defects must be met via visual inspection, and leak integrity via pressure decay testing and visual inspection, during and/or after 16 cycles of cryoablation in a vascular simulation apparatus.	Passed
Catheter steering function	Ensure the catheter tip can be deflected and held in a deflected shape using the handle knobs	The deflection angle of the tip must achieve and hold its minimum specified value when the tip is deflected and locked via the handle knobs.	Passed
Catheter steering reliability	Ensure the catheter steering will be reliable in use	The catheter must be visually intact after 50 steering cycles in both directions.	Passed
Contrast injection	Ensure the catheter can operate reliably with an automated contrast injection system operating at ≤ 500 psi injection pressure	When the guidewire lumen is modified to allow pressurization and pressurized to failure, the burst pressure must meet its specified minimum value.	Passed
Leak integrity	Ensure the catheter will not leak refrigerant during use	When tested in pressure or vacuum decay testing, the catheter inner balloon channel pressure and vacuum decay rates and outer balloon channel vacuum decay rate must meet their specified maximum values.	Passed
Guidewire lumen reliability	Ensure the guidewire lumen can operate reliably when pressurized and aspirated in use	The guidewire lumen must be free of leaks or aspirated air in accordance with ISO 10555-1 (Intravascular Catheters – Sterile and Single-Use Catheters – Part 1: General Requirements), Annexes C and D.	Passed

Tensile strength	Ensure the catheter components and assembly joint tensile strengths are consistent and adequate to be reliable in use	All 40 tensile strengths measured must meet specified minimum values.	Passed
Buckling force	Ensure that appropriate use of the catheter will not damage the surrounding tissue	The force required to buckle the distal 3.5 inches of the catheter must meet specified maximum values.	Passed
Kink resistance	Ensure that appropriate use of the catheter will not kink the catheter shaft	The catheter must be free of visual evidence of kinks or bond separation when subjected to a bend radius of 0.6 inches.	Passed
Torque response	Ensure that balloon will turn in response to turning the catheter handle	The torque induced at the balloon when the catheter handle is rotated 180° must meet the specified minimum value.	Passed
Torque strength	Ensure that catheter mechanical integrity is adequate to be reliable when the handle is turned in use	The specifications for leak integrity via pressure decay testing and visual inspection must be met when the catheter handle is turned 360° relative to the balloon.	Passed
Relief pressure	Ensure the catheter internal pressure will not exceed the burst pressure in use	When the catheter is modified to observe the relief valve in the handle, the valve must be closed at the maximum internal operating pressure and open at the minimum burst pressure.	Passed
Burst pressure	Ensure the catheter can reliably withstand the internal pressure it will experience in use	When the catheter is modified to disable the relief valve in the handle and pressurized to failure, the balloon must be observed to burst and the burst pressure must meet its specified minimum value.	Passed
Blood detection system	Ensure the system can detect presence of conductive liquid (e.g. blood) inside the catheter	The system must trigger a console error for blood detection when the blood detection sensor is exposed to physiologic saline.	Passed

Balloon over pressurization detection system	Ensure the system can detect over pressurization of the balloon	The balloon pressure sensors must report the same value as a calibrated pressure source within their specified tolerances.	Passed

Table 7: Summary of POLARSHEATH™ Bench Testing (FDA Cleared via K223824)

Test	Purpose	Acceptance Criteria	Results
Sheath dimensional requirements	Ensure the sheath and dilator dimensions are consistent and compatible with other devices	All 7 dimensions must meet specified tolerances.	Passed
Tensile strength	Ensure the sheath assembly joint tensile strengths are consistent and adequate to be reliable in use.	All 5 tensile strengths must meet specified minimum values.	Passed
Torque response	Ensure the shaft will turn in response to turning the sheath handle	The torque induced at the shaft tip when the sheath handle is rotated 180° must meet the specified minimum value.	Passed
Torque strength	Ensure the sheath mechanical integrity is adequate to be reliable when the handle is turned in use	The specifications for leak integrity via aspiration testing and visual inspection must be met when the sheath handle is turned 360° relative to the shaft tip.	Passed
Curve deflection	Ensure the sheath tip articulates, achieves specified deflection profiles, maintains deflection and articulates without failure for at least 16 cycles.	All specifications related to curve deflection must be met via dimensional inspection with specified tolerances or visual confirmation when the sheath tip is articulated.	Passed
Leak integrity	Ensure the sheath components related to the fluid pathway are free from fluid leakage or air ingress during use.	All specifications related to leak integrity must be met via visual confirmation during aspiration or fluid pressure testing.	Passed

Device compatibility – external interface	Ensure the sheath and dilator are compatible with external accessories such as an 18F inner diameter introducer sheath and a .035” guidewire.	The specifications related to external device compatibility must be met via successful insertion and removal of the subject device with the external accessory: 1) POLARSHEATH with an 18F introducer sheath and 2) dilator with a .035” guidewire.	Passed
Device compatibility – with POLARx™/POLARx FIT™	Ensures the sheath and POLARx™/POLARx FIT™ catheter are free from damage after 16 insertion and withdrawal cycles.	The specification related to freedom from damage after insertion and withdrawal cycling must be met via visual inspection for the POLARSHEATH™ and visual inspection and leak testing for the POLARx™/POLARx FIT™ catheter.	Passed
Device compatibility – with dilator	Ensure secure attachment of the dilator to the POLARSHEATH™ via the axial locking feature and an acceptably low force to withdraw the dilator from the hemostasis valve.	The force required to release the dilator from the locking feature must meet its specified minimum value. The force required to withdraw the dilator from the hemostasis valve must meet its specified maximum value.	Passed

Table 8: Summary of POLARMAP™ Bench Testing (FDA Cleared via K223824)

Test	Purpose	Acceptance Criteria	Results
Catheter dimensional requirements	Ensure the catheter dimensions are consistent and compatible with other devices	All 8 dimensions must meet specified tolerances.	Passed
Electrical continuity	Ensure sufficient number of functioning electrodes	A minimum of 7 electrodes must be free of open or short circuits with a resistance less than the specified maximum value.	Passed
Buckling force	Ensure that appropriate use of the catheter will not damage the surrounding tissue	The force required to buckle the distal 2.0 inches of the catheter must meet specified maximum values.	Passed

Stiffness	Ensure the distal section of the catheter has sufficient column strength to position the distal section of the catheter in the vein in use	The stiffness of the distal segment of the catheter must exceed the specified minimum value.	Passed
Kink resistance	Ensure that appropriate use of the catheter will not kink the catheter shaft.	The catheter must be free of visual evidence of kinks or defects when subjected to the specified bend radii.	Passed
Cryo fatigue cycling	Ensure sufficient number of functioning electrodes after simulating cryoablations.	A minimum of 7 electrodes must be free of bond joint failures and free of open or short circuits with a resistance less than the specified maximum value after simulating exposure to 16 cryoablation cycles.	Passed
Simulated use cycling	Ensure the mechanical and electrical integrity of the catheter can withstand repeated expected use with compatible devices.	The catheter must be free of kinks, material or bond joint failures, and free of opens or shorts on a minimum of 7 electrodes, and the distal loop shall conform to a percentage of the nominal loop diameter after cycling without damage that causes extraneous material to be expelled from the balloon catheter. The connector must be free of opens or shorts on a minimum of 7 electrodes after connection/disconnection cycles with the EP electrical cable.	Passed
Tensile strength	Ensure the catheter assembly joint tensile strengths are consistent and adequate to be reliable in use.	All 3 tensile strengths must meet specified minimum values.	Passed
Torque resistance	Ensure the catheter mechanical integrity is adequate to be reliable when turned in use	The catheter must be free of bond joint or material failures via visual inspection after rotating the connector 720° relative to a fixed tip.	Passed
Corrosion resistance	Ensure catheter meets applicable requirements	The metallic components of the catheter intended for fluid path	Passed

	for corrosion resistance per ISO 10555-1.	contact shall show no signs of corrosion via visual inspection.	
Electrical safety	Ensure the catheter is compliant to basic safety and essential performance requirements.	IEC 60601-1:2005/A1:2012 (Third Edition)	Passed

Table 9: Summary of SMARTFEEZE™ System Bench Testing

Test	Purpose	Acceptance Criteria	Results
Electrical Safety	Ensure the SMARTFREEZE™ System is compliant to basic safety and essential performance requirements.	IEC 60601-1:2005/AMD2:2020 (edition 3.2)	Passed
Electromagnetic Compatibility	Ensure the SMARTFREEZE™ System is compliant to basic safety and essential performance requirements with respect to electromagnetic disturbances and emissions.	IEC 60601-1-2:2014+A1:2020 (edition 4.1)	Passed
System Verification	Ensure the SMARTFREEZE™ System meets the design requirements.	SMARTFREEZ™E System must meet the design inputs defined in the product requirements.	Passed
System Validation	Ensure the SMARTFREEZE™ System meets the user needs.	SMARTFREEZE™ System must meet the design inputs defined in the user requirements.	Passed

Biocompatibility Testing

Biocompatibility testing of the Cryoablation Balloon Catheters, POLARMAP™ Circular Mapping Catheter, and POLARSHEATH™ Steerable Sheath was conducted in accordance with ISO 10993-1 Biological Evaluation of Medical Devices – Part 1: *Evaluation and Testing within a Risk Management Process*, FDA Guidance – Use of International Standard ISO 10993-1 – *Guidances for Industry and Food and Drug Administration Staff*, and Boston Scientific's internal procedures for Biocompatibility.

The summary data in Table 10 supports that the Cryoablation Balloon Catheters, POLARMAP™, and POLARSHEATH™ devices have acceptable biological risk and remain biocompatible for their intended uses as an externally communicating, limited (<24 hours) contact devices with circulating blood.

