SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Cardiac Cryoablation Catheter

Device Trade Name:
Arctic Front Advance™ Cardiac Cryoablation Catheter
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/S098

Date of FDA Notice of Approval: June 23, 2020

The original PMA P100010 was approved on December 17, 2010 and is indicated for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation (PAF). The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Arctic Front Advance, Arctic Front Advance Pro and Freezor *MAX* Cardiac Cryoablation Catheters to include treatment of symptomatic drug refractory recurrent persistent AF of less than 6 months duration.

II. INDICATIONS FOR USE

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

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

Use of the Freezor *MAX* Cardiac Cryoablation Catheter is contraindicated in patients with the following conditions:

- active systemic infections
- cryoglobulinemia
- other conditions where the manipulation of the catheter would be unsafe (for example, intracardiac mural thrombus)

IV. WARNINGS AND PRECAUTIONS

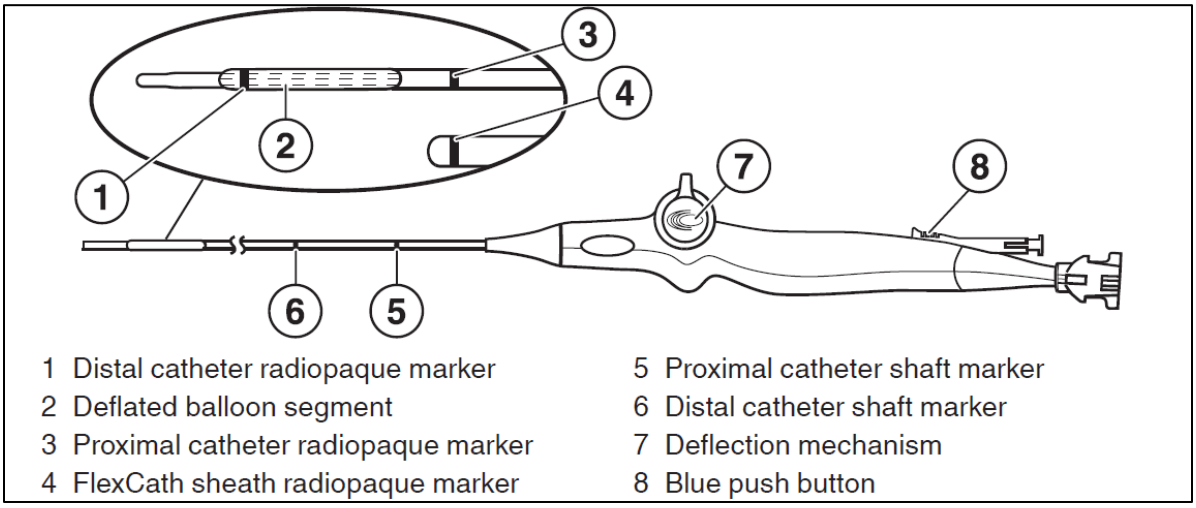
The warnings and precautions can be found in the Arctic Front Advance and Arctic Front Advance Pro Cardiac Cryoablation Catheters' labeling.

The warnings and precautions can be found in the Freezor *MAX* Cardiac Cryoablation Catheters' labeling.

V. DEVICE DESCRIPTION

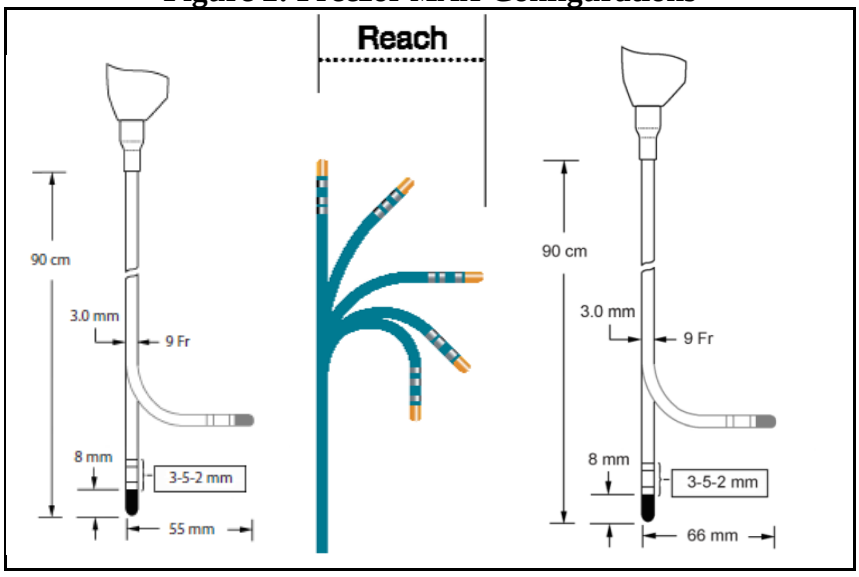
The Arctic Front Advance and the Arctic Front Advance Pro Cardiac Cryoablation Catheter (the catheter or the Arctic Front Advance or the Arctic Front Advance Pro Cryoballoon) is a flexible, over-the-wire balloon catheter used to ablate cardiac tissue. It is used together with a compatible Medtronic 12 Fr inner diameter sheath (the sheath), the CryoConsole, and related components. 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 Error! R eference source not found.).

