SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Cardiac Cryoablation Catheter

Device Trade Name:
Arctic Front Advance™ Cardiac Cryoablation Catheters
Arctic Front Advance Pro™ Cardiac Cryoablation Catheters
Freezor™ Max Cardiac Cryoablation Catheter
CryoConsole
Manual Retraction Kit

Device Procode: OAE

Applicant's Name and Address: Medtronic Inc.
8200 Coral Sea Street N.E., MVS46
Mounds View, MN 55112

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P100010/S110

Date of FDA Notice of Approval: June 18, 2021

The original PMA P100010 was approved on December 17, 2010 and is currently indicated for the treatment of drug refractory recurrent symptomatic paroxysmal and persistent atrial fibrillation (episode duration less than 6 months). The SSED to support the indications is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indications for the Arctic Front Advance and Arctic Front Advance Pro Cardiac Cryoablation Catheters to also treat patients with recurrent symptomatic paroxysmal atrial fibrillation who have not previously received antiarrhythmic drug therapy for preventing atrial fibrillation recurrence.

II. INDICATIONS FOR USE

The Arctic Front Advance and Arctic Front Advance Pro Cardiac Cryoablation Catheter is indicated for the treatment of recurrent symptomatic paroxysmal atrial fibrillation and the treatment of drug refractory recurrent symptomatic persistent atrial fibrillation (episode duration less than 6 months).

The Arctic Front Advance and Arctic Front Advance Pro Cardiac Cryoablation Catheters are also indicated for the treatment of recurrent symptomatic paroxysmal atrial

fibrillation as an alternative to antiarrhythmic drug therapy as an initial rhythm control strategy.

The Freezor MAX Cardiac Cryoablation Catheter is used as an adjunctive device in the endocardial treatment of paroxysmal and persistent atrial fibrillation (episode duration less than 6 months) in conjunction with the Arctic Front Cryocatheter for the following uses:

- Gap cryoablation to complete electrical isolation of the pulmonary veins
- Cryoablation of focal trigger sites
- Creation of ablation line between the inferior vena cava and the tricuspid valve

III. CONTRAINDICATIONS

Use of the Arctic Front Advance and the Arctic Front Advance Pro Cardiac Cryoablation Catheter is contraindicated in patients with the following conditions:

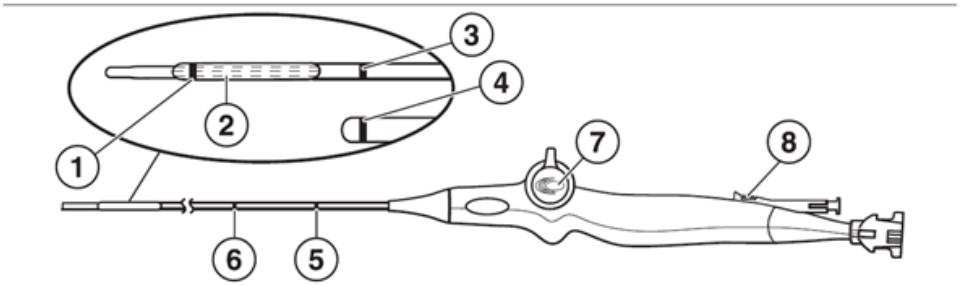
- in the ventricle because of the danger of catheter entrapment in the chordae tendineae
- in patients with active systemic infections
- in conditions where the manipulation of the catheter within the heart would be unsafe (for example, intracardiac mural thrombus)
- in patients with cryoglobulinemia
- in patients with one or more pulmonary vein stents

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Arctic Front Advance and Arctic Front Advance Pro Cardiac Cryoablation Catheters' labeling.

V. DEVICE DESCRIPTION

The Arctic Front Advance and the Arctic Front Advance Pro Cardiac Cryoablation Catheter (the catheter or the Arctic Front Advance or the Arctic Front Advance Pro Cryoballoon) is a flexible, over-the-wire balloon catheter used to ablate cardiac tissue. It is used together with a compatible Medtronic 12 Fr inner diameter sheath (the sheath), the CryoConsole, and related components. For device compatibility questions, contact Medtronic Technical Support. The balloon reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the balloon segment. A thermocouple positioned inside the balloon provides temperature reading capability. The catheter is introduced into the vasculature by traditional, minimally invasive techniques. There are two radiopaque markers on the catheter to confirm the position of the balloon using fluoroscopy. The proximal radiopaque marker is located approximately 10 mm (0.394 in) proximal to the balloon. The distal radiopaque marker is located at the end of the injection tube. (See **Figure 1**).



1 Distal catheter radiopaque marker
2 Deflated balloon segment
3 Proximal catheter radiopaque marker
4 FlexCath sheath radiopaque marker
5 Proximal catheter shaft marker
6 Distal catheter shaft marker
7 Deflection mechanism
8 Blue push button

Figure 1: Arctic Front Advance and Arctic Front Advance Pro Cardiac Cryoablation Catheter

The Arctic Front Advance and Arctic Front Advance Pro Catheters were approved under P100010/S015, and P100010/S070 and there is no difference in the design from the commercially available devices.

Please refer to the Arctic Front Advance and Arctic Front Advance Pro Cardiac CryoAblation Catheter Technical Manuals for more information.

For details about the CryoConsole and how to use it with the device to perform cryoablation procedures, see the *CryoConsole Operator's Manual*.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of recurrent symptomatic paroxysmal atrial fibrillation and the treatment of drug refractory recurrent symptomatic persistent atrial fibrillation (episode duration less than 6 months). The following alternative practices and procedures are available, in addition to the Arctic Front family devices for the treatment of atrial fibrillation:

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

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 Arctic Front Advance has been marketed in the United States for drug refractory recurrent symptomatic paroxysmal atrial fibrillation since April 2012, and is marketed in the following countries: Argentina, Australia, Belarus, Brazil, Canada, China, Colombia, Costa Rica, Croatia, Ecuador, Egypt, Honduras, Hong Kong, Indonesia, Israel, Japan, Kazakhstan, Malaysia, Mexico, Moldova, New Zealand, Nicaragua, Peru, Philippines, Russia, Saudi Arabia, Serbia, Singapore, South Korea, Taiwan, Thailand, Turkey, Ukraine and Vietnam.

Arctic Front Advance Pro has been marketed in the United States for drug refractory recurrent symptomatic paroxysmal atrial fibrillation since May 2018, and is marketed in the following countries: Australia, Belarus, Brazil, Canada, China - Hainan Colombia, Hong Kong, India, Indonesia, Israel, Japan, Kazakhstan, Malaysia, Mexico, New Zealand, Russia, Saudi Arabia, Serbia, Singapore, South Korea South Africa, Turkey, and Ukraine.

These devices have not been withdrawn from market in any country for any reason related to safety or effectiveness.

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 Arctic Front and Arctic Front Pro Catheter.

- Access site complications (e.g. bruising, ecchymosis)
- Anemia
- Anxiety
- Arrhythmia (e.g. atrial flutter, bradycardia, heart block, tachycardia)
- Back pain
- Bleeding from puncture sites
- Bronchial constriction
- Bronchial fistula
- Bronchitis
- Bruising
- Cardiac ischemia
- Cardiac tamponade
- Cardiopulmonary arrest
- Cerebral vascular accident
- Chest discomfort/pain/pressure
- Cold feeling
- Coronary artery spasm
- Cough
- Death
- Diarrhea
- Dizziness
- Embolism

- Mitral entrapment
- Esophageal damage (including atrioesophageal fistula)
- Fatigue
- Fever
- Headache
- Hemoptysis
- Hypotension/hypertension
- Infection (e.g. pericarditis, sepsis, urinary)
- Lightheadedness
- Myocardial infarction
- Nausea/vomiting
- Perforation
- Pericardial effusion
- Pericarditis
- Phrenic nerve injury
- Pleural effusion
- Pneumonia
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary hemorrhage
- Pulmonary vein dissection
- Pulmonary vein stenosis
- Renal insufficiency or renal failure
- Shivering
- Shortness of breath
- Sore throat
- Tissue infarction (such as myocardial infarction or renal infarction)
- Transient ischemic attack
- Vagal nerve injury (e.g. gastroparesis)
- Vasovagal reaction
- Visual changes (e.g. blurred vision)

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

IX. SUMMARY OF NONCLINICAL STUDIES

Bench testing was performed for the Arctic Front Family of Cryoablation catheters, the Freezor MAX Catheter, and the CryoConsole. This testing included verification and validation (reliability, mechanical, electrical, and software) to demonstrate design integrity. Biocompatibility testing was conducted in accordance with the ISO 10993 standard and FDA/CDRH/ODE Blue Book Memorandum G95-1, "Use of International Standard ISO-10993". Sterilization, packaging, and shelf life testing was performed to

demonstrate appropriate sterility, packaging integrity, and shelf life duration. Animal studies were conducted to demonstrate the safety and performance of using cryoenergy to ablate the pulmonary veins and atrial tissue.

Similar testing was conducted to support the Arctic Front Advance Catheter and the Arctic Front Advance Pro Catheter. The original Arctic Front Catheter is not subject to this Premarket Approval Application.

The results of the preclinical testing submitted under PMA P100010 can be found in the SSED at: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100010b.pdf

There have been no changes to the design or materials for this application. No further laboratory preclinical testing was needed for the current submission.

X. SUMMARY OF PRIMARY CLINICAL STUDY(IES)

Table 1 provides an overview of prior clinical trials supported by the applicant to evaluate the cryoablation system.

Table 1: Previously Completed Clinical Trials Assessing the Cryoablation System

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects	Atrial Fibrillation (AF) Population
Feasibility: CryoSTOP AF	Non-randomized, multicenter, feasibility study	To provide an initial evaluation of the Arctic Circler® Balloon and Arctic Front® Cardiac CryoAblation Systems in patients with paroxysmal AF (PAF)	4 (US)	Enrolled: 39 Treated: 33 (15 Arctic Circler balloon, 18 Arctic Front)	Paroxysmal
Pivotal: STOP AF (NCT00523978)	Prospective, multi-center, randomized, controlled clinical trial	To demonstrate safe and effective use of the investigational devices when used to treat PAF	26 (23 US, 3 Canada)	Enrolled: 304 Randomized: 245 (163 Cryo, 82 AAD)	Paroxysmal
Continued Access: CAP AF (NCT00889681)	Non-randomized, multi-center study	To provide continued access to the investigational devices as well as provide scientific evidence regarding the safety and effectiveness of the modified investigational devices	10 (US)	Enrolled: 81 Treated: 78	Paroxysmal
Post-Approval: STOP AF PAS (NCT01456949)	Non-randomized, multi-center study	To provide long-term safety and effectiveness of the Arctic Front and Arctic Front Advance™ Cardiac Cryoablation Catheter System, including the Freezor® *MAX* Cardiac cryoablation catheter	39 (32 US, 7 Canada)	Enrolled: 402 Treated: 354	Paroxysmal
Post-Approval: Fire and ICE (NCT01490814)	Controlled, prospective, non-inferiority, parallel group, randomized, interventional	To compare the efficacy and safety of pulmonary vein isolation with Arctic Front and Arctic Front Advance cryoballoon catheters versus radiofrequency ablation with ThermoCool family of catheters guided by the CARTO 3D mapping system	19 (Europe)	Enrolled: 762 (378 cryoballoon, 384 radiofrequency)	Paroxysmal

Post-Market Surveillance: PMS Japan	Prospective multi-center, non-randomized single arm, unblinded clinical study	To provide long-term safety and effectiveness of the Arctic Front Advance® Cardiac CryoAblation System according to the product labeling in Japan	33 (Japan)	Enrolled: 616 Treated: 607	Paroxysmal
Post-Approval: Cryo4Persistent (NCT02213731)	Prospective, multicenter, single arm	Designed to assess single-procedure outcomes of PVI using the cryoballoon in persistent atrial fibrillation (PerAF) patients	11 (Europe)	Enrolled: 130 Treated: 107	Persistent
Pivotal: STOP Persistent AF (NCT03012841)	Prospective, multicenter, single arm	Designed to demonstrate the safety and effectiveness of the Arctic Front Advance and Freezor MAX Cardiac CryoAblation Catheters for the treatment of drug refractory recurrent symptomatic persistent atrial fibrillation	25 (US, Canada, and Japan)	Enrolled: 186 Treated: 165	Persistent
Post-Approval: Cryo-FIRST (NCT01803438)	Prospective, multicenter, randomized	Designed to evaluate the effectiveness of pulmonary vein isolation performed with the Arctic Front™ Advance Cardiac CryoAblation Catheter System as a first-line therapy in comparison with antiarrhythmic drugs in patients with paroxysmal atrial fibrillation	18 (Australia, Argentina and 7 countries in Europe)	Enrolled: 220 Randomized: 218 (107 Cryo, 111 AAD)	paroxysmal

STOP AF FIRST CLINICAL STUDY

The applicant performed the STOP AF First clinical study to establish a reasonable assurance of safety and effectiveness of pulmonary vein isolation with the Arctic Front Advance for antiarrhythmic drug (AAD) naïve patients with recurrent symptomatic paroxysmal AF in the US under IDE # G160219. Data from this clinical study formed the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The study was a prospective, multi-center, randomized, controlled, unblinded pivotal study conducted in the US. Subjects with recurrent symptomatic paroxysmal AF for which they had not previously received rhythm control therapy using a class 1 or 3 AAD were randomized in a 1:1 ratio to either AAD therapy (control arm) or cryoballoon ablation (also referred to as cryoablation; treatment arm).