Table 10: **Biocompatibility Testing Summary**

Test	**Result**
MEM Elution Cytotoxicity	Pass
Guinea Pig Maximization/Sensitization	Pass
Intracutaneous Reactivity	Pass
Acute Systemic Toxicity	Pass
Material-Mediated Rabbit Pyrogenicity	Pass
SC5b-9 Complement Activation Assay	Pass
Hemolysis (Direct Contact and Extract)	Pass
In-Vivo Thrombogenicity (Heparinized)	Pass
In-Vivo Thrombogenicity (Non-Heparinized)	Met Expected Outcome*
Genotoxicity: Ames Bacterial Reverse Mutation Study	Pass

* Test and predicate control responses are equivalent in the absence of heparin. Test Article Scores: 4/4/4 and Control Article Scores: 4/4/4

Patient contacting materials of the POLARx™ Cryoablation Balloon Catheters, POLARMAP™, and POLARSHEATH™ tested for biocompatibility are listed in Table 11.

Table 11: Patient Contacting Material Tested for Biocompatibility

POLARx™ Cryoablation Balloon Catheters		
Component	**Material**	**Color**
Balloon Protector	Polyetrafluoroethylene (PTFE)	Natural
Adhesive	Loctite 3321	Natural
Luer Lock Connector	Makrolon 2658-550115	Natural
Steerable Shaft	Pebax 3533 Pebax 4533 Pebax 5533 Pebax 7233	Pantone 292C Pantone 295C
Outer Balloon	Pellethane 2363-90AE Pebax 6333 SA01 MED	Natural
Guidewire Lumen	Evonik Vestamid Care ML32 Pebax 6333 SA01 MED Pebax 7233	Pantone 295C
Metallic Indicator	Sharpie Silver Marker	Natural
POLARMAP™ (FDA Cleared via K223824)		
Component	**Material**	**Color**
Introducer	FEP	

Distal Shaft	Pebax 6333 SA01 Med (20% Barium Sulfate + PROPELL) Pebax 5533 SA01 Med	Pantone 295C
Hypotube	304 Stainless Steel	Natural
Adhesive	Adhesive, Dymax, 203A-CTH-F-VT	Natural
Electrode Band	Platinum, Irridium	Natural
POLARSHEATH™ (FDA Cleared via K223824		
Component	**Material**	**Color**
Adhesive	Adhesive, Loctite 3321	Natural
Steerable Shaft	PTFE Pebax 3533 Pebax 5333 Pebax 6333 Pebax 7233	 Pantone 292C Pantone 6C Pantone 11C Pantone 11C
Dilator L	HDPE DMDA-8904 LDPE 2020T	
Extension Line, Female Luer Lock to Male Luer Slip	PolyOne PVC Geon M4910TN29494 Natvar Non-DEHP PVC	
Silicon Sheet	Silastic Q7-4850	Natural
Valve, Housing	Lexan Polycarbonate HP1-1H112	Natural

Valve, Cap	Lexan HP1-1H112	Natural
Silicone Oil	Silicone Oil	Natural

B. Animal Studies

The sponsor submitted one (1) non-GLP and one (1) GLP animal study to support their IDE application (G190060) using the Boston Scientific Cardiac Cryoablation System. Testing demonstrated that the system rapidly and successfully delivered cryo energy to targeted left superior and right superior pulmonary veins in the left atria. Lesions were created using nominal (240 sec) and "worst case" (480 sec) refrigerant applications and myocardial lesions were visually verified grossly and microscopically. The overall device performance from a pathological perspective was characteristic of cardiac ablation and the electrophysiologists who conducted the studies found the catheter easy to navigate to each PV. There were no procedural complications, such as myocardial infarction, myocardial perforation, or esophageal/lung/pericardial/phrenic nerve injury, with any test subject. However, several significant adverse events occurred:

1. Clinically significant PV stenosis, i.e., >70%, was observed in one (1) non-GLP study animal and two (2) GLP study animals, all with 240 sec refrigerant application. Also, mild (<50%) to moderate (>50%, <70%) PV stenosis was frequently observed, primarily in the LSPV per the 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement. Canine PVs are small in diameter relative to human anatomy. Close review of procedural imaging provided convincing evidence that the protocol instruction to achieve a full occlusion of the targeted PV with the balloon before delivering cryo energy exerted greater axial force in the smaller diameter PVs which resulted in compression of anatomical structures. Data from a small OUS CE Mark clinical study with forty-eight (48) patients treated at the time of the IDE submission showed that, to date, no patient reported symptoms of PV stenosis. which supported the conclusion that challenging anatomy of the animal model contributed to the stenotic observations.
2. A clinically significant thrombus in one (1) high dose (480 sec) GLP study animal was found; however, downstream microemboli were not observed. Minimal thrombosis was observed at a markedly stenotic LSPV in another animal, also high dose, that the pathologist suggested was secondary to ostial healing and adjacent focal endocardial trauma from the transseptal puncture. Neurological deficits were observed in this animal that may have been associated with the thrombus observed at the LSPV. The neurological symptoms were not life-threatening and resolved prior to the 30-day pre-termination examination. Observations of thrombus were restricted to PVs that were cryoablated with a double dose (2 x 240 sec) and the dogs did not receive anti-coagulation therapy post-procedure per standard clinical practice. If the dogs had received anti-coagulation therapy this may have minimized this risk. In the OUS CE Mark study with forty-eight (48) patients treated at the time of the IDE submission four

(4/48) patients had AF recurrence and were admitted for follow-up RF ablation. Prior to the procedure patients were screened for LA thrombus and PV stenosis with ICE and 3D EAMs; there was no evidence of thrombus or PV stenosis at the time of the second RF procedure.

Table12: Summary of the *in vivo* Animal Studies

Animal Model	21 CFR § 58 Compliant	Type of Study	Time Point	Number of Animals	Study Groups	
					Acute	Chronic
Canine	No	Safety Assessment	Acute/Chronic (34-35 days)	5	n=2	n=3
Canine	Yes	Safety and Effectiveness	Acute/Chronic (34-35 days)	12	n=8*	n=8*

*In the GLP study, groups were designated by the number of treatments a PV received. Two (2) PVs were targeted in each animal (n=8, total) with one PV receiving 240 sec refrigerant application and one (1) PV receiving two (2) 240 sec refrigerant applications separated by five (5) minutes between applications.

A non-GLP Animal Study was conducted to assess adverse events (AEs) associated with the pulmonary vein (PV) isolation (PVI) procedure evaluating the subject device at acute and chronic time points. Two (2) electrophysiologists conducted the study. The study enrolled five (5) mongrel dogs as follows:

- Acute: n=2 (a second dog was added from the chronic cohort after the dog experienced non-device related complications that necessitated early euthanasia).
- Chronic: n=3 animals.
- Ten (10) PVs were targeted for ablation:
  - Nine (5/10, RSPV plus 4/10 LSPV) PVs were ablated with a single 240sec application of refrigerant.
  - One (1/10) LSPV was too small for targeted ablation.
  - The phrenic nerve was monitored during RSPV ablation with no detrimental effects noted.
- Animals were maintained for ~35 days. Prior to euthanasia animals were anesthetized to assess PVI durability via pacing EGMs and PV stenosis (PVS) by ICE or fluoroscopy (compared to baseline).

Results:

- PV ablations in the acute animals were uneventful; necropsies were not performed.

- In chronic animals (n=3), six (6) PVs were ablated, targeted pathology of PVs performed:
    - Ablations averaged 24-30sec to reach target temperature with time-to-isolation (TTI) of 17-42sec.
    - 100% acute PVI was achieved following a single cryoablation.
    - 100% chronic PVI assessment demonstrated lesion durability.
    - 5/6 ablated PVs had 100% circumferential lesions.
- Clinically significant PV stenosis was observed in one (1) ablated PV.
    - A single LSPV was completely occluded.
    - Additional data was provided for FDA review that supported the observation that the balloon catheter was placed too deep into the PV and that the LSPV was very small (~6mm). The data and procedural images demonstrated that the balloon catheter significantly compressed the LSPV wall/myocardial sleeve.

Further evaluation of the procedural images allowed calculation of PV vascular compression. Greater levels of vascular compression resulted in more severe stenosis, which was further corroborated by larger lesion widths, as would be expected with compressed PVs. Overall, the cryoballoon appeared too large for the small diameter PVs of the canine heart.

A GLP Animal Study conducted to demonstrate the overall safety of the Boston Scientific Cardiac Cryoablation System when used for pulmonary vein (PV) isolation (PVI) in a chronic canine model. Four (4) electrophysiologists performed the cryoablations with the Polar X Cryoablation Catheter System. The study enrolled eight (8) mongrel dogs, distributed between two (2) groups (n=4, each), as follows:

- In all animals two PVs (RSPV, LSPV) were targeted for ablation.
- In Group 2 animals, the two 240 sec ablations were delivered five (5) minutes apart for a total of 480 sec ablation.
- Animals were maintained for ~35 days. Prior to euthanasia animals were anesthetized to assess PVI durability and PV stenosis (PVS) by ICE (compared to baseline).
- Safety of the test device was further characterized through gross necropsy and histopathology.

Results:

- Cryoablation was completed per the protocol except ablation was terminated early due to transient phrenic nerve palsy (nerve function returned) in a Group 1 animal and a Group 2 animal, each.
- Average time-to-isolation (TTI) was 22sec (range: 13sec – 28sec).

- All treated PVs were evaluated microscopically, and lesions appeared to be circumferential and transmural.
    - 87.5% (14/16 PVs) achieved Acute PVI
    - Chronic PVI was confirmed in 9/14 (64.3%) treated PVs as verified by pacing EGMs prior to euthanasia.
- Two (2/16) PVs had severe PVS > 70% when compared to baseline.
    - Both animals were in Group 1 treatment, i.e., 240 sec refrigerant application.
    - Neither animal had clinical signs of stenosis such as coughing, dyspnea, or hemoptysis.