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



The Freezor *MAX* Cardiac CryoAblation Catheter (hereafter referred to as Freezor *MAX*) is a 9F, flexible, steerable catheter specifically designed for tissue cryoablation. It is used together with the CryoConsole and related components for performing focal endocardial cryoablation as an adjunctive device in the treatment of paroxysmal and persistent atrial fibrillation in conjunction with the Arctic Front Advance and Arctic Front Advance Pro Cardiac Cryoablation catheters. The tip of the Freezor *MAX* Cryocatheter reaches cryoablation temperatures when refrigerant is injected from the CryoConsole to the tip of the catheter, freezing the adjacent tissue. The Freezor *MAX* is available in two configurations, representing two different deflection or "reach" lengths. Model 239F3 features a medium length deflection reach of 55 mm, model 239F5 features a long length deflection reach of 66 mm (see Error! Reference source not found.).

Figure 2: Freezor *MAX* Configurations



The Arctic Front Advance, the Arctic Front Advance Pro, and the Freezor *MAX* Catheters were approved under P100010, 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, Arctic Front Advance Pro and Freezor *MAX* Catheters 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 drug refractory recurrent symptomatic paroxysmal or persistent atrial fibrillation (episode duration less than 6 months). The following alternative practices and procedures are available, in addition to the Arctic Front family and Freezor *MAX* 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
- Ablation of the AV node and insertion of a permanent pacemaker 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 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, European Union, Hong Kong, Indonesia, Israel, Japan, Kazakhstan, Mexico, Moldova, New Zealand, Russia, Saudi Arabia, Serbia, Singapore, South Korea, Taiwan, and Ukraine.

The 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/New Zealand, Belarus, Brazil, Canada, China - Hainan, Colombia, European Union, Hong Kong, Israel, Japan, Malaysia, Mexico, New Zealand, Russia, Saudi Arabia, Serbia, Singapore, South Korea South Africa, Turkey, and Ukraine.

The Freezor *MAX* Catheter has been marketed in the United States since December 2010 as a surgical device for minimally invasive cardiac surgery procedures, including surgical treatment of cardiac arrhythmias. In addition, the Freezor *MAX* Catheter was also approved in Japan as of 2014.

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 Advance and Arctic Front Advance 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 tamponade
- Cardiopulmonary arrest
- Cerebral vascular accident
- Chest discomfort/pain/pressure
- Cold feeling
- Coronary artery spasm
- Cough
- Death
- Diarrhea
- Dizziness
- Embolism
- 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
- Phrenic nerve injury
- Pleural effusion

- Pneumonia
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary hemorrhage
- Pulmonary vein dissection
- Pulmonary vein stenosis
- Shivering
- Shortness of breath
- Sore throat
- Transient ischemic attack
- Vagal nerve injury (e.g. gastroparesis)
- Vasovagal reaction
- Visual changes (e.g. blurred vision)

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the Freezor *MAX* Catheter.

- Anemia
- Anxiety
- Atrial flutter
- Back pain
- Bleeding from puncture sites
- Blurred vision
- Bradycardia
- Bronchitis
- Bruising
- Cardiac tamponade
- Cardiopulmonary arrest
- Cerebral vascular accident
- Chest discomfort/pain/pressure
- Cold feeling
- Cough
- Death
- Diarrhea
- Dizziness
- Esophageal damage
- Fatigue
- Fever
- Headache
- Hemoptysis
- Hypotension/hypertension
- Lightheadedness
- Myocardial infarction

- Nausea/vomiting
- Nerve injury
- Pericardial effusion
- Pulmonary vein stenosis
- Shivering
- Shortness of breath
- Sore throat
- Tachycardia
- Transient ischemic attack
- Urinary infection
- Vasovagal reaction
- Visual changes

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 Advance Catheter, the Arctic Front Advance Pro Catheter, 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 guidance documents. 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. A summary of preclinical testing submitted under PMA P100010 for the original Arctic Front Catheter and the Freezor *MAX* Catheter can be found in the SSED at: https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100010B.pdf. 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.