Subjects in the treatment arm underwent a pulmonary vein isolation (PVI) ablation procedure with the Arctic Front Advance™ Cardiac Cryoablation Catheter within 30 days after randomization. At the end of the procedure entrance block into all targeted PVs was assessed to determine acute procedural success. Treatment with a class 1 or 3 AAD (excluding amiodarone) was permitted for up to 80 days after the procedure to allow complete washout by the end of the 90-day blanking period (i.e., 90 days after ablation procedure) and to decrease the risk of a protocol violation.

Subjects in the control arm received a class 1 or 3 AAD within 30 days after randomization. The investigator chose the appropriate AAD per his or her standard of care; however, it was recommended that amiodarone only be used if other AADs were not tolerated or failed. The 2014 AHA/ACC/HRS Guideline for the Management of Patients with AF (January, et al., 2014) were consulted for AAD prescriptions. Modifications to AADs (type or dosage increase) could be made for up to 90 days after AAD initiation. This was referred to as the AAD optimization period. Dosing of AADs could be individually tailored until the end of the AAD optimization period. After the optimization period, further AAD therapy optimization or change was discouraged.

All randomized subjects were followed from the time of consent through 12 months post-treatment initiation to assess recurrence of atrial tachyarrhythmias and adverse events. Arrhythmia monitoring included 12-lead ECG at 1, 3, 6, and 12 months, weekly and symptom-driven patient-activated ambulatory monitoring during months 3 through 12, and 24-hour ambulatory ECG monitoring at 6 and 12 months.

Crossover from AAD therapy to cryoablation was permitted only when a subject in the control arm was deemed a treatment failure.

Subjects were exited from the study at the 12-month follow-up visit.

1. Inclusion and Exclusion Criteria

   Enrollment in the STOP AF First study was limited to patients who met the following inclusion criteria:

   - A diagnosis of symptomatic paroxysmal AF with the following documentation: (1) physician's note indicating recurrent self- terminating AF or paroxysmal AF; and (2) any ECG documented AF within 6 months prior to enrollment.
   - Age 18-80

   Patients were not permitted to enroll in the STOP AF First study if they met any of the following exclusion criteria:

   - History of AF treatment with class I or III AAD, including sotalol, with the intention to prevent an AF recurrence. However, patients pretreated

with above AAD for less than 7 days with the intention to convert an AF episode are allowed.

- Prior persistent AF (continuous AF that is sustained >7 days)
- Left atrial diameter greater than 5.0 cm
- Prior left atrial ablation or left atrial surgical procedure
- Presence or likely implant of a permanent pacemaker, biventricular pacemaker, loop recorder, or any type of implantable cardiac defibrillator (with or without biventricular pacing function)
- Presence of any pulmonary vein stents
- Known presence of any pre-existing pulmonary vein stenosis
- Pre-existing hemidiaphragmatic paralysis
- Presence of any cardiac valve prosthesis
- Moderate or severe mitral valve regurgitation or stenosis
- Any cardiac surgery, myocardial infarction, percutaneous coronary intervention / percutaneous transluminal coronary angioplasty or coronary artery stenting which occurred during the 90-day interval preceding the date the subject signed the Informed Consent Form
- Unstable angina
- NYHA class III or IV congestive heart failure and/or known left ventricular ejection fraction (LVEF) less than 45%
- Diagnosis of primary pulmonary hypertension
- Rheumatic heart disease
- Thrombocytosis, thrombocytopenia
- Contraindication to anticoagulation therapy
- Active systemic infection
- Hypertrophic cardiomyopathy
- Cryoglobulinemia
- Known reversible causes of AF, including but not limited to uncontrolled hyperthyroidism, severe obstructive sleep apnea, and acute alcohol toxicity.
- Any cerebral ischemic event (strokes or transient ischemic attacks) which occurred during the 180-day interval preceding the date the subject signed the Informed Consent Form, or any known unresolved complications from previous stroke/transient ischemic attack
- Existing thrombus
- Pregnancy
- Patient with life expectancy that makes it unlikely 12 months of follow-up will be completed.
- Current or anticipated participation in any other clinical trial of a drug, device or biologic during the duration of this study not pre-approved by Medtronic
- Patients with contraindications to a Holter monitor
- Unwilling or unable to comply fully with study procedures and follow-up

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 1, 3, 6, and 12 months after the cryoablation procedure or antiarrhythmic drug initiation. Additionally, subjects in the cryoablation arm completed a hospital discharge visit.

Table 2 lists the protocol-required baseline, procedural, and follow-up assessments for all study participants.

Table 2: Visit Schedule and Data Collection Requirements

Activity	Baseline	Procedure (Treatment Arm Only)	Hospital Discharge (Treatment Arm Only)	1 Month	3 Month	6 & 12 Months	Unscheduled	Reablation or Crossover Ablation
Informed Consent	X							
Randomization	X							
Inclusion/Exclusion	X							
Medical History	X							
Physical Exam	X							
Pregnancy Screening[1]	X							
Review Medications	X		X	X	X	X	X	X
Review of AF Symptoms	X			X	X	X	X	X
Collect Health Care Utilization Information				X	X	X	X	X
12 Lead ECG	X		X	X	X	X	X	
EQ-5D & AFEQT	X					X		X
Transthoracic Echocardiogram (TTE)[2]	X							
Transesophageal Echocardiogram (TEE)[3]		X						X
Ablation Procedure Data		X						X
24-hour continuous ambulatory ECG monitoring						X		
Patient Activated Ambulatory ECG Monitoring[4]					X			
Adverse Events	X	X	X	X	X	X	X	X
Device Deficiencies	As they occur							
Study Deviations	As they occur							
Chest X-ray (treatment arm only)	If phrenic nerve injury is detected during the procedure, the subject will be evaluated with inspiration/expiration chest x-ray at PHD and all follow-up visits until resolved.							
MRI or CT Scan (treatment arm only)	Required only for subjects with suspected PV stenosis.							

[1] Required only for female subjects of childbearing potential.

[2] Only required if data not available from within 6 months prior to consent date.

[3] TEE was required in all subjects who presented to the ablation procedure in AF lasting more than 48 hours in duration (or of an unknown duration). However, the TEE was not required if the subject had adequate systemic anticoagulation that had been maintained for at least 3 weeks prior to presenting to the ablation procedure in AF. A TEE was required if subjects had a CHA_2DS_2-VASc ≥2 and presented to the

procedure with a sub-therapeutic INR (<2.0) or if the subject had had a significant interruption of NOACs. A significant interruption of NOACs was defined as any missed dose within 21 days prior to the ablation procedure.

[4] Subjects submitted ECG transmissions weekly and whenever symptoms occur after the AAD optimization/post-ablation blanking periods through 12-month follow-up.

3. Study Endpoints

The endpoints for the study were as follows:

Primary Effectiveness Endpoint

The primary effectiveness endpoint was treatment success at 12 months after AAD initiation (control arm) or after the pulmonary vein isolation ablation procedure utilizing the Arctic Front Advance™ Cardiac CryoAblation Catheter (treatment arm). A treatment success was the opposite of a treatment failure. Treatment failure was defined as any of the following:

- Acute procedural failure (treatment arm only).
- Documented AF/atrial tachycardia (AT)/atrial flutter (AFL) on ambulatory monitoring/12-lead ECG after the 90-day post-ablation blanking period (treatment arm)/AAD optimization period (control arm).
    - Minimum of 30 seconds on ambulatory monitoring or 10 seconds on 12-lead ECG.
    - Note: Documented occurrence and treatment of typical right-sided cavotricuspid isthmus dependent atrial flutter was not considered a failure if confirmed by entrainment maneuvers during EP testing.
- Any subsequent AF surgery or ablation in the left atrium.
- Any subsequent cardioversion after the 90-day post-ablation blanking period (treatment arm)/AAD optimization period (control arm).
- Class I or III antiarrhythmic drug (or sotalol) use after the 90-day blanking period (treatment arm only).

The AAD optimization period was defined as the first 90 days after AAD initiation (control arm). The post-ablation blanking period was defined as the first 90 days after the index ablation procedure (treatment arm). Recurrences of atrial arrhythmias during the AAD optimization/blanking periods were not counted in the determination of the first clinical failure for the primary endpoint.

Within the AAD optimization period/post-ablation blanking period, recurrent arrhythmias could be managed with medications or cardioversions. Reablation was considered a primary endpoint failure at all times, including during the 90-day post-ablation blanking period.

Hypothesis

It was hypothesized that the proportion of subjects with treatment success at 12 months was greater in subjects randomized to cryoablation compared to those randomized to AAD therapy.

The following hypothesis was tested in a two-sided test with $\alpha = 0.05$:

H0: $\pi cryo = \pi AAD$

HA: $\pi cryo \neq \pi AAD$,

where $\pi cryo$ and πAAD were the proportion of treatment successes at 12 months in the modified intention-to treat (mITT) cohorts of the cryoablation and AAD arms, respectively. The mITT cohort included all randomized subjects for which treatment was initiated.

Analysis methods

The probability of a subject achieving success at 12 months (365 days) was estimated using Kaplan-Meier survival analysis. The standard error was approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the probability was constructed. A two-sided log rank test with $\alpha = 0.05$ was be used to assess whether the failure rate differs between study arms.

Primary Safety Endpoint

The primary safety endpoint was evaluated in the treatment arm only and was a composite of the following serious procedure-related or cryoablation system-related adverse events:

- Transient ischemic attack within 7 days of ablation procedure.
- Cerebrovascular accident within 7 days of ablation procedure.
- Major bleeding that requires transfusion or results in a 20% or greater fall in hematocrit (HCT) within 7 days of ablation procedure.
- Development of a significant pericardial effusion within 30 days of ablation procedure. A significant pericardial effusion was defined as resulting in hemodynamic compromise, requiring elective or urgent pericardiocentesis, or resulting in a 1-cm or more pericardial effusion as documented by echocardiography.
- Symptomatic pulmonary vein stenosis within 12 months of ablation procedure; accompanied by one of the following: 50%-70% reduction in diameter of the pulmonary vein with symptoms not explained by other conditions; OR>70% reduction in diameter of the pulmonary vein.
- Myocardial infarction within 7 days of ablation procedure.

- Phrenic nerve injury unresolved at 12 months post-procedure.
- Atrial-esophageal fistula within 12 months of ablation procedure.
- Major vascular complication that required intervention, prolonged the hospital stay, or required hospital admission (within 7 days of ablation procedure).

Hypothesis

To demonstrate an acceptable safety profile of the cryoballoon ablation procedure in the study population, the primary safety endpoint was compared against a performance goal of 12% developed largely on the basis of a review of historical studies of cryoballoon ablation of AF.

The following hypothesis was tested in a one-sided test with $\alpha = 0.025$:

H0: $Ps \geq 12\%$

Ha: $Ps < 12\%$,

where Ps is the probability of a safety event in the mITT cohort of the cryoablation arm.

Analysis Methods

The probability of a safety event within 12 months was estimated using Kaplan-Meier survival analysis. Greenwood's formula was used to approximate the standard error of the survival curve, and a two-sided log-log confidence interval at 12 months was reported.

Secondary Endpoints

- Difference in composite scores from the AFEQT quality of life questionnaire taken at baseline and 12-month visits;
- Difference in composite scores for the EQ-5D quality of life questionnaire taken at baseline and 12-month visits.

- 12-month rate of cardiovascular health care utilization (HCU) events (including cardiovascular-related hospitalizations, emergency department visits, and unscheduled office visits);
- 12-month rate of cardioversion (either electrical or pharmacological).

The Hochberg multiple testing procedure was pre-specified to adjust for the 4 hypotheses being tested for the secondary endpoints.

Ancillary Endpoints

- All reported adverse events.