The OUS CE Mark study reviewed at IDE submission (48 patients successfully treated) showed that no patient reported symptoms suggestive of PVS. The OUS data and the additional evidence provided FDA demonstrating small canine pulmonary veins, especially the LSPV, led to the determination of "reasonable safety prior to first use in man" for approval of the IDE application.

- Observation of thrombus in two (2) Group 2 (double dose) animals:
    - A significant thrombus (8-9mm in diameter and 20mm long) was observed in the LA via ICE, confirmed by gross necropsy, in a Group 2 animal.
        - Histopathology confirmed the thrombus overlay the cryoablation site and was independent of the transseptal puncture.
        - No downstream thrombotic emboli were observed in this animal.
    - In another Group 2 animal minimal thrombus on the LSPV cryolesion was observed microscopically by the pathologist.
        - The pathologist suggested the thrombus may have been secondary to a marked healing response of a stenotic LSPV ostium and a healing response from adjacent transseptal puncture site.
        - Non-life-threatening neurological deficits that spontaneously resolved were observed during the in-life phase of the study. The pathologist suggested these deficits may have been secondary to upstream thromboemboli from the thrombus.
- The electrophysiologists found performance of the catheter clinically acceptable, and they found the catheter easy to navigate. The EPs gave PV occlusion scores by the catheter balloon, prior to each ablation, as "4" (i.e., complete).

The results suggest that the double-dose refrigerant application is very risky, and the single-dose refrigerant application raises concerns, as well. Possibly the recommended dose should be lowered to minimize safety concerns. The pathologist suggested that the large mural thrombus resulted from increased levels of mural necrosis from the double-dose of cryoablation making the associated endocardium more thrombogenic. The animals did not receive anti-coagulation therapy post-procedure and if they had, this may have minimized thrombus formation. BSC argued that standard clinical practice, i.e., anti-coagulation therapy, will mitigate this risk in

patients. The minimal thrombus observed on the LSPV cryolesion may have contributed to the neurological deficits observed in this animal, i.e., transient cerebral ischemia that resolved.

C. Additional Studies

Packaging

All devices that comprise the Boston Scientific Cardiac Cryoablation System are packaged separately. Packaging verification testing was performed to demonstrate that the POLARx™ Cryoablation Balloon Catheters, POLARMAP™, and POLARSHEATH™ packaging can withstand the hazards of the distribution environment, and that the sterility of the device is maintained throughout the labeled shelf life. Package integrity testing included a visual assessment, bubble leak testing, and seal strength testing.

Testing was conducted on both packaging at the baseline condition and packaging aged to the product shelf life.

Bioburden

Bioburden data is generated to ensure that sterility assurance level (SAL) is not impacted by the product bioburden levels. Bioburden testing is routinely conducted for POLARx™ Cryoablation Balloon Catheters, POLARMAP™, and POLARSHEATH™ to meet the acceptance criteria of less than 10,000 CFU/device per Boston Scientific's internal procedures based upon EN ISO 11737-1.

The devices are manufactured and packaged in an ISO 8 controlled area.

Sterilization

POLARx™ Cryoablation Balloon Catheters, POLARMAP™, and POLARSHEATH™ are sterilized using ethylene oxide (EO) gas and has been validated per AAMI / ISO 11135:2014, Sterilization of health care products – Ethylene oxide; Requirements for the development, validation, and routine control of sterilization process for medical devices. Results from the sterilization studies demonstrate the product satisfies a minimum Sterility Assurance Level (SAL) of 10^{-6} and residual EO levels were within acceptable ranges in accordance with EN ISO 10993-7, Biological Evaluation of Medical Devices - Part 7: Ethylene Oxide Sterilization Residuals.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of catheter ablation with the Cryoablation System for the treatment of symptomatic, drug refractory, recurrent, Paroxysmal Atrial Fibrillation (PAF) in the US, Europe, Canada, Asia-Pacific under IDE # G190060. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

FRoZEN AF Clinical Study:
A maximum of 405 subjects treated with the Cryoablation System and POLARx™ Cryoablation Balloon Catheter were required to be enrolled in the study, inclusive of 325 non roll-in treatment subjects and a maximum of 80 roll-in treatment subjects undergoing the index ablation procedure. Up to 50 sites in North America, Europe and Asia-Pacific could participate in this study. At least 50% of the sites and 50% of the subjects were required to be enrolled in the United States, and potentially up to 10% of subjects were allowed to be enrolled in 3 to 5 combined sites from Hong Kong and Taiwan. Up to 10 sites in Europe could contribute to enrollments. No study site was allowed to contribute more than 15% of the required enrollment.

PV Stenosis Substudy:
A minimum of fifty (50) non roll-in treatment subjects were required to be enrolled in a PV Stenosis Substudy at up to 8 study sites. The PV Stenosis Substudy included 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 PV Stenosis substudy was allowed to enroll a maximum of 18 substudy subjects.

FROzEN-AF Extension Study:
In February 2022, the overall FROzEN-AF Clinical Study was expanded, to include the "POLARx FIT™: FROzEN-AF Extension Study", in addition to the FROzEN-AF Study. Details of the POLARx FIT™: FROzEN-AF Extension Study are included below.

FRoZEN AF Clinical Study

A. **Study Design**

The study was a prospective, single-arm, multi-center clinical study. Patients were treated between June 24, 2020 and August 24, 2021. The database for this PMA reflected data collected through September 14, 2022 and included 404 patients. There were 44 investigational sites.

An independent Clinical Events Committee (CEC) adjudicated all deaths, all composite primary safety endpoint events, all potentially procedure or POLARx™ Cardiac Cryoablation System related adverse events, and all unanticipated device effects. An independent Data Monitoring Committee (DMC) reviewed accumulating safety data to ensure patient safety. Additionally, several core laboratories were employed to provide external review of study data.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the FRoZEN AF study was limited to patients who met the following 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:

- 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
- 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.

Patients were <u>not</u> permitted to enroll in the FRoZEN AF study if they met any of the following 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:
    1. Left ventricular ejection fraction (LVEF) < 40% based on the most recent transthoracic echocardiogram (TTE) ≤180 days prior to enrollment);
    2. Left atrial diameter > 55 mm OR left atrial volume > 50 ml/m2 ml indexed based on the most recent TTE (≤ 180 days prior to enrollment);
    3. An implanted pacemaker, ICD, CRT device or an arrhythmia loop recorder;
    4. Previous cardiac surgery: i.e. ventriculotomy or atriotomy (excluding atriotomy for CABG);

5. Previous cardiac valvular surgical or percutaneous procedure, or prosthetic valve, including mitral valve clips;
6. Interatrial baffle, closure device, patch, or patent foramen ovale (PFO) occlude;
7. Presence of a left atrial appendage occlusion device;
8. Presence of any pulmonary vein stents;
9. Coronary artery bypass graft (CABG), PTCA/ PCI/ coronary stent procedures within 90 days prior to enrollment;
10. Unstable angina or ongoing myocardial ischemia;
11. myocardial infarction within 90 days prior to enrollment;
12. Moderate or severe mitral insufficiency assessed on the most recent TTE (≤180 days prior to enrollment, e.g. pulmonary artery pressure >30 mmHg);
13. 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;
- Subjects who in the judgment of the investigator have a life expectancy of less than two years.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at pre-discharge, day 7 follow-up, and at 3-, 6- and 12-months post index ablation procedure. Adverse events and device deficiencies were recorded at all visits. Table 13 lists the protocol-required baseline, procedural, and follow-up assessments.

Table 13: 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

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
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,
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, O2 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;
10Screening 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. TTE = trans-thoracic echocardiogram, TEE = trans-esophageal echocardiogram, CT = Computed Tomography, MRI = Magnetic Resonance Imaging, FU = follow-up.

3. Clinical Endpoints

With regards to safety, the primary safety endpoint was defined as the event free rate at 12 months post procedure. Primary safety events 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 was counted as a chronic primary endpoint. The study collected information on phrenic nerve palsy observed before the end of the index procedure and, when it occurred, potential recovery of the phrenic nerve was assessed during the subsequent study visits.

The secondary safety endpoint was defined as reportable Adverse Events rates at 12 months. Adverse events were 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

With regards to effectiveness, the primary effectiveness endpoint was assessed at the 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 counted for primary effectiveness endpoint assessment. Additional documentation of arrhythmias coming from sources different from those listed above were collected and analyzed separately.

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

The secondary effectiveness endpoint as assessed at the 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.

With regard to success/failure criteria, 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.

Primary Safety Endpoint Hypothesis

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%

The 12-month 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 the withdrawal. The 95% one-sided lower confidence limit (LCL) of the observed safety event-free rate will be compared to the PG of 89%. The null hypothesis will be rejected if the LCL is greater than the performance goal.

Primary Effectiveness Endpoint Hypothesis
Ho: The 12-month failure-free rate ≤ 50%
Ha: The 12-month failure-free rate > 50%

The Kaplan-Meier 12-month 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 the withdrawal. The 95% one-sided lower confidence limit (LCL) of the observed primary effectiveness event-free rate will be compared to the PG of 50%. The null hypothesis will be rejected if the LCL is greater than the performance goal.

B. Accountability of PMA Cohort

At the time of database lock, of 404 patients enrolled in the PMA study, 76% (308) patients are available for analysis at tthe 12-month post-operative visit.

All subjects who signed and dated the Informed Consent Form were considered enrolled in the study.

All treatment subjects (per definition below) were counted against the enrollment ceiling of 325 subjects. Subjects were classified as either part of the Roll-In cohort or the Non Roll-In cohort:

Roll-In Subject – To help facilitate investigators' familiarity with the new investigational system and avoid learning curve bias, Roll-in subjects were enrolled at each study site. Each ablating physician needed to treat 1 (one) Roll-in subject with the Cryoablation System.

Non Roll-In Subject – After the Roll-In subject criteria or case review was satisfied (documentation of waiver) for the treating physician, non Roll-in subjects could be enrolled.

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

Intent - Refers to a subject who was enrolled but did not have any study investigational devices inserted into the body.

Attempt - Refers to a subject who was enrolled and had any study device inserted into the body but did not receive any Cryoablation application.

Treatment - Refers to all enrolled subjects who had the study device inserted into the body and received at least one Cryoablation application.

Figure 8 shows the subject disposition for all Roll-In and Non Roll-In subjects in the FROzEN-AF study. Data from Roll-In subjects are not included in endpoint analyses.

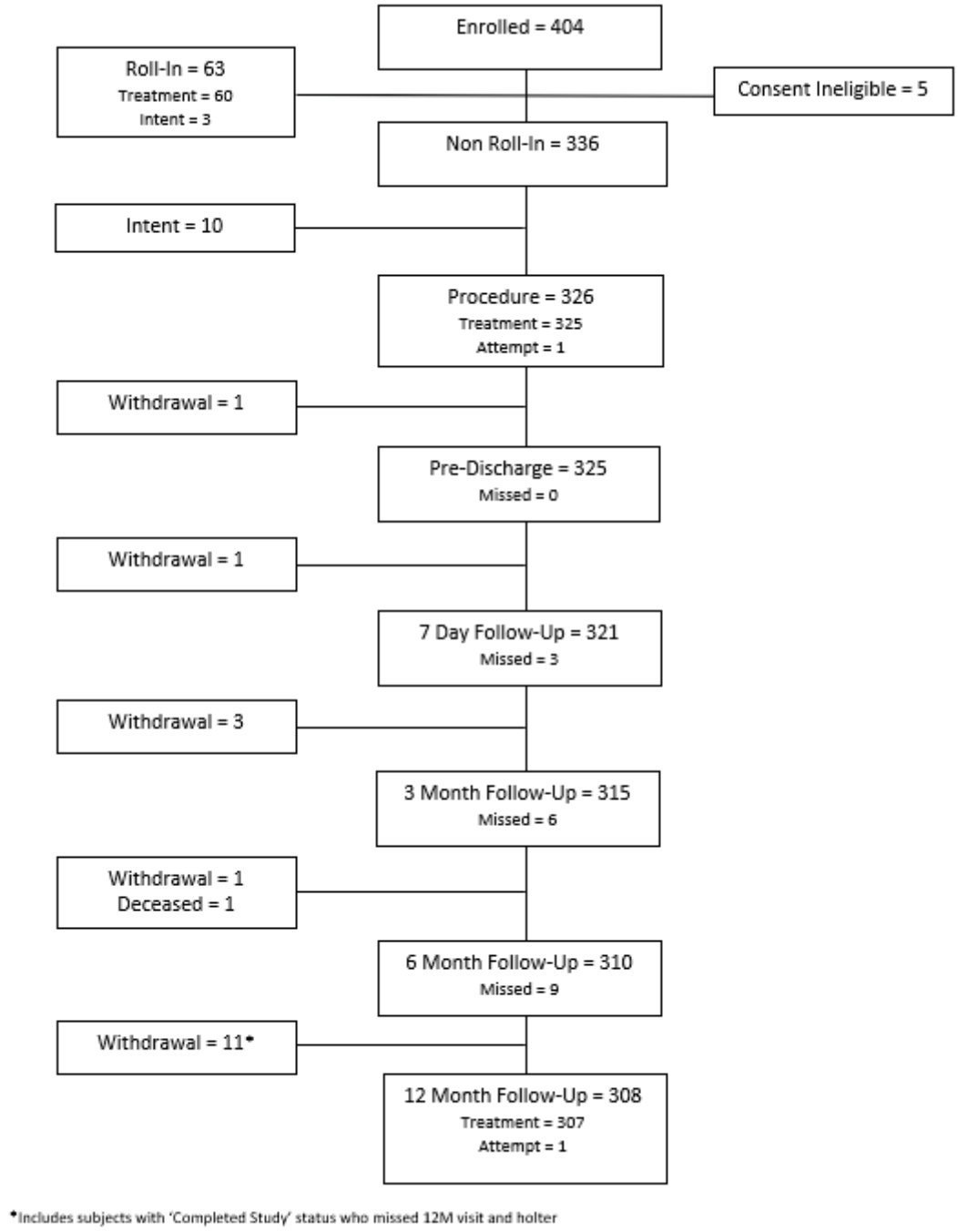

Figure 8 : Subject Disposition and Accountability for Endpoint Analysis

There were 15 Non Roll-In Treatment subjects that withdrew from the study.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are shown in table 14 below. However, as noted in Table 14, a limited number of Black subjects were enrolled in the study. Additional information on the use of the device on Black subjects will need to be collected by the sponsor in the Post Approval Study to understand if race has any impact in this subgroup on the safety and efficacy of the device.

The average age of the subjects was 62 years. The majority of subjects were male (61.8%). The male gender predominance is consistent with previous clinical studies on PAF ablation. The eligibility criteria involving age limit and BMI limit were removed as of protocol revision H. Thirty-five (35) subjects > 75 years were enrolled under protocol version H. Eight (8) patients with BMI >40 were enrolled under protocol version H.

Table 14 presents the demographics and physical assessment data for all Non Roll-In Treatment subjects.

Table 14: Subject Demographics and Physical Assessment Data

Characteristic	Measurement	Result
Age at Enrollment (years)	Mean +/- SD	62 +/- 11
	Min - Max	23 - 83
Gender [N (%)]	Female	124 (38.2)
	Male	201 (61.8)
Race* [N (%)]	Hispanic or Latino	5 (1.6)
	Native American	1 (0.3)
	Asian	35 (11.2)
	Black	4 (1.3)
	Pacific Islander	0 (0.0)
	White	274 (87.5)
	Other	1 (0.3)
	Race Undisclosed	12 (3.7)
Height (cm)	Mean +/- SD	174 +/- 10
	Min - Max	147 - 196
Weight (kg)	Mean +/- SD	86 +/- 19
	Min - Max	45 - 154

Characteristic	Measurement	Result
BMI	Mean +/- SD	29 +/- 6
	Min - Max	16 - 60
Pulse	Mean +/- SD	67 +/- 14
	Min - Max	40 - 130
Systolic BP	Mean +/- SD	133 +/- 18
	Min - Max	90 - 202
Diastolic BP	Mean +/- SD	79 +/- 11
	Min - Max	35 - 118
CHA2DS2-VASc Score [N (%)]	0	63 (19)
	1	82 (25)
	2	92 (28)
	3	59 (18)
	4	21 (6)
	5	8 (2)
*Subjects may contribute to more than one category		

Pre-existing conditions and arrhythmia history of Non Roll-In Treatment subjects are summarized in Table 15 and Table 16.

Table 15: Pre-Existing Conditions Recorded at Baseline

Characteristic	Measurement	Result
Cardiac Disease History [N (%)]	Ischemic Cardiomyopathy	8 (2.5)
	Non-ischemic Cardiomyopathy	11 (3.4)
	Myocardial Infarction	8 (2.5)
	Angina Pectoris	17 (5.2)
	Congenital Heart Disease	11 (3.4)
	Congestive Heart Failure	15 (4.6)
	Cerebrovascular Disease	8 (2.5)
	Peripheral Vascular Disease	11 (3.4)
	Hypertension	183 (56.5)
	Pulmonary Hypertension	10 (3.1)
	Dyslipidaemia	100 (31.0)

Characteristic	Measurement	Result
	Pulmonary Embolism	1 (0.3)
	DVT	2 (0.6)
	Other Cardiovascular Disease	13 (4.0)
Comorbidities [N (%)]	COPD	10 (3.1)
	Diabetes	36 (11.1)
	Type 2	36 (100.0)
	Hepatic Disease	7 (2.2)
	Renal Disease	4 (1.2)
	Gastrointestinal Disorder	57 (17.6)
	Sleep Disordered Breathing	67 (20.9)
	Blood Disorder	0 (0.0)
	Carotid Artery Disease	9 (2.8)
	TIA	2 (0.6)
	CVA	8 (2.5)
COVID-19 History [N (%)]	History of COVID-19	15 (4.6)
	Tested Positive for Virus	14 (93.3)
	Tested Positive for Antibodies	5 (33.3)
Cardiac Procedure History [N (%)]	PTCA	9 (2.8)
	Stent	14 (4.3)
	CABG	5 (1.5)
	Pacemaker/ICD/CRT	0 (0.0)
	Cardiac Valve	0 (0.0)
	LAAC	0 (0.0)
	PFO Intervention	0 (0.0)
	ASD Intervention	0 (0.0)
	Heart Transplant	0 (0.0)
	Other Cardiovascular Procedure	16 (4.9)
Other cardiovasular disease include: Other cardiovasular procedures include: Cardioversion, PAD/RCA stents, coronary angiogram, diagnostic heart cath, AAA repair		

Table 16: Arrhythmia History

Characteristic	Measurement	Result
Ventricular Arrhythmia History [N (%)]	Ventricular Tachycardia	11 (3.4)
	Ventricular Fibrillation	4 (1.2)
	Other Ventricular Arrhythmia	17 (5.2)
Atrial Arrhythmia History [N (%)]	Atrial Fibrillation	325 (100.0)
	Atrial Tachycardia	36 (11.1)
	Atrial Flutter	85 (26.4)
	Other Atrial Arrhythmia	7 (2.2)
Brady Arrhythmia History [N (%)]	Sinus Bradycardia	149 (45.8)
	Sinus Node Dysfunction	12 (3.7)
	Sick Sinus Syndrome Chronotropic Incompetence	6 (1.9)
	Sinus Arrest	1 (0.3)
	AV Block 1	27 (8.3)
	AV Block 2	1 (0.3)
	AV Block 3	0 (0.0)
	Other Brady Arrhythmia	4 (1.2)
Cardiac Ablation History [N (%)]	Any Cardiac Ablation	19 (5.8)
Previous Ablation Arrhythmia [N (%)]	Atrio-Ventricular Nodal Reentrant Tachycardia (AVNRT)	4 (1)
	Atypical AFl	1 (0)
	Concealed Accessory Pathway (AP)	1 (0)
	Other	3 (1)
	Premature Ventricular Contraction (PVC)	1 (0)
	Typical AFl (CW or CCW)	9 (3)
	WPW syndrome	2 (1)
Other ventricular arrhythmias include: premature ventricular contractions, rapid ventricular response, supraventricular tachycardia, LAD, LAFB Other atrial arrhythmias include: premature atrial contractions, supraventricular ectopy, AVRT, sinus tachycardia Other brady arrhythmias include: sinus pauses, AV node disease, brady-tachy syndrome, junctional rhythm Other previous ablation arrhythmias include: SVT		

The average time between first diagnosis and subject enrollment for the Non Roll-In Treatment subjects was 1.0 years (IQR:0.3 – 3.8 years).