- Composite adverse events over 12 months in the cryoablation arm and control arm, including the following:
    - Cerebrovascular accident
    - Transient ischemic attack
    - Major bleeding that required transfusion
    - Cardiac perforation, tamponade, or pericardial effusion
    - Symptomatic pulmonary vein stenosis within 12 months; accompanied by one of the following: 50%-75% reduction in diameter of the pulmonary vein with symptoms not explained by other conditions; OR >75% reduction in diameter of the pulmonary vein
    - Myocardial infarction
    - Phrenic nerve injury unresolved at 12 months
    - Atrial-esophageal fistula
    - Cardiovascular death
    - Bradycardia leading to pacemaker insertion
    - Syncope
    - Serious adverse event leading to drug discontinuation
    - QRS duration prolongation ≥ 50% of baseline QRS duration
    - Torsades de pointes
    - Anaphylactic reaction
    - Pulmonary hypertension
    - Hospitalizations for (primary reason): AF recurrence or ablation, atrial flutter ablation (except Type I), systemic embolization (not stroke), congestive heart failure, hemorrhagic event (not stroke), antiarrhythmic drug: initiation, adjustment or complication and symptomatic bradycardia requiring medication change.

- Acute procedural failure, defined as any of the following:
    - Inability to isolate all accessible targeted pulmonary veins (assessed for entrance block and, where assessable, exit block) during the index ablation procedure.
    - Left atrial non-PVI ablations including but not limited to, ablation of linear lesions.
    - Use of a non-study device for ablation in the left atrium.

- Cryoablation procedure parameters

- Atrial arrhythmias present or treated during the index ablation procedure

4. Sample Size

Assumptions used to calculate study sample size included that 45.0% of the patients in the control arm and 69.9% of the patients in the cryoablation arm would have treatment success and that 4.0% of the patients in the cryoablation arm would have a primary safety endpoint event within 12 months.

On the basis of these assumptions and an expected 10% attrition, a sample size of 210 was calculated to be sufficient to provide at least 90% power for the analysis of the primary effectiveness endpoint and 80% power for the analysis of the primary safety endpoint.

5. Study Success Criteria

   The study would be considered successful by demonstrating the superiority of cryoballoon ablation over AAD therapy in treatment success and meeting pre-defined safety performance goal of 12% for the primary safety endpoint.

6. Clinical Events Committee and Core Lab and Contract Research Organizations

   An independent Clinical Events Committee (CEC) was utilized to review and adjudicate all adverse events and deaths (if any had occurred).

   An independent core lab was utilized to review and adjudicate all ECG and ambulatory monitoring recordings. The core lab was responsible for adjudication of rhythm documentation for the primary effectiveness endpoint of the study. All study-required 12-lead ECGs were sent to the core lab.

   A contract research organization was utilized for site monitoring activities, CEC management, clinical safety management and potential complaint reporting, database development, data review, and SAS programming.

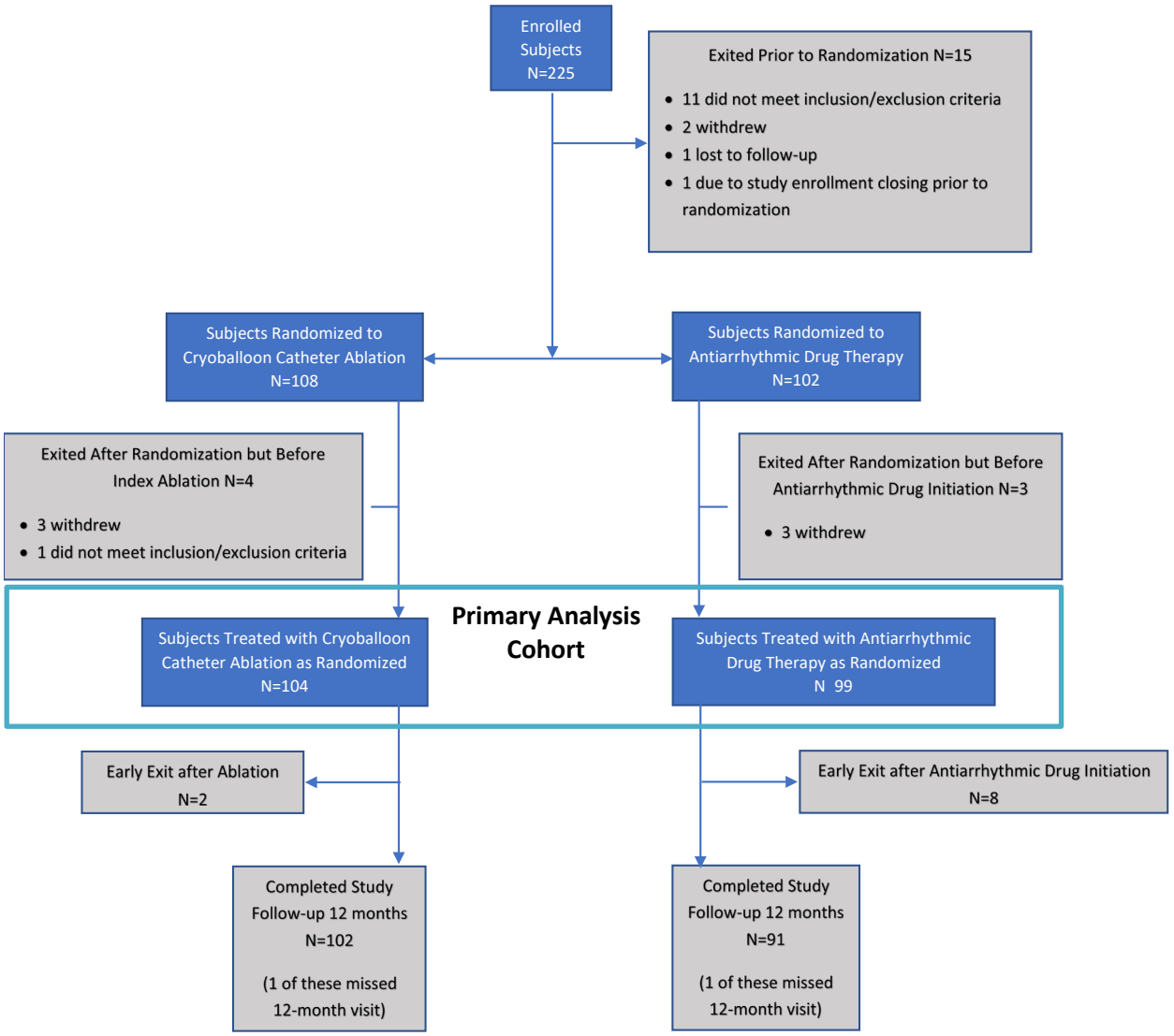
B. Accountability of PMA Cohort

The study was approved for up to 250 subjects from up to 30 centers in the US and up to 10 in Europe to ensure 210 subjects would be randomized. Study enrollment was completed in approximately 23 months, beginning in June 2017 and with completion in May 2019. The final subject visit occurred in June 2020. The database for this PMA reflected data collected through database lock on August 10, 2020. A total of 225 subjects were enrolled of which 210 were randomized across 24 sites in the US with all sites enrolling and randomizing at least one study subject.

Figure 1 shows the disposition of subjects. A total of 225 subjects signed the informed consent and thus were considered enrolled in the study. Of these, 15 exited the study prior to randomization. Of the 210 randomized subjects, 108 were randomized to the cryoablation arm and 102 randomized to the control arm. Of the 108 subjects randomized to the cryoablation arm, 104 received the treatment and were included in the mITT cohort. Of the 102 subjects randomized to control arm, 99 received AAD therapy

and were also included in the mITT cohort. Of the 203 subjects who received the randomized treatment, 193 (95.1%) completed 12 months of follow-up. A total of 10 (4.9% of mITT subjects) exited the study prior to 12 months on day 10-462 post-treatment initiation due to lost to follow-up (n = 4), subject requested study withdrawal (n = 5), or unwilling to wait 3 months before crossing over to cryoablation arm (n = 1). There were no deaths in the study.

Figure 1: Subject Flow Diagram



C. Study Population Demographics and Baseline Parameters

Table 3 and Table 4 summarize the demographics and clinical characteristics of the mITT subjects, respectively. The baseline characteristics were similar between the two study arms.

Table 3: Demographics in mITT Subjects

Subject Characteristics	Cryoablation (n = 104)	AAD Therapy (n = 99)	Total (n = 203)	P-value*
Sex (n,%)				
Male	63 (60.6%)	57 (57.6%)	120 (59.1%)	0.66
Female	41 (39.4%)	42 (42.4%)	83 (40.9%)	
Age (years)				
Mean ± Standard Deviation	60.4 ± 11.2	61.6 ± 11.2	61.0 ± 11.2	0.46
Median	62.0	65.0	64.0	
25th Percentile - 75th Percentile	53 - 69	54 - 70	53 - 70	
Minimum - Maximum	32 - 80	32 - 80	32 - 80	
Not reported (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Race (n,%)				
White or Caucasian	94 (90.4%)	91 (91.9%)	185 (91.1%)	0.32
Black	5 (4.8%)	5 (5.1%)	10 (4.9%)	
Asian Indian	0 (0.0%)	2 (2.0%)	2 (1.0%)	
Chinese	1 (1.0%)	0 (0.0%)	1 (0.5%)	
Race not reported by subject	4 (3.8%)	1 (1.0%)	5 (2.5%)	
Ethnicity (n,%)				
Hispanic ethnicity	2 (1.9%)	3 (3.0%)	5 (2.5%)	0.59
Non-Hispanic ethnicity	97 (93.3%)	91 (91.9%)	188 (92.6%)	
Not reportable per local laws or regulations	3 (2.9%)	1 (1.0%)	4 (2.0%)	
Subject/Physician chose not to provide	2 (1.9%)	4 (4.0%)	6 (3.0%)	

*Unadjusted for multiple comparisons.

Table 4: Clinical Characteristics in mITT Subjects

Subject Characteristics	Cryoablation (n = 104)	AAD Therapy (n = 99)	Total (n = 203)	P-value*
Body Mass Index (kg/m^2)				
Mean ± Standard Deviation	29.9 ± 5.4	30.9 ± 5.9	30.4 ± 5.7	0.22
Median	29.0	31.0	30.0	
25th Percentile - 75th Percentile	27 - 33	26 - 35	26 - 34	
Minimum – Maximum	19 - 47	19 - 47	19 - 47	
Not reported (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Systolic Blood Pressure (mmHg)				
Mean ± Standard Deviation	128.3 ± 18.0	128.0 ± 15.2	128.1 ± 16.6	0.90
Median	125.0	130.0	126.0	
25th Percentile - 75th Percentile	116 - 140	118 - 138	118 - 138	
Minimum – Maximum	84 - 182	93 - 174	84 - 182	
Not reported (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Diastolic Blood Pressure (mmHg)				

Subject Characteristics	Cryoablation (n = 104)	AAD Therapy (n = 99)	Total (n = 203)	P-value*
Mean ± Standard Deviation	77.6 ± 8.6	75.7 ± 9.9	76.7 ± 9.3	0.15
Median	78.0	76.0	78.0	
25th Percentile - 75th Percentile	71 - 84	70 - 84	70 - 84	
Minimum – Maximum	56 - 94	56 - 100	56 - 100	
Not reported (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Left Ventricular Ejection Fraction (%)				
Mean ± Standard Deviation	60.9 ± 6.0	61.1 ± 5.9	61.0 ± 5.9	0.85
Median	60.0	60.0	60.0	
25th Percentile - 75th Percentile	57 - 65	57 - 65	57 - 65	
Minimum – Maximum	45 - 75	45 - 75	45 - 75	
Not reported (%)	0 (0.0%)	1 (1.0%)	1 (0.5%)	
Left Atrial Diameter (mm)				
Mean ± Standard Deviation	38.7 ± 5.7	38.2 ± 5.4	38.5 ± 5.5	0.48
Median	39.0	39.0	39.0	
25th Percentile - 75th Percentile	36 - 42	34 - 42	35 - 42	
Minimum – Maximum	18 - 50	25 - 49	18 - 50	
Not reported (%)	0 (0.0%)	1 (1.0%)	1 (0.5%)	
Time since PAF onset (years)	1.3 ± 2.5	1.3 ± 2.3	1.3 ± 2.4	0.82
Cardioversions in previous 12 months				
Electrical	19 (18.3%)	15 (15.2%)	34 (16.7%)	0.55
Pharmacologic	8 (7.7%)	14 (14.1%)	22 (10.8%)	0.14
History of atrial flutter	19 (18.3%)	19 (19.2%)	38 (18.7%)	0.87
History of atrial tachycardia	6 (5.8%)	6 (6.1%)	12 (5.9%)	0.93
AFEQT Summary Score	58.5 ± 23.4	62.9 ± 21.7	60.6 ± 22.7	0.17
Composite EQ-5D Score	0.89 ± 0.13	0.88 ± 0.12	0.89 ± 0.13	0.89
EQ-5D VAS Score	80.4 ± 14.0	78.7 ± 14.2	79.6 ± 14.1	0.39
NYHA Class (N, %)				
Classification not available	7	12	19	
No heart failure	89 (91.8%)	78 (89.7%)	167 (90.8%)	0.39
I	7 (7.2%)	6 (6.9%)	13 (7.1%)	
II	1 (1.0%)	3 (3.4%)	4 (2.2%)	
III	0 (0.0%)	0 (0.0%)	0 (0.0%)	
IV	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Medical History				
Coronary artery disease	13 (12.5%)	12 (12.1%)	25 (12.3%)	0.93
Myocardial infarction	4 (3.8%)	2 (2.0%)	6 (3.0%)	0.44
Congestive heart failure	1 (1.0%)	3 (3.0%)	4 (2.0%)	0.29
Diabetes	15 (14.4%)	17 (17.2%)	32 (15.8%)	0.59
Hypertension	58 (55.8%)	57 (57.6%)	115 (56.7%)	0.80
Cardiac valve dysfunction	8 (7.7%)	9 (9.1%)	17 (8.4%)	0.72
Prior cardiac valvular surgery	0 (0.0%)	1 (1.0%)	1 (0.5%)	0.30
Stroke	0 (0.0%)	3 (3.0%)	3 (1.5%)	0.07
Transient ischemic attack	2 (1.9%)	0 (0.0%)	2 (1.0%)	0.17
Sleep apnea	26 (25.0%)	20 (20.2%)	46 (22.7%)	0.41