Historical anti-arrhythmic medication status is summarized in Table 17.

Table 17: Historical Anti-Arrhythmic Medication Status

Category	N (%)
History of Amiodarone use	26/325 (8)
Subject refractory or intolerant to any Class I or Class III anti-arrhythmic drug taken prior to enrollment*	268/325 (82.5)
Subject with contraindication to Class I or III anti-arrhythmic medications*	88/325 (27.1)
*Subjects may contribute to both categories. All subjects contributed to at least one category	

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the the Non Roll-In Treatment and Attempt subjects (N= 326). The reults of the main analysis for the primary safety endpoint of the safety event free rate at 12 months post procedure are presented in Figure 9. Adverse effects are reported in Tables 18 to 19.

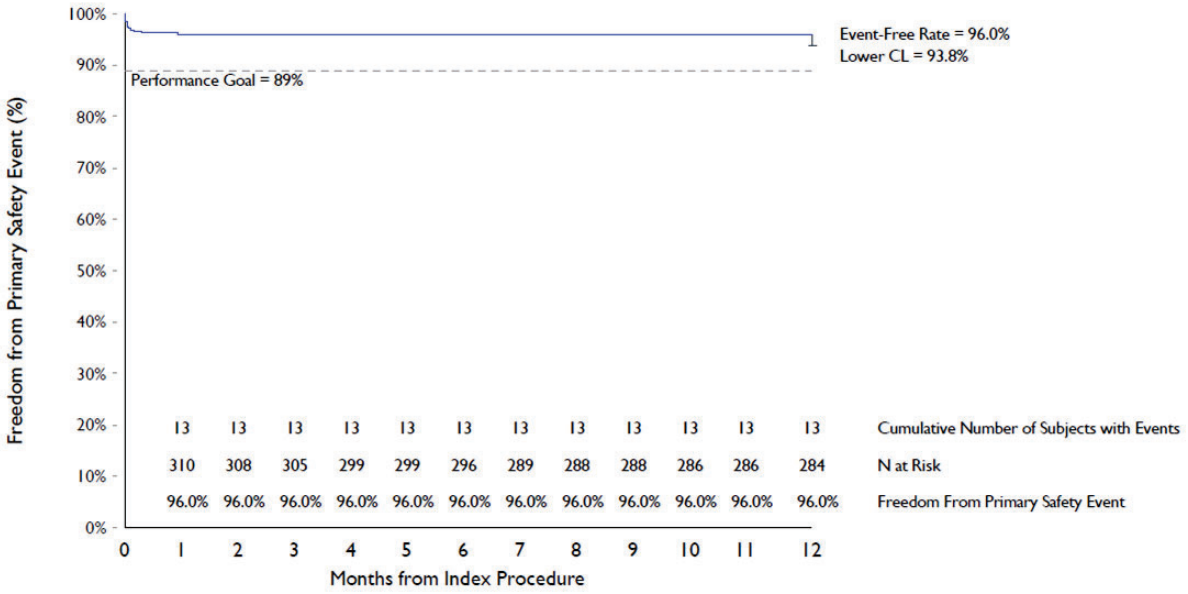

Figure 9: Primary Safety Endpoint Main Analysis

The observed event-free rate at 12 months follow-up was 96.0% with a one-sided 95% lower confidence limit of 93.8%. The lower confidence limit is greater than the performance goal of 89%, resulting in a rejection of the null hypothesis and the primary safety endpoint is passed.

Thirteen (13) subjects out of the 326 subjects in the primary safety endpoint analysis experienced a safety endpoint event prior to 12 months follow-up Table 18).

Table 18: Summary of Primary Safety Events in Non Roll-In Subjects

Endpoint Event	N (% Subjects)
MI	1 (0.3)
Pulmonary edema / heart failure	1 (0.3)
Thromboembolism/Air embolism	1 (0.3)
Cardiac Tamponade/Perforation	2 (0.6)
Gastroparesis / Injury to vagus nerve	3 (0.9)
Vascular Access Complication	5 (1.5)
Total	**13 (4)**

Adverse effects that occurred in the PMA clinical study:

A total of 100 serious adverse events (SAEs) in 73 study subjects were reported by Investigators during the first 12 months of study follow-up: 79 SAEs occurred in 60 Non Roll-In subjects and 21 SAEs occurred in 13 Roll-In subjects. The overall proportion of Non Roll-In subjects with SAEs was 17.9% and for the Roll-In subjects 20.6%. There were no confirmed PV stenosis events. No persistent phrenic nerve palsies were reported. No Atrioesophageal Fistulas were reported.

The SAEs occurring in Non Roll-In and Roll-In subjects are listed in the following tables. SAEs were further classified between serious adverse events and serious adverse device effects (SADE) per ISO classification.

Table 19: Serious Adverse Events in Non Roll-In Subjects

	ISO Classification					
	Serious Adverse Event		Serious Adverse Device Effect		Total	
Adverse Event	N events	N subjects (%)	N events	N subjects (%)	N events	N subjects (%)
Total Adverse Events	**41**	**33 (9.8)**	**38**	**32 (9.5)**	**79**	**60 (17.9)**

	ISO Classification					
	Serious Adverse Event		Serious Adverse Device Effect		Total	
Adverse Event	N events	N subjects (%)	N events	N subjects (%)	N events	N subjects (%)
Ablation Related (N=326)	**0**	**0 (0)**	**38**	**32 (9.8)**	**38**	**32 (9.8)**
Ablation induced arrhythmia	0	0 (0)	2	2 (0.6)	2	2 (0.6)
Angina/Chest pain	0	0 (0)	3	3 (0.9)	3	3 (0.9)
Atrial Fibrillation (AF)	0	0 (0)	3	3 (0.9)	3	3 (0.9)
Atrial flutter, not specified	0	0 (0)	2	2 (0.6)	2	2 (0.6)
Edema	0	0 (0)	1	1 (0.3)	1	1 (0.3)
Embolism – Air	0	0 (0)	1	1 (0.3)	1	1 (0.3)
Esophagitis	0	0 (0)	1	1 (0.3)	1	1 (0.3)
Gastroparesis	0	0 (0)	1	1 (0.3)	1	1 (0.3)
Hematoma	0	0 (0)	4	4 (1.2)	4	4 (1.2)
Myocardial infarction	0	0 (0)	1	1 (0.3)	1	1 (0.3)
Myocardial perforation with tamponade	0	0 (0)	2	2 (0.6)	2	2 (0.6)
Oozing/Bleeding	0	0 (0)	4	4 (1.2)	4	4 (1.2)
Pericarditis	0	0 (0)	4	4 (1.2)	4	4 (1.2)
Phrenic nerve injury temporary	0	0 (0)	4	4 (1.2)	4	4 (1.2)
Post procedure infection/Sepsis	0	0 (0)	1	1 (0.3)	1	1 (0.3)
Procedure related Hypertension	0	0 (0)	1	1 (0.3)	1	1 (0.3)
Procedure related Neurological (Non-TIA, non-stroke, dysphagia, speech disturbance/dysarthria)	0	0 (0)	1	1 (0.3)	1	1 (0.3)
Procedure related Pulmonary (including cough, hemoptysis)	0	0 (0)	2	2 (0.6)	2	2 (0.6)

	ISO Classification					
	Serious Adverse Event		Serious Adverse Device Effect		Total	
Adverse Event	N events	N subjects (%)	N events	N subjects (%)	N events	N subjects (%)
Cardiovascular (N=336)	**22**	**19 (5.7)**	**0**	**0 (0)**	**22**	**19 (5.7)**
1st degree AV block	1	1 (0.3)	0	0 (0)	1	1 (0.3)
Atrial Fibrillation (AF)	6	6 (1.8)	0	0 (0)	6	6 (1.8)
Atrial flutter	2	2 (0.6)	0	0 (0)	2	2 (0.6)
Atypical (Type II) atrial flutter	2	1 (0.3)	0	0 (0)	2	1 (0.3)
Chest pain - Other	2	1 (0.3)	0	0 (0)	2	1 (0.3)
Hypertension/Hypertensive crisis	1	1 (0.3)	0	0 (0)	1	1 (0.3)
Palpitations	1	1 (0.3)	0	0 (0)	1	1 (0.3)
Peripheral vascular disease	1	1 (0.3)	0	0 (0)	1	1 (0.3)
Sinus bradycardia	3	3 (0.9)	0	0 (0)	3	3 (0.9)
Syncope	1	1 (0.3)	0	0 (0)	1	1 (0.3)
Ventricular Tachycardia (VT)/Monomorphic VT	2	2 (0.6)	0	0 (0)	2	2 (0.6)
Non-Cardiovascular (N=336)	**19**	**15 (4.5)**	**0**	**0 (0)**	**19**	**15 (4.5)**
COPD Exacerbation	1	1 (0.3)	0	0 (0)	1	1 (0.3)
Cancer	1	1 (0.3)	0	0 (0)	1	1 (0.3)
Death	1	1 (0.3)	0	0 (0)	1	1 (0.3)
Gastrointestinal	5	3 (0.9)	0	0 (0)	5	3 (0.9)
Genitourinary	1	1 (0.3)	0	0 (0)	1	1 (0.3)
Hematological	4	4 (1.2)	0	0 (0)	4	4 (1.2)
Musculoskeletal	2	2 (0.6)	0	0 (0)	2	2 (0.6)
Neurological	2	2 (0.6)	0	0 (0)	2	2 (0.6)
Physical trauma	1	1 (0.3)	0	0 (0)	1	1 (0.3)
Vasovagal reaction	1	1 (0.3)	0	0 (0)	1	1 (0.3)

Table 20: Serious Adverse Events in Roll-In Subjects

	ISO Classification					
	Serious Adverse Event		Serious Adverse Device Effect		Total	
Adverse Event	N events	N subjects (%)	N events	N subjects (%)	N events	N subjects (%)
Total Adverse Events	**16**	**10 (15.9)**	**5**	**5 (7.9)**	**21**	**13 (20.6)**
Ablation Related (N=60)	**0**	**0 (0)**	**5**	**5 (8.3)**	**5**	**5 (8.3)**
Ablation induced arrhythmia	0	0 (0)	1	1 (1.7)	1	1 (1.7)
Atrial Fibrillation (AF)	0	0 (0)	1	1 (1.7)	1	1 (1.7)
Atrial tachycardia/Other SVT (e.g. AVRT, AVNRT, EAT)	0	0 (0)	1	1 (1.7)	1	1 (1.7)
Pulmonary edema	0	0 (0)	1	1 (1.7)	1	1 (1.7)
Right atrial (Type I) atrial flutter	0	0 (0)	1	1 (1.7)	1	1 (1.7)
Cardiovascular (N=63)	**4**	**4 (6.3)**	**0**	**0 (0)**	**4**	**4 (6.3)**
Atrial tachycardia/Other SVT (e.g. AVRT, AVNRT, EAT)	1	1 (1.6)	0	0 (0)	1	1 (1.6)
Chest pain - Other	1	1 (1.6)	0	0 (0)	1	1 (1.6)
Multiple symptoms	1	1 (1.6)	0	0 (0)	1	1 (1.6)
Peripheral vascular disease	1	1 (1.6)	0	0 (0)	1	1 (1.6)
Non-Cardiovascular (N=63)	**12**	**8 (12.7)**	**0**	**0 (0)**	**12**	**8 (12.7)**

	ISO Classification					
	Serious Adverse Event		Serious Adverse Device Effect		Total	
Adverse Event	N events	N subjects (%)	N events	N subjects (%)	N events	N subjects (%)
Abnormal laboratory values	1	1 (1.6)	0	0 (0)	1	1 (1.6)
Cancer	2	2 (3.2)	0	0 (0)	2	2 (3.2)
Fever and/or virus	1	1 (1.6)	0	0 (0)	1	1 (1.6)
Gastrointestinal	2	2 (3.2)	0	0 (0)	2	2 (3.2)
Hematological	2	2 (3.2)	0	0 (0)	2	2 (3.2)
Musculoskeletal	1	1 (1.6)	0	0 (0)	1	1 (1.6)
Physical trauma	1	1 (1.6)	0	0 (0)	1	1 (1.6)
Pulmonary	2	1 (1.6)	0	0 (0)	2	1 (1.6)

Summary of Clinical Trial Adverse Events

There were a total of 226 adverse events (AEs), inclusive of serious and non-serious events, reported in 145 study subjects (119 Non Roll-In and 26 Roll-In) during the 12 month period of study follow-up:

- 92 subjects (78 Non Roll-In and 14 Roll-In) experienced at least one procedure-related AE.
- 46 subjects (40 Non Roll-In and 6 Roll-In) experienced at least one device-related AE.

A summary of the adverse events can be found in Table 20. Two hundred fifty-four (254) study subjects had no AEs reported, 217 non Roll-Ins and 37 Roll-Ins. A greater proportion of Non Roll-In subjects (12.2%) experienced at least one device-related AE compared to the Roll-In subjects (10.0%).

Table 21: Summary of Total Adverse Events

	Non Roll-In Subjects		Roll-In Subjects		Total Subjects	
	Events	Subjects (%)	Events	Subjects (%)	Events	Subjects (%)
Adverse Events Reported[1]	**178**	**119/336 (35.4)**	**48**	**26/63 (41.3)**	**226**	**145/399 (36.3)**
Device-related AE[2]	44	40/326 (12.2)	8	6/60 (10.0)	52	46/386 (11.9)
Procedure-related AE[2]	102	78/326 (23.9)	22	14/60 (23.3)	124	92/386 (23.8)
Serious Adverse Events Reported[1]	**79**	**60/336 (17.9)**	**21**	**13/63 (20.6)**	**100**	**73/399 (18.3)**
Device-related SAE[2]	16	16/326 (4.9)	1	1/60 (1.7)	17	17/386 (4.4)
Procedure-related SAE[2]	37	31 (9.5)	5	5/60 (8.3)	42	36/386 (9.3)
No Adverse Events Reported[1]	**NA**	**217/336 (64.6)**	**NA**	**37/63 (58.7)**	**NA**	**254/399 (63.7)**

Note 1: Overall adverse event rates reported out of all enrolled subjects

Note 2: Procedure and device related adverse event rates reported out of Attempt and Treatment subjects

The most frequently reported procedure-related AEs (higher than 10%) were hematoma (13 events), temporary phrenic nerve injury (13 events), and pericarditis (14 events). The most frequently reported device-related AEs (higher than 10%) were hematoma (8 events), temporary phrenic nerve injury (13 events), and pericarditis (7 events).

Two (2) patients died during the course of the study. The deaths were classified by the Clinical Events Committee (CEC) as unrelated to the ablation procedure or to the investigational devices.

Pulmonary Vein Stenosis Substudy

No subjects in the 49 subject PV Stenosis Substudy population with baseline and 3-6 month follow-up cardiac CT/MRI imaging were assessed by the corelab as

having moderate or severe PV stenosis (Table 22). Two cases of mild stenosis were noted by the corelab in the LIPV. At study completion, no adverse events have been reported by either subject.

Table 22: PV Stenosis Sub-Study

PV Stenosis Severity	N (%)
None	47 (95.9)
Mild Stenosis (< 50%)	2 (4.1)
Moderate Stenosis (50%-70%)	0 (0.0)
Severe Stenosis (≥70%)	0 (0.0)

No adverse events associated with symptomatic PV stenosis were reported by any subject participating in the trial.

2. Effectiveness Results

The analysis of effectiveness was based on the 317 evaluable patients at the 12 month time point. The observed event-free rate at 12 months follow-up was 59.9% with a one-sided 95% lower confidence limit of 55.2%. The results of the main analysis for the primary effectiveness endpoint of are presented in Figure 10. The lower confidence limit is greater than the performance goal of 50%, resulting in a rejection of the null hypothesis and the primary effectiveness endpoint is passed.

One hundred twenty-nine (129) subjects out of the 325 subjects in the primary effectiveness endpoint analysis experienced an endpoint event prior to 12 months follow-up.

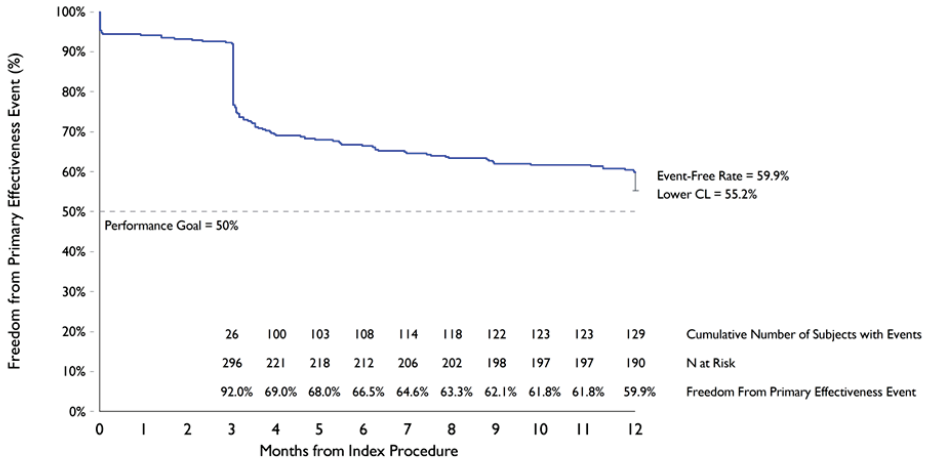

Figure 10: Primary Effectiveness Endpoint Main Analysis

A summary of the primary effectiveness events can be found in Table 23.

Table 23: Summary of Primary Effectiveness Events

Failure Component	N (%)
Overall Event-Free Rate at 12 Months	**59.9%**
Amiodarone/AAD Failure	86 (26.5)
Event Monitor Failure	58 (17.8)
Acute Failure	14 (4.3)
Repeat Procedure Failure	14 (4.3)
Holter Failure	11 (3.4)
Cardioversion Failure	9 (2.8)
ECG Failure	7 (2.2)
Non-study catheter for AF target at Repeat Procedure	6 (1.8)
Non-study catheter for AF target at Index Procedure	4 (1.2)
Surgical Treatment for AF/AFL/AT Failure	0 (0.0)
*Subjects may contribute to more than one category if multiple failure types were observed	

The secondary effectiveness endpoint is the rate of acute procedural success, defined as achievement of electrical isolation of all PVs by using the POLARx^{TM} Cryoablation System only, where electrical isolation of PVs is demonstrated by entrance and exit block. The acute procedural success results are shown in Table 23 below. Of the 14 subjects who were acute procedural failures, 6/14 subjects were acute procedural failures due to protocol requirements not being met where entrance/exit block testing was not performed or documented in one or more veins.