Subject Characteristics	Cryoablation (n = 104)	AAD Therapy (n = 99)	Total (n = 203)	P-value*
Renal dysfunction	1 (1.0%)	2 (2.0%)	3 (1.5%)	0.53
Chronic obstructive pulmonary disease	5 (4.8%)	6 (6.1%)	11 (5.4%)	0.69
Alcoholism	2 (1.9%)	3 (3.0%)	5 (2.5%)	0.61
CHA2DS2-VASc Score (N, %)				
0	20 (19.2%)	16 (16.2%)	36 (17.7%)	0.23
1	28 (26.9%)	28 (28.3%)	56 (27.6%)	
2	33 (31.7%)	19 (19.2%)	52 (25.6%)	
3	12 (11.5%)	22 (22.2%)	34 (16.7%)	
>3	11 (10.6%)	14 (14.1%)	25 (12.3%)	
Not reported	0	0	0	
Baseline medications				
Beta-blocker	6 (5.8%)	9 (9.1%)	15 (7.4%)	0.37
Nondihydropyridine calcium-channel blocker	10 (9.6%)	3 (3.0%)	13 (6.4%)	0.06
Warfarin	3 (2.9%)	0 (0.0%)	3 (1.5%)	0.09
Non-vitamin K antagonist oral anticoagulant	69 (66.4%)	68 (68.7%)	137 (67.5%)	0.72
Aspirin	21 (20.2%)	13 (13.1%)	34 (16.7%)	0.18
Time from randomization to treatment initiation (days)	24.4 ± 15.2	8.7 ± 28.5	16.8 ± 23.9	<0.0001

*Unadjusted for multiple comparisons.

D. Treatment Characteristics

Procedural Data

Total number of AF ablation procedures performed in the study

A total of 138 subjects underwent 138 cryoablation procedures including 104 cryoablation subjects and 34 control subjects who received crossover ablation. There were no repeat ablations in either the cryoablation subjects or the control subjects who had a crossover ablation.

Catheters used in the index procedure

The Arctic Front Advance™ Cardiac CryoAblation Catheter was used in the pulmonary vein isolation ablation procedure for all 104 cryoablation arm subjects. Both the Arctic Front Advance™ Cardiac CryoAblation Catheter and Freezor® MAX Cardiac CryoAblation Catheter were used in one subject for PV isolation.

The following additional catheters were used during the ablation procedure, but not directly on the pulmonary veins:

- Non-Medtronic RF catheters were used 23 times on the cavotricuspid isthmus (CTI), 2 times in other right atrial locations and once each on the superior vena cava, mitral annular region, and left atrial roof
- Arctic Front Advance™ was used once on a CTI
- Freezor® MAX was used once in the right atrium
- A non-Medtronic cryocatheter was used on a CTI

Other arrhythmias present and treated during the index procedure

The table below summarizes arrhythmias other than AF present and treated during the index ablation procedure below.

Table 5: Other Arrhythmias During the Index Ablation Procedure

Arrhythmia	Subjects with Arrhythmia Present n (%)	Subjects with Arrhythmia Treated n (%)
Atrioventricular nodal reentry tachycardia (AVNRT)	4 (3.8%)	3 (2.9%)
Cavotricuspid isthmus (CTI)-dependent Atrial Flutter	25 (24.0%)	25 (24.0%)
PV tachycardia	1 (1.0%)	0 (0.0%)
Atrial tachycardia	1 (1.0%)	0 (0.0%)

Acute procedural success

Three (3) of the 104 mITT subjects in the cryoablation arm did not have acute procedural success, resulting in an acute procedural success rate of 97.1% (95% CI: 91.8%-99.4%).

The reasons for acute procedural failures were inability to isolate PVs (n = 2) and the use of a non-study ablation device in the LA plus LA non-PVI ablation (n = 1).

Procedure parameters

The table below summaries the procedure parameters for the index procedures performed in the 104 mITT cryoablation subjects.

Table 6: Index Ablation Procedure Parameters

Procedure Parameters (minutes)	mITT subjects in cryoablation arm (n=104)
Total Procedure Time	139 ± 74
Left Atrial Dwell Time	60 ± 24
Fluoroscopy Time	18.2 ± 11.8
Application Duration	20.9 ± 7.8

Values are mean ± standard deviation

AAD therapy in the control arm

All 99 mITT control subjects received a class 1 or 3 AAD after randomization. The table below summarizes the antiarrhythmic agents and daily doses at the initiation of AAD therapy, at the end of the AAD optimization period, and at the time of the primary effectiveness failure, study exit or at 12 months.

Table 5: AAD Dosing in the Control Arm

Antiarrhythmic Agent	Total Daily Dose (mg)	Initiation of AAD Therapy (n = 99)	End of AAD Optimization Period (n = 94)*	At Effectiveness Failure, 12 Months, or Exit (n = 94)*
Flecainide	50	1 (1%)	2 (2.1%)	2 (2.1%)
	100	28 (28%)	22 (23.4%)	21 (22.3%)
	150	0 (0.0%)	0 (0.0%)	1 (1.1%)
	200	33 (33%)	28 (29.8%)	27 (28.7%)
	300	3 (3%)	3 (3.2%)	2 (2.1%)
	375	0	1 (1.1%)	1 (1.1%)
	PRN (as needed)	1 (1%)	2 (2.1%)	2 (2.1%)
Propafenone	225	1 (1%)	0 (0.0%)	0 (0.0%)
	450	5 (5%)	6 (6.4%)	7 (7.4%)
	650	2 (2%)	1 (1.1%)	1 (1.1%)
Dronedarone E-4031	800	13 (13%)	11 (11.7%)	10 (10.6%)
Sotalol	80	2 (2%)	1 (1.1%)	1 (1.1%)
	160	8 (8%)	6 (6.4%)	6 (6.4%)
	240	1 (1%)	0 (0.0%)	0 (0.0%)
Amiodarone	200	1 (1%)	1 (1.1%)	0 (0.0%)
	400	0 (0.0%)	1 (1.1%)	1 (1.1%)
Not on a Class I or III Antiarrhythmic Drug		0 (0.0%)	9 (9.6%)	12 (12.8%)

Values are n (%). *This does not include 5 subjects who were exited or lost to follow-up prior to the end of the 90-day AAD optimization period.

As indicated in the table above, flecainide was the most frequently prescribed AAD. The vast majority of control subjects (92% or 91/99) received one AAD, eight subjects (8% or 8/99) received two AADs, and none received three or more AADs during the AAD optimization period.

The majority of the control subjects (77% or 76/99) only received one AAD without dose up-titration and only a small proportion of the control subjects (18% or 18/99) had AAD dose titrated or switched to a different AAD during the AAD optimization period.

Five control subjects (5% or 5/99) exited the study prior to the end of the AAD optimization period. Among the remaining 94 subjects, nine (9) had discontinued AAD therapy by the end of the AAD optimization period. All these nine (9) subjects discontinued AAD therapy due to side effects from their initial AAD and none of them had AAD dose down-titration or tried a different class 1 or 3 AAD during the AAD optimization period.

After the 90-day AAD optimization period, another three (3) control subjects discontinued AAD therapy prior to the occurrence of a primary effectiveness endpoint event or study exit, due to AAD side effects (n=2) or possible atrial flutter documented on a personal monitor (n=1).

Crossover ablation

The study protocol stipulates that crossover from AAD therapy to cryoablation would be allowed only if the subject in the control arm is deemed a treatment failure.

During follow-up, 34 (34.3%) of 99 mITT control subjects underwent crossover ablation at a median of 185 days (range 41 to 365) after the initiation of AAD therapy. Among them, 19 received cryoablation after having a primary effectiveness endpoint event and the remaining 15 had not had a primary effectiveness endpoint event prior to crossover ablation. The reasons for crossover ablation in these 15 subjects are discussed in the "Safety and Effectiveness Results" section of the summary.

Post-Ablation AAD therapy in the cryoablation arm

Prescription of a class 1 or 3 AAD for up to 80 days post-ablation procedure was permitted by the study protocol. Subjects were required to discontinue all class 1 or 3 AADs before day 81 post-ablation. Use of amiodarone was not permitted. Class 1 or 3 AAD use after the 90-day blanking period would be considered a primary effectiveness endpoint failure.

Of the 104 mITT cryoablation subjects, nine (9) received AAD therapy during the 90-day blanking period. All these nine (9) subjects remained in the study through 12 months post-ablation, with four (4) failing the primary effectiveness endpoint. Three of the four (4)

failures were due to AAD use after the 90-day post-ablation blanking period. None of these three (3) subjects had documented atrial tachyarrhythmia after the blanking period.

E. Rhythm monitoring compliance

Compliance with weekly patient-activated ambulatory monitoring (across weeks 13-51) was 80% in the cryoablation arm and 82% in the control arm.

The tables below summarize compliance with 24-hour ambulatory monitoring and 12-lead ECG during follow-up in the cryoablation and control arms.

Table 8: 24-hour Ambulatory ECG Monitoring (Holter) Compliance (mITT Cohort)

	Cryoablation (n=104)			AAD Therapy (n=99)		
Visit Name	**Cumulative Exited Subjects**	**Expected 24-hour Holters**	**Holters Analyzed by Core Lab**	**Cumulative Exited Subjects**	**Expected 24-hour Holters**	**Holters Analyzed by Core Lab**
6 Month Follow-up	1	103	97 (94.2%)	4	95	82 (86.3%)
12 Month Follow-up	1	103	90 (87.4%)	8	91	75 (82.4%)
Total	N/A	206	187 (90.8%)	N/A	186	157 (84.4%)

Table 9: 12-Lead ECG Compliance (mITT Cohort)

	Cryoablation (n=104)			AAD Therapy (n=99)		
Visit Name	**Cumulative Exited Subjects**	**Expected ECGs**	**ECGs Analyzed by Core Lab**	**Cumulative Exited Subjects**	**Expected ECGs**	**ECGs Analyzed by Core Lab**
3 Month Follow-up	1	103	99 (96.1%)	3	96	87 (90.6%)
6 Month Follow-up	1	103	95 (92.2%)	4	95	89 (93.7%)
12 Month Follow-up	1	103	85 (82.5%)	8	91	74 (81.3%)
Total	N/A	309	279 (90.3%)	N/A	282	250 (88.7%)

F. Safety and Effectiveness Results

1. Safety Results

Primary Safety Endpoint

Among the 104 mITT cryoablation subjects, two (2) had a primary safety event during 12 months of follow-up.

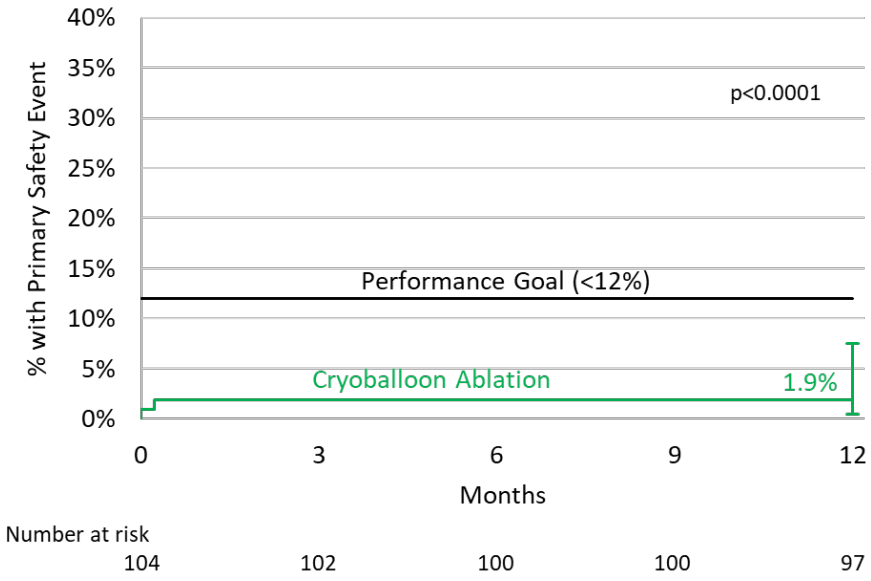
The two primary safety events were the following:

- One significant pericardial effusion that occurred during the procedure and required pericardiocentesis;
- One acute myocardial infarction (AMI) that occurred on day 7 post-ablation and required stenting of the left anterior descending artery.

Both complications resolved after intervention. The pericardial effusion was adjudicated as definitively related to the cryoablation procedure and possibly related to the study device. The AMI was adjudicated as possibly related to both the ablation procedure and the study device.

Figure 2 below depicts the Kaplan-Meier curve for the primary safety event rate through 12 months post-procedure. The rate of primary safety event at 12 months was estimated to be 1.92% (95% CI: 0.48% – 7.47%). Because the upper confidence bound was less than the predefined performance goal of 12%, the primary safety endpoint was considered met.

Figure 2: Primary Safety Events through 12 Months



All Reported Adverse Events (AEs)

There were no unanticipated adverse device effects reported in the study.

A total of 153 AEs were reported in the 203 mITT subjects, including four (4) AEs that occurred prior to the receipt of study treatment (cryoablation or AAD therapy) and 149 AEs that occurred during or after the initiation of study treatment.

A total of 67 AEs occurred in 34 (32.7%) cryoablation subjects and 82 AEs occurred in 45 (45.5%) control subjects during or after the initiation of study treatment. The table below summarizes these 149 AEs in their relationship to the device, procedure, AAD and cardiovascular system.

Table 10: Summary of Adverse Events Reported During or After Treatment Initiation

Adverse Event Classifications	Cryoablation (n=104)	AAD Therapy (n=99)
Total Adverse Events	**67 (34, 32.7%)**	**82 (45, 45.5%)**
Relationship to Cryoablation Procedure		
Not related	42 (21, 20.2%)	77 (44, 44.4%)
Related	18 (16, 15.4%)	5 (3, 3.0%)
Unknown	7 (6, 5.8%)	0 (0, 0.0%)
Relationship to Cryoablation System		
Not related	44 (22, 21.2%)	78 (45, 45.5%)
Related	12 (12, 11.5%)	3 (2, 2.0%)
Unknown	11 (10, 9.6%)	1 (1, 1.0%)
Relationship to Other Devices		
Not related	66 (33, 31.7%)	82 (45, 45.5%)
Related	0 (0, 0.0%)	0 (0, 0.0%)
Unknown	1 (1, 1.0%)	0 (0, 0.0%)
Relationship to Other Procedure		
Not related	65 (33, 31.7%)	81 (45, 45.5%)
Related	0 (0, 0.0%)	0 (0, 0.0%)
Unknown	2 (2, 1.9%)	1 (1, 1.0%)
Relationship to Antiarrhythmic Drugs		
Not related	66 (34, 32.7%)	43 (24, 24.2%)
Related	1 (1, 1.0%)	21 (18, 18.2%)
Unknown	0 (0, 0.0%)	18 (14, 14.1%)
Relationship to Cardiovascular System		
Not related	15 (11, 10.6%)	24 (22, 22.2%)
Related	47 (26, 25.0%)	51 (31, 31.3%)
Unknown	5 (5, 4.8%)	7 (5, 5.1%)

Values are the number of events (number of subjects, % of subjects)

Serious Adverse Events (SAEs)

Of the 149 AEs that occurred during or after treatment initiation, 38 were classified as SAEs. The table below summaries these 38 SAEs. The proportion of subjects who had at least one SAE was almost identical between the two study arms (14.4% in the cryoablation arm vs. 14.1% in the control arm).

Table 11: Summary of Serious Adverse Events During or After Treatment Initiation (Number of Subjects, % of Subjects)

Serious Adverse Event	Cryoablation (n=104)	AAD Therapy (n=99)
Acute myocardial infarction	2 (1, 1.0%)	1 (1, 1.0%)
Unstable angina	0 (0, 0.0%)	1 (1, 1.0%)
Atrial fibrillation	3 (2, 1.9%)	1 (1, 1.0%)
Sinus bradycardia	0 (0, 0.0%)	1 (1, 1.0%)
Chest pain	1 (1, 1.0%)	0 (0, 0.0%)
Fluid overload	0 (0, 0.0%)	1 (1, 1.0%)
AF with rapid ventricular response	1 (1, 1.0%)	0 (0, 0.0%)
Hypertension	1 (1, 1.0%)	0 (0, 0.0%)
Hypotension	1 (1, 1.0%)	0 (0, 0.0%)
Hematoma	1 (1, 1.0%)	0 (0, 0.0%)
Palpitations	0 (0, 0.0%)	1 (1, 1.0%)
Pericardial effusion	1 (1, 1.0%)	0 (0, 0.0%)
Pericarditis	0 (0, 0.0%)	1 (1, 1.0%)
Presyncope	0 (0, 0.0%)	1 (1, 1.0%)
Pulmonary embolism	0 (0, 0.0%)	1 (1, 1.0%)
Syncope	0 (0, 0.0%)	2 (2, 2.0%)
Ventricular tachyarrhythmia	1 (1, 1.0%)	0 (0, 0.0%)
Other	10† (9, 8.7%)	5‡ (5, 5.1%)
Total	**22 (15, 14.4%)**	**16 (14, 14.1%)**

† Other includes appendicitis, cardiac sarcoidosis, encephalopathy, hepatic cyst, migraine, nephrolithiasis, noncardiac chest pain, and obesity (in 1 patient each) and osteoarthritis (in 2 patients).
‡ Other includes chronic obstructive pulmonary disease, influenza, osteoarthritis, rotator cuff syndrome, and spinal stenosis (in 1 patient each).

Among the 22 SAEs in the cryoablation arm, six (6) SAEs (occurred in 5/104 or 4.8% of cryoablation subjects) were adjudicated as device or cryoablation procedure-related, and 13 related to cardiovascular system. Among the 16 SAEs in the control arm, one (1) SAE (occurred in 1/99 or 1% of control subjects) was

adjudicated as related to AAD, three (3) as device or cryoablation procedure-related (due to crossover ablation), and nine (9) related to cardiovascular system.

Device or cryoablation procedure-related SAEs

A total of nine (9) device or cryoablation procedure-related SAEs occurred in 7 (5.1%) of the 138 subjects (104 mITT cryoablation subjects and 34 mITT control subjects who received crossover ablation) who underwent a cryoablation procedure in the study. The table below summaries the nine (9) device or cryoablation procedure-related SAEs.

Table 12:. Device or cryoablation procedure-related serious adverse events

Serious Adverse Events	Number of Events (Number of Subjects, % of Subjects) Total subjects: N=138
Acute myocardial infarction	1 (1, 0.7%)
Significant pericardial effusion	1 (1, 0.7%)
Pulmonary embolism	1 (1, 0.7%)
Pericarditis	1 (1, 0.7%)
Fluid overload	1 (1, 0.7%)
Hypotension	1 (1, 0.7%)
Hematoma	1 (1, 0.7%)
Chest pain	1 (1, 0.7%)
AF with rapid ventricular response	1 (1, 0.7%)
Total	**9 (7, 5.1%)**

AAD-related SAEs

One AAD-related SAE occurred in one (1%) of the 99 mITT control subjects. The subject had symptomatic sinus bradycardia caused by flecainide and metoprolol. The event resolved after discontinuation of AAD therapy.

There was no class 1 or 3 AAD-related Torsades des pointes, hypotension, heart failure, pulmonary toxicity, liver injury/failure, hyper-or hypothyroidism, renal failure, or blindness reported in any of the control subjects.

Phrenic nerve palsy

Phrenic nerve palsy, a common complication associated with cryoballoon ablation of AF occurred in two (1.4%) of the 138 subjects who underwent a cryoablation

procedure in the study. Both events resolved before discharge and neither was classified as a SAE.

Composite adverse events

Of the 203 mITT subjects, 5 (4.8%) of the 104 cryoablation and 4 (4.0%) of the 99 control subjects reported one pre-specified composite AE. The table below lists the composite AEs that occurred in the two study arms.

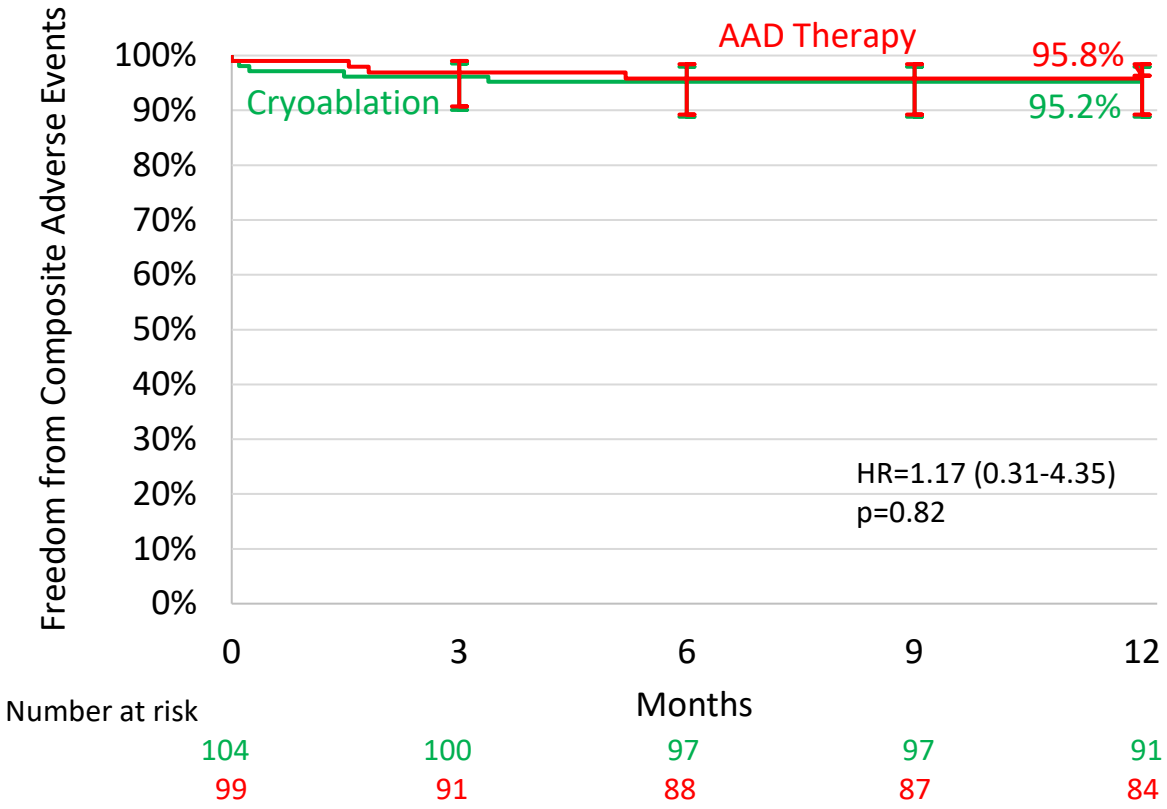
Table 13: Composite Adverse Event Summary

Adverse Event	Cryoablation (n=104)	AAD Therapy (n=99)
Cerebrovascular accident	0 (0.0%)	0 (0.0%)
Transient ischemic attack	1 (1.0%)	0 (0.0%)
Major bleeding that requires transfusion	0 (0.0%)	0 (0.0%)
Cardiac perforation, tamponade, or pericardial effusion	1 (1.0%)	1 (1.0%)
Symptomatic PV stenosis within 12 months; accompanied by one of the following: 50%-70% reduction in diameter of the pulmonary vein, with symptoms not explained by other conditions; OR >70% reduction in diameter of the pulmonary vein	0 (0.0%)	0 (0.0%)
Myocardial infarction	1 (1.0%)	1 (1.0%)
Phrenic nerve injury unresolved at 12- months	0 (0.0%)	0 (0.0%)
Atrio-esophageal fistula	0 (0.0%)	0 (0.0%)
Cardiovascular deaths	0 (0.0%)	0 (0.0%)
Bradycardia leading to pacemaker insertion	0 (0.0%)	0 (0.0%)
Syncope	0 (0.0%)	1 (1.0%)
Serious adverse event leading to drug discontinuation	0 (0.0%)	0 (0.0%)
QRS duration prolongation ⩾ 50% of baseline QRS duration	0 (0.0%)	0 (0.0%)
Torsades de pointes	0 (0.0%)	0 (0.0%)
Anaphylactic reaction	0 (0.0%)	0 (0.0%)
Pulmonary hypertension	0 (0.0%)	0 (0.0%)
Hospitalizations for (primary reason): AF recurrence or ablation, atrial flutter ablation (except Type I), systemic embolization (not stroke), congestive heart failure, hemorrhagic event (not stroke), antiarrhythmic drug: initiation, adjustment or complication and symptomatic bradycardia requiring medication change.	2* (1.9%)	1** (1.0%)
Total	**5 (4.8%)**	**4 (4.0%)**

*The primary reason for the two hospitalizations was AF recurrence.
**The primary reason for the hospitalization was AF recurrence.