Table 23: Secondary Effectiveness: Acute Procedural Success

N Total	N Success	Acute Success Rate (%)	95% Confidence Interval
325	311	95.69	(92.88, 97.63)

3. Pediatric Extrapolation
   In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

POLARx FIT Extension Study

A. Study design

The POLARx FIT™ Extension Study was a prospective, single-arm, multi-center investigation conducted at 16 Investigational sites in the US. While conducting the FROzEN-AF clinical trial, the sponsor decided to introduce the POLARx FIT™ catheter models, which have the capability to increase the balloon diameter from 28 mm to 31 mm on demand. Subjects were enrolled between April 14, 2022 and August 2, 2022. The last Three-Month follow-up took place on November 10, 2022. The last Twelve-Month follow-up is expected to take place in September 2023. The database for this PMA reflects data collected through three months follow-up and includes 54 subjects.

1. Subject inclusion and exclusion criteria

   Inclusion and exclusion criteria in the POLARx FIT™ Extension Study were exactly the same as in the FROzEN-AF study.

2. Follow-Up Schedule

   All patients were scheduled to return for follow-up examinations at pre-discharge, day 7 follow-up, and at 3-, 6- and 12-months post index ablation procedure. Adverse events and device deficiencies were recorded at all visits. Table 24 lists the protocol-required baseline, procedural, and follow-up assessments.

Table 24 Data Collection Schedule POLARx FIT™ Extension Study

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]								
TTE (medical history)		X[2]								
NIH Stroke Scale (NIHSS)		X[3]		X[3]						
Neurology Consultation[4]				(X)[4]						
Brain MRI Scan[5]				(X)[5]						

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
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.

3. Clinical Endpoints

With regards to safety, 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 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 counted 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 counted as primary safety endpoint events.

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

With respect to effectiveness, the 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.

At the time of PMA approval, the endpoints had been assessed up to 3 months. Additional endpoints with 12 months of follow-up will be reported once follow-up is completed.

B. Accountability of PMA Cohort

All subjects who signed and dated the Informed Consent Form were considered enrolled in the study.

All TREATMENT subjects (per definition below) were counted against the enrollment ceiling of 75 subjects.

Subjects were further classified as Intent, Attempt, and Treatment as described below.

Intent - Refers to a subject who was enrolled but did not have any study investigational devices inserted into the body.

Attempt - Refers to a subject who was enrolled and had any study device inserted into the body but did not receive any POLARx FIT™ Cryoablation application.

Treatment - Refers to all enrolled subjects who had the study device inserted into the body and received at least one POLARx FIT™ Cryoablation application, regardless of the balloon size.

31 mm Treatment - Refers to all enrolled subjects who had the study device inserted into the body and received at least one POLARx FIT™ Cryoablation application using the 31 mm balloon configuration.

Figure 11 shows the subject disposition for all subjects in the POLARx FIT™ Extension Study. Data from Treatment subjects are included in endpoint analyses.

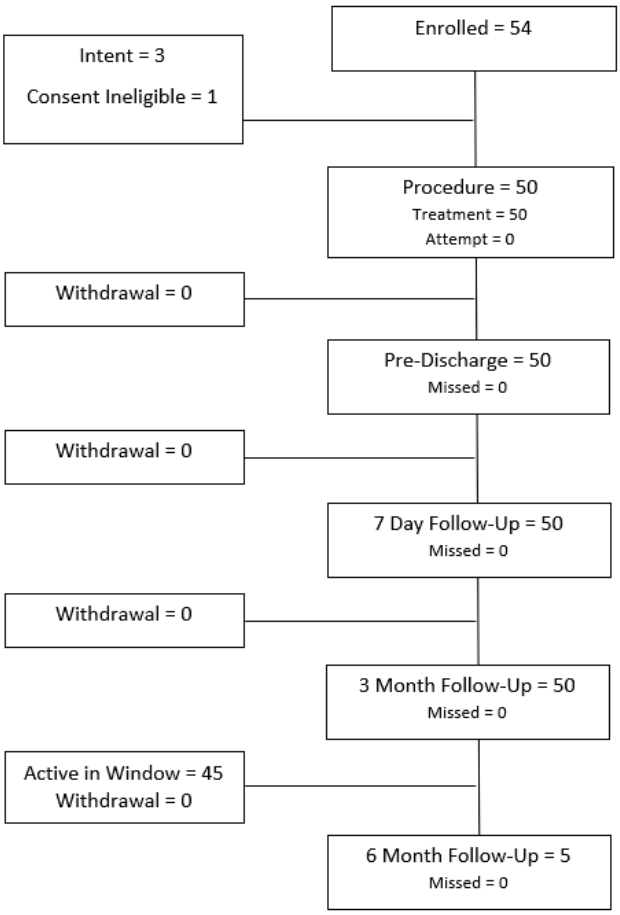

Figure 11: Disposition of Study Subjects in the POLARx FIT™ Extension Study

There were no Treatment subjects that withdrew from the study.

C. Study Population Demographics and Baseline Parameters

This section includes data from all Treatment subjects in the POLARx FIT™ Extension Study (N=50).

The average age of the subjects was 64 years. The majority of subjects were male (54%). The male gender predominance is consistent with previous clinical studies on PAF ablation.

Table 25 presents the demographics and physical assessment data for all Treatment subjects.

Table 25: Subject Demographics and Physical Assessment Data in POLARx FIT™ Extension Study

Characteristic	Measurement	Result
Age at Enrollment (years)	Mean +/- SD	64 +/- 13
	Min - Max	20 - 84
Gender [N (%)]	Female	23 (46.0)
	Male	27 (54.0)
Race [N (%)]	Hispanic or Latino	0 (0.0)
	Native American	0 (0.0)
	Asian	0 (0.0)
	Black	1 (2.0)
	Pacific Islander	0 (0.0)
	White	49 (98.0)
	Other	0 (0.0)
	Race Undisclosed	0 (0.0)
Height (cm)	Mean +/- SD	173 +/- 10
	Min - Max	149 - 198
Weight (kg)	Mean +/- SD	93 +/- 22
	Min - Max	49 - 159
BMI	Mean +/- SD	31 +/- 7
	Min - Max	19 - 50
Pulse	Mean +/- SD	66 +/- 13

Characteristic	Measurement	Result
	Min - Max	50 - 118
Systolic BP	Mean +/- SD	134 +/- 16
	Min - Max	106 - 185
Diastolic BP	Mean +/- SD	76 +/- 9
	Min - Max	56 - 106
CHA2DS2-VASc Score [N (%)]	0	3 (6)
	1	15 (30)
	2	16 (32)
	3	5 (10)
	4	6 (12)
	5	4 (8)

Table 26: Pre-Existing Conditions Recorded at Baseline in POLARx FIT™ Extension Study

Characteristic	Measurement	Result
Cardiac Disease History [N (%)]	Ischemic Cardiomyopathy	0 (0.0)
	Non-ischemic Cardiomyopathy	0 (0.0)
	Myocardial Infarction	2 (4.0)
	Angina Pectoris	4 (8.0)
	Congenital Heart Disease	1 (2.0)
	Congestive Heart Failure	3 (6.0)
	Cerebrovascular Disease	1 (2.0)
	Peripheral Vascular Disease	0 (0.0)
	Hypertension	36 (72.0)
	Pulmonary Hypertension	1 (2.0)
	Dyslipidaemia	21 (42.0)
	Pulmonary Embolism	3 (6.0)
	DVT	1 (2.0)
	Other Cardiovascular Disease	6 (12.0)
Comorbidities [N (%)]	COPD	4 (8.0)
	Diabetes	8 (16.0)

Characteristic	Measurement	Result
	Type 2	8 (100.0)
	Hepatic Disease	0 (0.0)
	Renal Disease	1 (2.0)
	Gastrointestinal Disorder	8 (16.0)
	Sleep Disordered Breathing	10 (20.4)
	Blood Disorder	0 (0.0)
	Carotid Artery Disease	2 (4.1)
	TIA	1 (2.0)
	CVA	1 (2.0)
COVID-19 History [N (%)]	History of COVID-19	10 (20.8)
	Tested Positive for Virus	10 (100.0)
	Tested Positive for Antibodies	1 (10.0)
Cardiac Procedure History [N (%)]	PTCA	2 (4.0)
	Stent	3 (6.0)
	CABG	0 (0.0)
	Pacemaker/ICD/CRT	0 (0.0)
	Cardiac Valve	0 (0.0)
	LAAC	0 (0.0)
	PFO Intervention	0 (0.0)
	ASD Intervention	0 (0.0)
	Heart Transplant	0 (0.0)
	Other Cardiovascular Procedure	4 (8.0)

Table 28: Arrhythmia History in POLARx FIT™ Extension Study

Characteristic	Measurement	Result
Ventricular Arrhythmia History [N (%)]	Ventricular Tachycardia	4 (8.0)
	Ventricular Fibrillation	1 (2.0)
	Other Ventricular Arrhythmia	4 (8.0)
Atrial Arrhythmia History [N (%)]	Atrial Fibrillation	50 (100.0)
	Atrial Tachycardia	3 (6.0)
	Atrial Flutter	20 (40.0)
	Other Atrial Arrhythmia	0 (0.0)

Characteristic	Measurement	Result
Brady Arrhythmia History [N (%)]	Sinus Bradycardia	33 (66.0)
	Sinus Node Dysfunction	3 (6.0)
	Sick Sinus Syndrome Chronotropic Incompetence	0 (0.0)
	Sinus Arrest	0 (0.0)
	AV Block 1	1 (2.0)
	AV Block 2	0 (0.0)
	AV Block 3	0 (0.0)
	Other Brady Arrhythmia	0 (0.0)
Cardiac Ablation History [N (%)]	Any Cardiac Ablation	3 (6.0)
Previous Ablation Arrhythmia [N (%)]	Atrio-Ventricular Nodal Reentrant Tachycardia (AVNRT)	1 (2)
	Atypical AFl	1 (2)
	Other	2 (4)

The average time between first diagnosis and subject enrollment for the Treatment subjects was 0.4 years (IQR:0.2 – 1.0 years).