As shown in the figure below, freedom from the pre-specified composite AEs at 12 months was estimated to be 95.2% (95% CI: 88.8%-98.0%) for the cryoablation arm and 95.8% (95% CI:89.2%-98.4%) for the control arm using the Kaplan-Meier method. The log-rank test p-value was 0.82. There was no evidence for significant difference in the composite event rate between the two study arms.

Figure 3: Freedom from Composite Adverse Events by Treatment Arm



2. Effectiveness Results

Primary Effectiveness Endpoint

Per study protocol, the analysis of the primary effectiveness endpoint was based on treatment success using the mITT cohort as the primary analysis population. Therefore, all 203 mITT subjects were included in the analysis.

Summary of primary effectiveness endpoint analysis

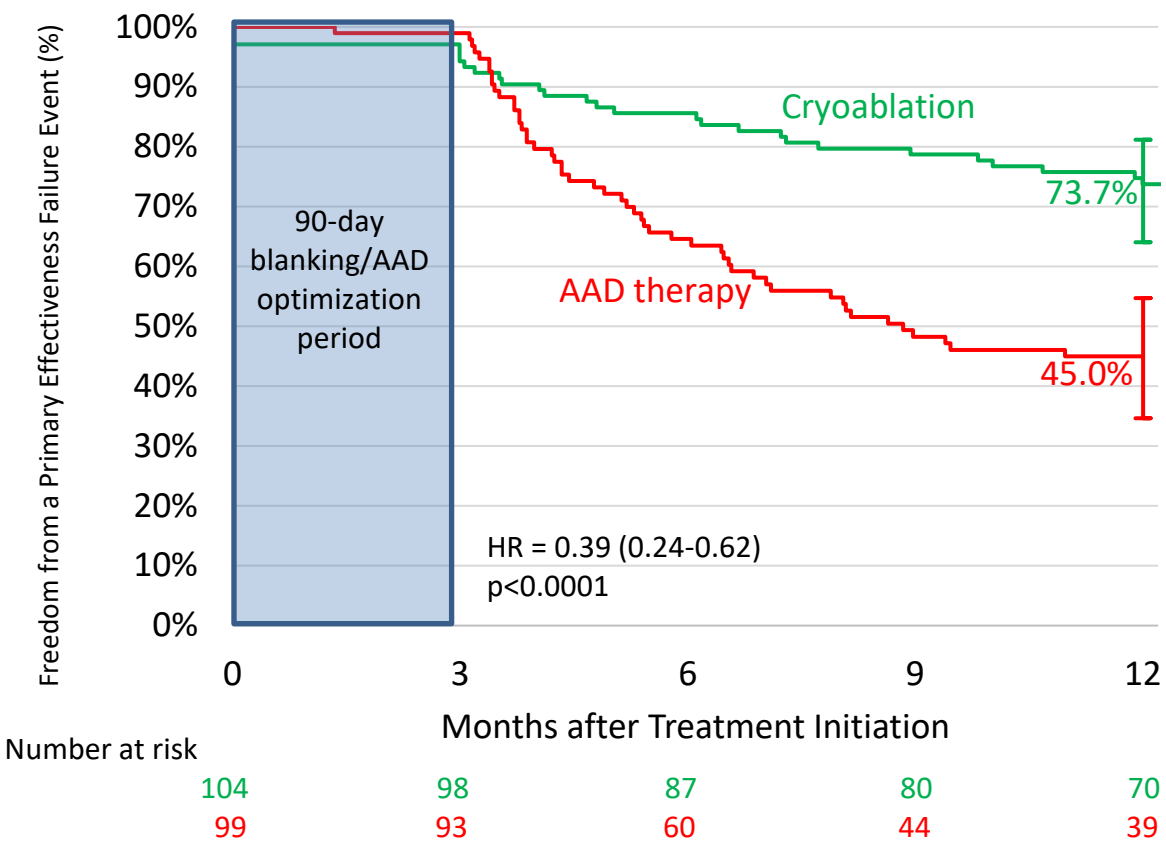
In total, 27 of 104 mITT cryoablation and 51 of 99 mITT control subjects reported at least one primary effectiveness failure event through 12 months of follow-up. The distribution of first primary effectiveness failure events is shown in the table below.

Table 6 First Primary Effectiveness Failure Events

	Cryoablation n=104	AAD Therapy n=99
Did Not Have a Primary Effectiveness Failure Event	**77 (74.0%)**	**48 (48.5%)**
Had a Primary Effectiveness Failure Event	**27 (26.0%)**	**51 (51.5%)**
Acute procedure failure	3 (2.9%)	NA
Documented AF/AT/AFL after 90 days	21 (20.2%)	35 (35.4%)
• Documented AF	17 (16.3%)	31 (31.3%)
• Documented AFL	4 (3.9%)	3 (3.0%)
• Documented AT	0 (0.0%)	1 (1.0%)
Ablation in left atrium (post-index procedure)	0 (0.0%)	15 (15.2%)
Cardioversion after 90 days	0 (0.0%)	1 (1.0%)
Class I or III AAD use after 90 days	3 (2.9%)	NA

Figure 3 displays the Kaplan-Meier curve for freedom from primary effectiveness failure through 12 months post-treatment initiation. Freedom from primary effectiveness failure at 12 months was estimated to be 73.7% (95% CI: 64.0%-81.2%) for the cryoablation arm and 45.0% (95% CI: 34.6%-54.7%) for the control arm using the Kaplan-Meier method. The 12-month treatment success rate was higher in the cryoablation arm than that in the control arm, with a log-rank test p-value of <0.0001.

Figure 4: Freedom from Primary Effectiveness Failure at 12 Months



Primary effectiveness endpoint results in the cryoablation arm

Among the 104 cryoablation subjects included in the primary effectiveness analysis, one (1) did not have a primary effectiveness outcome due to lost to follow-up after last contact at 176 days post-ablation and was censored in the Kaplan-Meier analysis.

As indicated in the table above, there were 27 (26%) primary effectiveness failures in the cryoablation arm.

Primary effectiveness endpoint results in the control arm

Among the 99 control subjects included in the primary effectiveness analysis, seven (7) did not have a primary effectiveness outcome due to lost to follow-up (n = 3), subject-requested study withdrawal (n = 3), and unwilling to wait 3 months prior to crossing over to cryoablation arm (n = 1). The follow-up duration of these seven (7) subjects ranged from 1 to 209 days post-AAD initiation and five of these subjects exited the study before the end of the 90-day AAD optimization

period. For the purpose of the primary analysis, these 7 subjects with incomplete effectiveness data were censored in the Kaplan-Meier analysis.

As indicated in the table above, there were 51 (51.5%) primary effectiveness failures in the control arm.

Primary effectiveness failures in the control arm

As indicated in the table above, a total of 51 control subjects were classified as primary effectiveness failures due to arrhythmia recurrence documented on protocol-specified cardiac monitoring after 90 days post-AAD initiation (n = 35), crossover ablation (n = 15), or cardioversion after 90 days post-AAD initiation (n = 1).

Among the 15 AAD failures due to crossover ablation, three (3) had atrial tachyarrhythmia recurrence detected by rhythm monitoring (using a conventional ECG device) conducted outside of the study protocol after 90 days post-AAD initiation, and nine (9) had documented AAD side effects prior to crossover ablation. The remaining three (3) AAD failures underwent crossover ablation without ECG-documented AF/AFL/AT recurrence or documented AAD side effects, but due to ongoing symptoms (n =2) or possible atrial flutter documented on a personal monitor (n = 1).

A review of the AAD therapy received by each of the 51 treatment failures in the control arm was performed by the FDA to assess potential undertreatment in these subjects. It identified 11 (21.6%) AAD failures who were prescribed a class 1 or 3 AAD with a dose lower than a "reasonable dose" (defined as ≥ 200 mg daily dose of flecainide, ≥ 160 mg daily dose of sotalol, ≥ 450 mg daily dose of propafenone, or ≥ 200 mg daily dose of amiodarone) at the time of AAD initiation and had no dose up-titration in the absence of documented side effects during the AAD optimization period. The "reasonable dose" definition was derived from FDA's review of the relevant professional society guidelines and publications that included but were not limited to the 2016 ESC Guidelines for the Management of AF Developed in Collaboration with EACTS (Kirchhof, et al., 2016), 2014 AHA/ACC/HRS Guideline for the Management of Patients with AF (January, et al., 2014), Use of Flecainide for the Treatment of AF (Echt, et al., 2020), as well as FDA drug labels for Tambocor (flecainide acetate) and Betapace AF (sotalol HCI). Of note, one of these 11 AAD failures was among the three (3) AAD failures discussed above who underwent crossover ablation without ECG-documented arrhythmia recurrence or documented AAD side effects.

Therefore, there were a total of 13 AAD failures who either were on a class 1 or 3 AAD with a dose lower than the "reasonable dose" defined above at the time of AAD initiation and had no dose up-titration in the absence of documented side effects during the AAD optimization period, or underwent crossover ablation

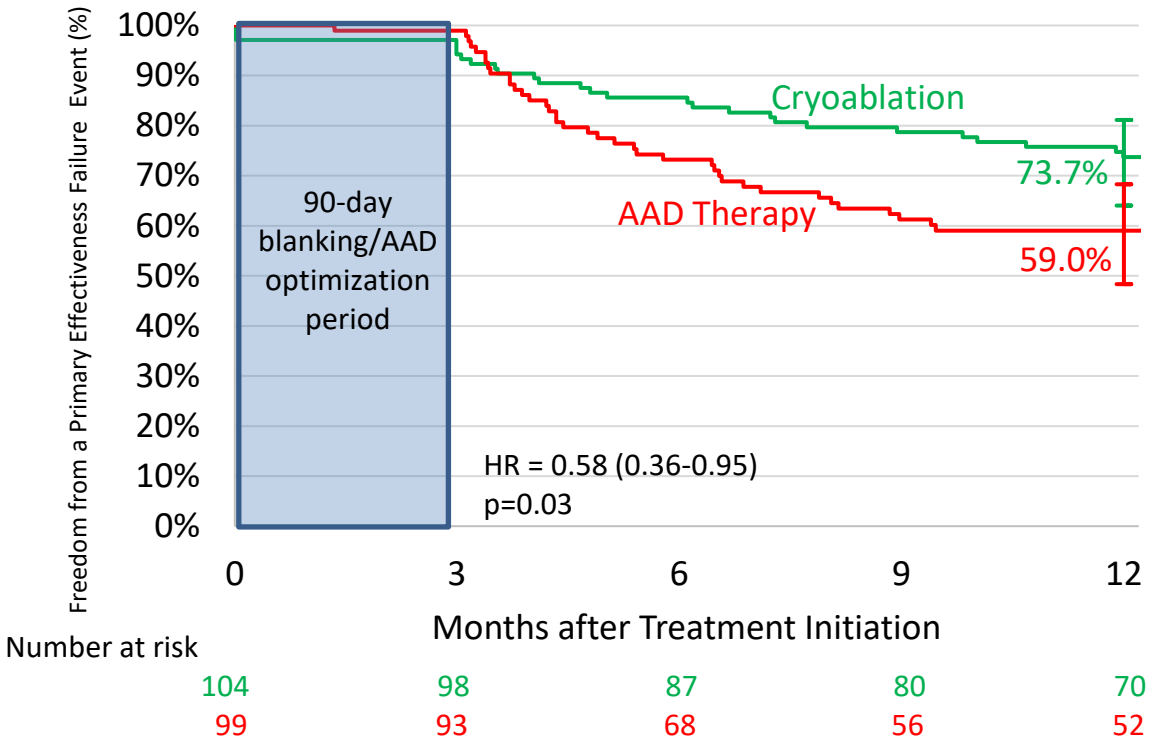
without ECG-documented arrhythmia recurrence or documented AAD side effects.

Sensitivity analysis of primary effectiveness endpoint

A post-hoc analysis was performed to evaluate the impact of not receiving a reasonable therapeutic trial of AAD therapy using a class 1 or 3 AAD or undergoing crossover ablation without ECG-documented arrhythmia recurrence or documented AAD side effects on the primary effectiveness results.

In this sensitivity analysis, the primary effectiveness analysis was repeated by counting the 13 AAD failures discussed above (who either were on a class 1 or 3 AAD with a dose lower than the "reasonable dose" defined above at the time of AAD initiation and had no dose up-titration in the absence of documented side effects during the AAD optimization period, or underwent crossover ablation without ECG-documented arrhythmia recurrence or documented AAD side effects) as successes. As indicated in the figure below, cryoablation was still associated with a statistically greater treatment success at 12 months compared with AAD therapy in the sensitivity analysis.

Figure 5: Freedom from primary effectiveness failure at 12 months, assuming 13 selected control subjects did not fail



Ancillary analysis of primary effectiveness outcome in control subjects taking a "reasonable dose" of AAD throughout the trial

Another post-hoc analysis was performed to estimate treatment success at 12 months in the control subjects who were taking a "reasonable dose" of a class 1 or 3 AAD (defined above) throughout the trial. Among the 99 mITT control subjects, 55 completed the 90-day AAD optimization period and were on a "reasonable dose" of a class 1 or 3 AAD at the time of study completion, treatment failure, or study exit. Four (4) of the 55 subjects underwent crossover ablation before ECG-documented arrhythmia recurrence. Of the remaining 51 subjects (18 women, mean age 61.3 ± 10.8 years) with "clearer" primary effectiveness outcome, 28 (54.9%) were free from a primary effectiveness failure event.

Quality of Life Results

It was pre-specified in the study protocol that the secondary endpoints relating to quality of life scores (i.e., changes in AFEQT and EQ-5D scores from baseline to 12 months visit) would not be compared between the two study arms. This is because it was expected that some control subjects would undergo cryoablation during the study and thus their 12-month quality of life scores would not necessarily reflect the impact of AAD therapy. In fact, 34 of 99 control subjects underwent a cryoablation procedure during the course of the study.

Per study protocol, the analysis of changes in AFEQT and EQ-5D scores only included subjects randomized to the cryoablation arm who completed the questionnaires at both baseline and 12-months (n = 99 for both questionnaires).

The AFEQT score is an AF-specific quality of life measure with a summary score ranging from 0 – 100, with 0 corresponding to complete disability and 100 corresponding to no disability. As shown in the table below, there was a statistically significant improvement in the AFEQT summary score from baseline to 12 months post-ablation.

Table 15: AFEQT Summary Score

n	Baseline (Mean ± SD)	12-Month Visit (Mean ± SD)	Difference (95% CI)	p-value
99	58.6 ± 23.0	91.9 ± 12.8	33.3 (29.1- 37.5)	<0.0001

The Euroqol EQ-5D questionnaire (which consists of a 5-question survey and a visual analog scale) is a standardized instrument for measuring generic health status.

The composite EQ-5D score derived from the 5-question survey ranges from 0 (least healthy) to 1 (most healthy). As shown in the table below, there was a statistically significant improvement in the composite EQ-5D score from baseline to 12-months post-ablation.

Table 16: Composite EQ-5D Score

n	Baseline (Mean ± SD)	12-Month Visit (Mean ± SD)	Difference (95% CI)	p-value
99	0.89 ± 0.14	0.92 ± 0.13	0.04 (0.01- 0.06)	0.002

Post-hoc analyses were performed to explore changes in AFEQT summary score, composite EQ-5D score and EQ-VAS score from baseline through 6 months and 12 months post treatment, and the proportion of subjects who improved their AFEQT summary score by at least 19 points from baseline to 12 months, a clinically important change reported in the literature (Dorian, et al., 2013) in both study arms. As indicated in the table below, all three scores increased at 6 months and the improvements persisted at 12 months post treatment in both study arms. The improvement in the AFEQT summary score was numerically greater in the cryoablation arm at 6 months and 12 months than that in the control arm. Moreover, there was a numerically greater proportion of subjects in the cryoablation arm than

in the control arm who improved at least 19 points on the AFEQT summary score from baseline to 12 months.

Table 17: Quality of Life Comparison: Cryoablation vs. AAD Therapy

		Cryoablation (n=104)	AAD Therapy (n=99)
AFEQT Summary Score	Baseline	58.5 ± 23.4 (n=104)	62.9 ± 21.7 (n=98)
	6 Months	87.2 ± 19.8 (n=101)	80.1 ± 19.1 (n=91)
	12 Months	91.9 ± 12.8 (n=99)	84.9 ± 17.2 (n=90)
	Change from Baseline to 6M	28.6 ± 22.5 (n=101)	17.3 ± 24.6 (n=91)
	Change from Baseline to 12M	33.3 ± 20.8 (n=99)	21.5 ± 24.0 (n=90)
	Percent (%) who Improved ≥19 Points from Baseline to 12M	76.8% (n=99)	46.7% (n=90)
Composite EQ-5D Score	Baseline	0.887 ± 0.133 (n=104)	0.885 ± 0.123 (n=98)
	6 Months	0.923 ± 0.141 (n=101)	0.908 ± 0.114 (n=91)
	12 Months	0.922 ± 0.129 (n=99)	0.916 ± 0.114 (n=90)
	Change from Baseline to 6M	0.037 ± 0.114 (n=101)	0.019 ± 0.109 (n=91)
	Change from Baseline to 12M	0.036 ± 0.114 (n=99)	0.025 ± 0.140 (n=90)
EQ-5D VAS Score	Baseline	80.4 ± 14.0 (n=104)	78.7 ± 14.2 (n=98)
	6 Months	84.5 ± 13.9 (n=101)	83.3 ± 12.4 (n=91)
	12 Months	86.2 ± 12.9 (n=99)	82.7 ± 13.2 (n=90)
	Change from Baseline to 6M	4.2 ± 14.7 (n=101)	4.2 ± 12.6 (n=91)
	Change from Baseline to 12M	5.5 ± 14.5 (n=99)	3.5 ± 14.5 (n=90)

After applying the pre-specified Hochberg multiple testing procedure, changes in AFEQT summary score and composite EQ-5D score were considered statistically significant (since the larger p-value of 0.002 was less than the threshold of 0.025/2). The following two secondary

endpoints could not be considered statistically significant because their initial p-values did not pass the threshold of the Hochberg test.

Cardiovascular Healthcare Utilization

Per study protocol, the analysis of this secondary endpoint include all 203 mITT subjects.

A total of 31 subjects (29.8%) in the cryoablation arm and 43 (43.4%) in the control arm reported at least one cardiovascular-related healthcare utilization through 12 months of follow-up. The distribution of healthcare utilizations is summarized in the table below.

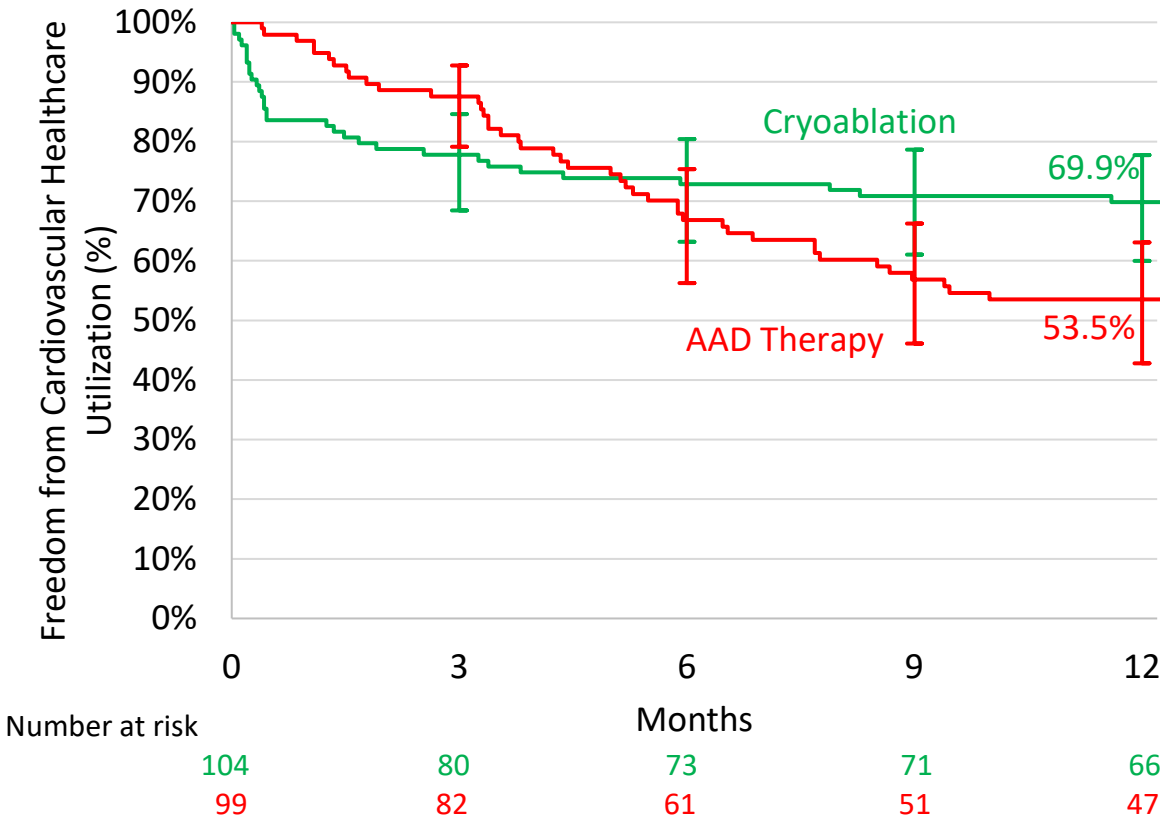
Table 7: Cardiovascular Healthcare Utilization by Treatment Arm

	Cryoablation (105.69 Total Years of Follow-up)			AAD Therapy (96.81 Total Years of Follow-up)		
Cardiovascular HCU	**Number of Subjects (%) (n=104)**	**Number of HCUs**	**Average Number per Subject-Year**	**Number of Subjects (%) (n=99)**	**Number of HCUs**	**Average Number per Subject-Year**
Hospitalization	9 (8.7%)	13	0.12	26 (26.3 %)	32	0.33
ED Visit	7 (6.7%)	10	0.09	12 (12.1%)	17	0.18
Unscheduled Office Visit	24 (23.1%)	44	0.42	24 (24.2%)	39	0.40
Hospitalization, ED Visit, or Unscheduled Office Visit	31 (29.8%)	67	0.63	43 (43.4%)	88	0.91

As indicated in the figure below, freedom from cardiovascular HCU at 12 months post-treatment estimated by using the Kaplan-Meier survival analysis was 69.9%

(95% CI: 60.0%-77.8%) for the cryoablation arm and 53.5% (95% CI: 42.8%-63.1%) for the control arm.

Figure 6: Freedom From Cardiovascular Healthcare Utilization at 12 months



A review of limited data collected on the primary reason or diagnosis for cardiovascular HCU suggested that the difference in cardiovascular-related hospitalization (13 times in the cryoablation arm vs 32 times in the control arm) was largely driven by crossover ablations, and the difference in cardiovascular-related emergency department (ED) visit (10 times in the cryoablation arm vs 17 times in the control arm) was likely caused by more AF recurrences in the control subjects.