Table 29: Historical Anti-Arrhythmic Medication Status in POLARx FIT™ Extension Study

Category	N (%)
History of Amiodarone use	5/50 (10)
Subject refractory or intolerant to any Class I or Class III anti-arrhythmic drug taken prior to enrollment*	33/50 (66)
Subject with contraindication to Class I or III anti-arrhythmic medications*	24/50 (48)
*Subjects may contribute to both categories. All subjects contributed to at least one category	

D. Safety and Effectiveness Results

1. Safety Results

Primary Safety Endpoint

The analysis of safety was based on the Treatment subjects (N= 50). The results of the main analysis for the primary safety endpoint of the safety event free rate at 3 months post procedure are presented in Figure 12.

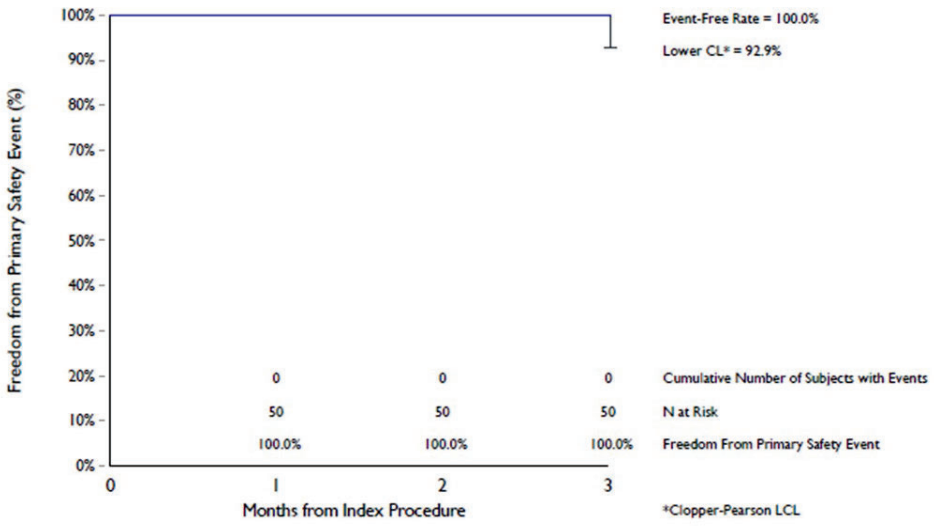

Figure 12: Primary Safety Endpoint Main Analysis

The observed event-free rate at 3 months follow-up was 100% with a one-sided 95% lower confidence limit of 92.9%. None of the subjects in the primary safety endpoint analysis experienced a safety endpoint event prior to 3 months follow-up. The primary safety endpoint data supports the safety of the POLARx FIT™ catheter for the treatment of PAF.

Serious Adverse Events

A total of 7 serious adverse events (SAEs) in 6 study subjects were reported by Investigators during the first 3 months of study follow-up. There were no confirmed PV stenosis events. No persistent phrenic nerve palsies were reported. No Atrioesophageal Fistulas were reported.

The SAEs occurring in Treatment subjects are listed in the following tables. SAEs were further classified between serious adverse events and serious adverse device effects (SADE) per ISO classification.

Table 30: Serious Adverse Events in Treatment subjects

	ISO Classification					
	Serious Adverse Event		Serious Adverse Device Effect		Total	
Adverse Event	N events	N subjects (%)	N events	N subjects (%)	N events	N subjects (%)

	ISO Classification					
	Serious Adverse Event		Serious Adverse Device Effect		Total	
Adverse Event	N events	N subjects (%)	N events	N subjects (%)	N events	N subjects (%)
Total Adverse Events	**2**	**2 (3.8)**	**5**	**4 (7.5)**	**7**	**6 (11.3)**
Ablation Related (N=50)	**0**	**0 (0)**	**5**	**4 (8)**	**5**	**4 (8)**
Angina/Chest pain	0	0 (0)	1	1 (2)	1	1 (2)
Oozing/Bleeding	0	0 (0)	1	1 (2)	1	1 (2)
Phrenic nerve injury temporary	0	0 (0)	1	1 (2)	1	1 (2)
Procedure related Pulmonary (including cough, hemoptysis)	0	0 (0)	1	1 (2)	1	1 (2)
Pulmonary edema	0	0 (0)	1	1 (2)	1	1 (2)
Cardiovascular (N=53)	**1**	**1 (1.9)**	**0**	**0 (0)**	**1**	**1 (1.9)**
Sinus bradycardia	1	1 (1.9)	0	0 (0)	1	1 (1.9)
Non-Cardiovascular (N=53)	**1**	**1 (1.9)**	**0**	**0 (0)**	**1**	**1 (1.9)**
Integumentary	1	1 (1.9)	0	0 (0)	1	1 (1.9)

Summary of Clinical Trial Adverse Events

There were a total of 14 adverse events (AEs, inclusive of serious and non-serious events) reported in 11 study subjects during the 3 month period of study follow-up. Forty-two (42) study subjects had no AEs reported.

In total, 7 Treatment subjects experienced at least one procedure-related AE.
One (1) Treatment subject experienced a device-related AE of Angina/Chest pain.

No patients died during the course of the study.
There were no subjects for whom PV stenosis was suspected.

2. Effectiveness Results

The results of the analysis for the primary effectiveness endpoint are presented in Table 31.

Table 31: Primary Effectiveness: Acute Procedural Success

N Total	N Success	Acute Success Rate (%)	95% Confidence Interval
50	50	100	(92.9, 100)

All subjects in the primary effectiveness endpoint analysis were acute procedural successes. The observed acute success rate was 100% with a one-sided 95% lower confidence limit of 92.9%. The data for the primary effectiveness endpoint supports the effectiveness of the POLARx FIT™ catheter for the treatment of PAF.

3. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 156 investigators of which none were full-time or part-time employees of the sponsor and 4 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 4
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness outcomes of the FROZEN AF study demonstrated that the study catheters are effective for the treatment of symptomatic drug refractory recurrent paroxysmal AF. The clinical study met its primary effectiveness endpoint of 50% to reject the null hypothesis. Specifically, the analysis of effectiveness was based on the 317 evaluable patients at the 12 month time point. The observed event-free rate at 12 months follow-up was 59.9% with a one-sided 95% lower confidence limit of 55.2%.

B. Safety Conclusions

The risks of the device are based on data collected in the clinical studies conducted to support PMA approval as described above. The safety results of the clinical studies indicate that the device is safe for the intended use.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above.

The probable risks of the device are also based on data collected in a clinical studies conducted to support PMA approval as described above.

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for treatment of patients with drug refractory, recurrent symptomatic paroxysmal atrial fibrillation (PAF) the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on 8/08/2023. The final clinical conditions of approval cited in the approval order are described below.

The sponsor must conduct a traditional or registry-based post-approval study (PAS) as described below:

The Boston Scientific Corporation (BSC) Cardiac Cryoablation System Post-Approval Study is a prospective, non-randomized, single-arm, multi-center study to confirm the safety and effectiveness of drug refractory recurrent symptomatic paroxysmal AF (PAF) ablation with the BSC Cardiac Cryoablation System. Approximately 200 adult patients who intend to undergo their first atrial fibrillation ablation with the BSC Cardiac Cryoablation System to treat symptomatic PAF refractory or intolerant to at least one Class I or III antiarrhythmic medication will be enrolled and ablated using the BSC Cardiac Cryoablation System, with at least 50% of patients treated in the United States. The study will include a diverse (i.e., race, ethnicity, gender) patient population. At least 50 subjects participating in the trial will have a LUX-Dx Insertable Cardiac Monitor placed within 7 days of the ablation procedure. Follow up clinical data will be collected at pre-discharge, 3 months, 6 months, and 12 months post-procedure. Subjects with a LUX-Dx implanted prior to the ablation procedure will have arrythmia recurrence monitored remotely via the LATITUDE Home Monitoring System to assess for arrhythmia recurrence for a minimum of 3 years.

The primary objectives of the PAS will be the following:

> The primary safety endpoint will be evaluated by the safety event free rate at 12 months post-index procedure using the BSC Cardiac Cryoablation System.
>
> The primary effectiveness endpoint will be evaluated by the failure-free rate at 12 months post-index procedure using the BSC Cardiac Cryoablation System.

The secondary objectives of the PAS will include the following:

> Failure-free rate at 12 months post-index procedure for those subjects with the LUX-Dx using the Primary Effectiveness Endpoint definition with detectable AF identified by the LUX-Dx containing at least 120 seconds of continuous interpretable signal.
>
> Detectable AF with the LUX-Dx containing at least 120 seconds of continuous interpretable signal through the lifetime of the LUX-Dx up to 36 months.

The sponsor is required to submit a progress report every six months for this PAS during the first two years, and annually thereafter. The sponsor is also required to report any early mortality (through 3 months post-procedure) to the FDA within 10 days after you first receive notice of the event.

In addition, the results from any surveillance should be included in the labeling as these data become available. Any updated labeling must be submitted to FDA in the form of a PMA Supplement.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.