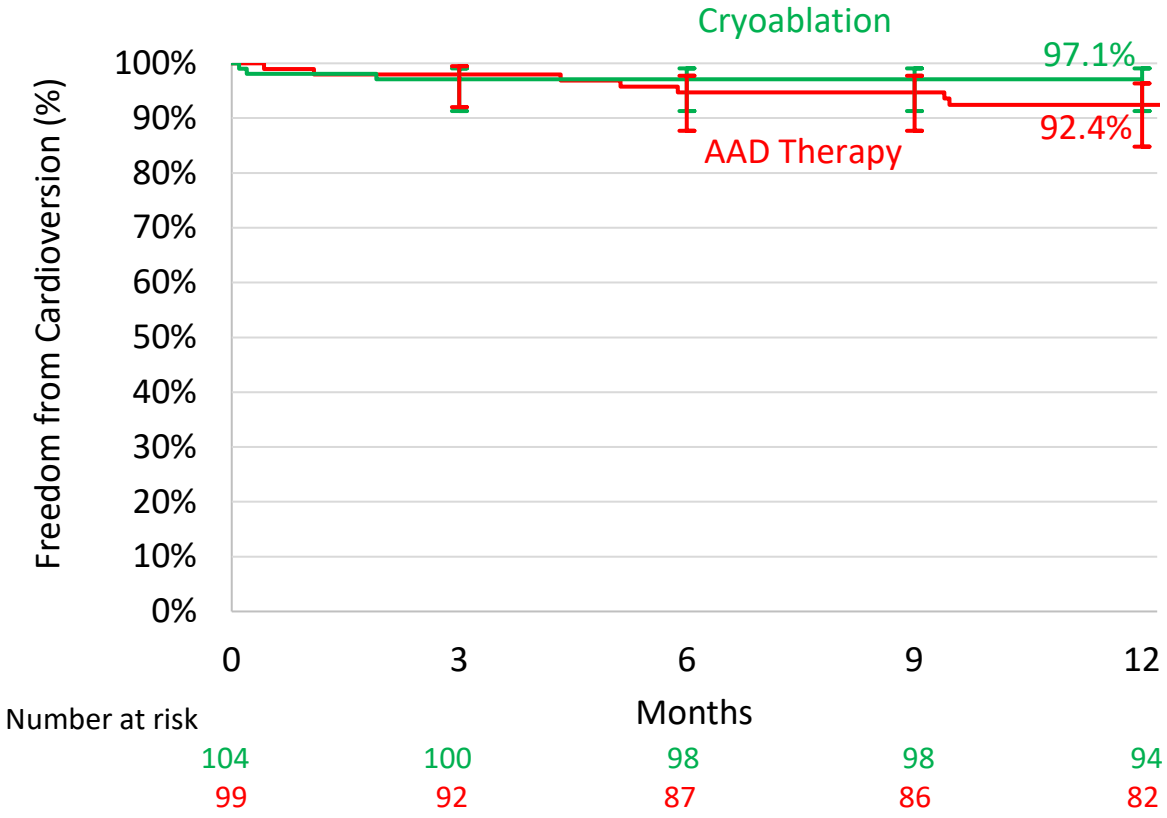
Cardioversions

Per study protocol, the analysis of this secondary endpoint included all 203 mITT subjects.

Three (3) cryoablation subjects had a total of 5 cardioversions (all electrical cardioversions) and 7 control subjects had a total of 8 cardioversions (7 electrical and 1 pharmacological cardioversions) through 12 months of follow-up. As indicated in the figure below, freedom from cardioversion at 12 months post-

treatment estimated by using the Kaplan-Meier survival analysis was 97.1% (95% CI: 91.3%-99.1%) for the cryoablation arm and 92.4% (95% CI: 84.8%-96.3%) for the control arm.

Figure 7: Freedom from Cardioversion at 12 months



3. Subgroup Analyses

Subgroup analyses were performed to assess the consistency of the primary effectiveness outcome across the following preoperative characteristics: Age, gender, race, and ethnicity. Subgroup analysis on age was performed by dividing age into quartiles.

The proportion of subjects in each subgroup with a primary effectiveness endpoint failure event is shown in the table below. Major associations between the subgroups and the primary effectiveness outcome were not observed.

Table 8: Subgroup Analysis of Primary Effectiveness Outcome

Subgroup	Cryoablation		AAD Therapy	
	Number of Subjects	Number of Failures (%)	Number of Subjects	Number of Failures (%)
Age				
18-53	29	5 (17.2%)	24	8 (33.3%)
54-62	24	5 (20.8%)	22	13 (59.1%)
63-69	27	7 (25.9%)	25	12 (48.0%)
>70	24	9 (37.5%)	28	18 (64.3%)
Gender				
Male	41	13 (31.7%)	42	24 (57.1%)
Female	63	13 (20.6%)	57	27 (47.4%)
Race				
White	94	22 (23.4 %)	91	47 (51.7%)
Other	6	3 (50.0%)	7	3 (42.9%)
Not Stated	4	1 (25.0%)	1	1 (100.0%)
Ethnicity				
Hispanic	2	1 (50.0%)	3	2 (66.7%)
Non-Hispanic	97	22 (22.7%)	91	48 (52.8 %)
Not reported	5	3 (60.0%)	5	1 (20.0%)

4. Pediatric Extrapolation

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

G. 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 93 investigators of which none were full-time or part-time employees of the sponsor and 3 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: 3
- 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 concluded that it is unlikely that financial interests/arrangements had any impact on the clinical study outcome.

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 Advisory 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 STOP AF First study demonstrated that Arctic Front Advance and Freezor MAX Cardiac Cryoablation Catheters are effective for the treatment of recurrent symptomatic paroxysmal AF in AAD naïve patients.

The primary effectiveness results of the pivotal study supported a substantial treatment effect and the superiority of cryoballoon PV isolation over a trial of AAD therapy using a class 1 or 3 AAD in preventing atrial tachyarrhythmia recurrence in this patient population. Specifically, cryoablation resulted in a 12-month treatment success of 73.7% (95% CI: 64.0%-81.2%), which was significantly greater than that observed in the control arm treated with a class 1 or 3 AAD (45.0%, 95% CI: 34.6%-54.7%) with a log-rank test p-value of <0.0001. Freedom from atrial tachyarrhythmia recurrence has been widely used as a surrogate for improvement in patient's quality of life and symptom relief in patients with symptomatic AF, which is the recognized primary objective and an important clinical benefit of an AF ablation procedure (Calkins, et al., 2017).

The pivotal study also showed that cryoablation was associated with a significant improvement in the quality of life scores. Although a placebo effect cannot be excluded in this unblinded study without a sham control arm, the finding of sustained improvement in the qualify of life scores over 12 months post ablation was supportive of a quality of life treatment benefit in this group of highly symptomatic patients.

The following aspects of the pivotal study resulted in uncertainties in the treatment benefits:

1. A sizable proportion of control subjects may have been undertreated due at least in part to the lack of a standardized AAD titration protocol used in the

study. This introduced uncertainty in the comparative effectiveness between cryoballoon PV isolation vs a trial of AAD therapy for initial rhythm control in this patient population, even though the results of a post-hoc sensitivity analysis and a recent external study (EARLY-AF. Andrade, et al. 2021) that implemented a standardized AAD titration protocol are supportive of the robustness of the primary effectiveness conclusions.

2. The study did not employ continuous ECG monitoring. Therefore, the 12-month treatment success reported in the cryoablation arm of the pivotal study may have overestimated the true ablation success.

3. The study was unblinded and did not include a sham control arm. Since it is known that AF ablation is subject to placebo effect, it is unclear how much improvement in the quality of life scores was attributable to cryoablation vs. a placebo effect.

4. Patients with significant left ventricular dysfunction, advanced heart failure, severe left atrial enlargement or significant structural heart disease were excluded from the pivotal study. Therefore, it is unknown if the results of the pivotal study reflect the outcomes of cryoballoon PV isolation in those AF patients.

B. Safety Conclusions

The adverse effects of the device are based on data collected in the STOP AF First study to support PMA approval as described above. Two (2) of the 104 subjects in the cryoablation arm had a primary safety event each (one significant pericardial effusion and one acute myocardial infarction; both were adjudicated as device or cryoablation procedure-related events and resolved after intervention), resulting in a primary safety event rate of 1.92% [95% CI: 0.48% - 7.47%]. Since the 95% upper confidence bound of the primary safety event rate was less than the pre-defiend safety performance goal of 12%, the study met its primary safety endpoint.

The rate of overall serious adverse events (SAEs) was similar between the cryoablation arm and the control arm (22 SAEs in 15/104 or 14.4% of cryoablation subjects vs 16 SAEs in 14/99 or 14.1% of control subjects). Of note, three (3) SAEs that occurred in two (2) control subjects were related to crossover ablation. In terms of SAEs related to the assigned treatment (cryoablation or AAD therapy), only one SAE in the control arm (in 1/99, or 1% of control subjects) was adjudicated as AAD-related, while six (6) SAEs in the cryoablation arm (in 5/104, or 4.8% of cryoablation subjects) was adjudicated as device or cryoablation procedure-related. Freedom from pre-specified composite adverse events at 12 months was also similar between the two study arms.

A total of nine (9) device or cryoablation procedure-related SAEs occurred in 7 (5.1%) of a total of 138 subjects who underwent a cryoablation procedure in the study. Phrenic nerve palsy, a common complication associated with cryoballoon ablation of AF occurred in two (2) subjects (1.4%). Both events resolved before discharge and neither was classified as a SAE.

The results of the pivotal study showed that the incidence of major complications associated with cryoballoon PV isolation was low. The frequency, severity and nature of the procedural complications reported in the study were in line with the published literature of cryoballoon ablation for the treatment of AF (Knight, et al., 2019; Packer, et al., 2013; Kuck, et al., 2016).

C. Benefit-Risk Determination

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Although there was some uncertainty in the comparative effectiveness between cryoballoon PV isolation vs. a trial of AAD therapy, the overall effectiveness and safety data reported in the STOP AF First study support the notion that the probable benefits outweigh the probable risks when the Arctic Front Advance and Freezor MAX Cardiac Cryoablation Catheters are used as an alternative to AAD therapy for initial rhythm control in patients with recurrent symptomatic paroxysmal AF.

1. Patient Perspectives

   This submission did not include specific information on patient perspectives for this device.

D. Overall Conclusions

The results of the STOP AF First study provided valid scientific evidence in support of effectiveness and safety of the study device as an alternative to AAD therapy for initial rhythm control in patients with recurrent symptomatic paroxysmal AF.

This prospective multi-center randomized controlled pivotal study was powered to demonstrate the superiority of cryoballoon PV isolation over a trial of AAD therapy in preventing atrial tachyarrhythmia recurrence and an acceptable safety profile of the study device in treating AAD naïve patients with recurrent symptomatic paroxysmal AF.

Of the 203 study participants who underwent randomization and received treatment, 104 underwent cryoablation and 99 initially received AAD therapy (34 of whom subsequently underwent crossover ablation). In the cryoablation arm, acute procedural success was achieved in 97% of the subjects. Treatment success at 12

months was achieved in 73.7% (95% CI: 64.0%-81.2%) of the cryoablation subjects and in 45.0% (95% CI: 34.6%-54.7%) of the control subjects ($p < 0.0001$ by log-rank test). The primary effectiveness results supported the treatment benefit of cryoballoon PV isolation in reducing atrial tacharrhythmia recurrence. Although some control subjects may have been undertreated, the 12-month treatment success rates reported in the pivotal study were consistent with a previous randomized controlled study comparing RF catheter ablation vs AAD therapy as an initial rhythm control strategy in patients with paroxysmal AF (RAAFT-2. Morillo, et al., 2014). Moreover, the between-study arm difference in treatment success observed in the pivotal study was well in line with the findings of a recent multicenter randomized controlled trial (EARLY-AF. Andrade, et al., 2021) in which cryoballoon PV isolation was compared to AAD therapy using a standardized AAD titration protocol for initial rhythm control in a very similar patient population.

The pivotal study also showed that cryoballoon PV isolation was associated with a significant improvement in the quality of life scores. Although a placebo effect cannot be excluded in this unblinded study without a sham control arm, the finding of sustained improvement in the qualify of life scores over one year post procedure and the magnitude of changes in the quality of life scores provided additional support for a quality of life benefit offered by the study device in symptomatic paroxysmal AF patients whose quality of life is impaired by AF.

Two of the 104 subjects in the cryoablation arm had a primary safety event each (one significant pericardial effusion and one acute myocardial infarction), resulting in a primary safety event rate of 1.92% (95% CI: 0.48% - 7.47%) and the pre-defined safety performance goal of 12% being met. Moreover, the frequency, severity and nature of the device or cryoablation procedure-related SAEs reported in the study were in line with the published literature of cryoballoon AF ablation that showed a low risk of major procedural complications (Knight, et al., 2019; Packer, et al., 2013; Kuck, et al., 2016).

The rates of overall SAEs and pre-specified composite adverse events were similar between the two study arms. This did not raise a signal of harm in the use of cryoballoon PV isolation as an initial rhythm control strategy, acknowledging that the study was not powered to examine cardiovascular outcomes and that a significant proportion of the control subjects underwent crossover cryoablation during the study. On the other hand, cryoablation was associated with a higher treatment-related SAE rate than a trial of AAD therapy, evidenced by 4.8% of the cryoablation subjects having a device or cryoablation procedure-related SAE vs. 1% of the control subjects having an AAD-related SAE.

The effectiveness and safety data from the STOP AF First study appeared to support the notion that as an initial rhythm control strategy for the treatment of recurrent symptomatic paroxysmal AF, cryoballoon PV isolation is more effective than a trial of AAD therapy using a class 1 or 3 AAD in preventing atrial tachyarrhythmia

recurrence at the expense of a greater (albeit low) risk of treatment-related SAE due to its invasive nature.

Taken together, the results of the STOP AF First study demonstrated that there is a reasonable assurance of safety and effectiveness of the Arctic Front Advance and Freezor MAX Cardiac Cryoablation Catheters when used for the treatment of recurrent symptomatic paroxysmal AF as an alternative to AAD therapy as an initial rhythm control strategy.

XIII. CDRH DECISION

CDRH issued an approval order on June 18, 2021.

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.

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