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 STUDIES

Table 1 provides an overview of prior clinical trials supported by the applicant to evaluate the cryoablation system. The applicant performed the *STOP Persistent AF* study to establish a reasonable assurance of safety and effectiveness of cryoablation with the Arctic Front Advance and Freezor *MAX* catheters for the treatment of patient with symptomatic drug refractory recurrent persistent atrial fibrillation of less than 6 months duration in the US under IDE G160177. Data from this clinical study formed the basis for the PMA approval decision. A summary of the clinical study is presented below.

Table 1: Previously Completed Clinical Trials Assessing the Cryoablation System

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects	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 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

A. Study Design

The STOP Persistent AF study was a prospective, multi-center, non-randomized, single-arm, unblinded, global clinical study that enrolled patients with a history of symptomatic drug refractory persistent atrial fibrillation of less than 6 months duration.

Patients were treated between March 28, 2017 and July 12, 2018. The database for this PMA/Panel Track Supplement reflected data collected through August 13, 2019 and included 186 subjects of which 165 subjects underwent ablation in the US, Canada and Japan. Subjects were enrolled at 25 sites located in the United States (19 sites), Canada (3 sites) and Japan (3 sites).

In the US and Canada, 169 subjects were enrolled of which 150 underwent a pulmonary vein (PV) isolation procedure using the study catheters. These 150 subjects comprised the primary cohort submitted and reviewed by FDA to determine results for the study objectives.

Subjects were followed for 12 months post procedure to assess adverse events and recurrence of atrial tachyarrhythmias and then exited from the study. The study was closed after completion of the last 12-month visit.

1. Inclusion and Exclusion Criteria

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

- Documentation of symptomatic persistent AF

  Defined as having a continuous episode lasting longer than 7 days but less than 6 months documented by consecutive ECG recordings
  OR
  Defined as having a continuous episode lasting longer than 7 days but less than 6 months documented by an ECG recording and one doctor note indicating patient had symptoms consistent with AF

- Failure or intolerance of at least one Class I or III antiarrhythmic drug
- Age 18 or older (or older than 18 if required by local law)

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

- Left atrial diameter > 5.0 cm (anteroposterior)
- Prior left atrial ablation or surgical procedure (including left atrial appendage closures)

- 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) within 12 months
- Presence of any pulmonary vein stents
- Presence of any pre-existing pulmonary vein stenosis
- Pre-existing hemidiaphragmatic paralysis
- Presence of any cardiac valve prosthesis
- +3 and +4 mitral valve regurgitation or stenosis
- Any cardiac surgery, myocardial infarction, PCI/PTCA or coronary artery stenting which occurred during the 3 month interval preceding the consent date
- Unstable angina
- NYHA Class III or IV congestive heart failure and/or documented left ventricular ejection fraction (LVEF) less than or equal to 35% measure by acceptable cardiac testing (e.g., TTE)
- Primary pulmonary hypertension
- Rheumatic heart disease
- Thrombocytosis, thrombocytopenia
- Any condition contraindicating chronic anticoagulation
- Active systemic infection
- Hypertrophic cardiomyopathy
- Cryoglobulinemia
- Uncontrolled hyperthyroidism
- Any cerebral ischemic event (strokes or TIAs) which occurred during the 6-month interval preceding the consent date
- Any woman known to be pregnant or breastfeeding, or any woman of childbearing potential who is not on a reliable form of birth regulation method or abstinence
- Life expectancy less than one year
- Current or anticipated participation in any other clinical trial of a drug, device or biologic during the duration of the study not pre-approved by Medtronic
- Known allergies or hypersensitivities to adhesives
- Known drug or alcohol dependency
- Unwilling or unable to comply fully with study procedures and follow-up

2. Follow-up Schedule

After discharge, all patients were scheduled to have a telephone interview at 6 weeks and return for follow-up examinations at 3 months, 6 months and 12 months, and at any repeat ablations. The follow-up visit schedule was not reset if the subject underwent a repeat AF ablation procedure with the study catheters.

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

Table 2: Study Procedures and Data Collection per Subject Visit

	Baseline	Cryoablation Procedure	Hospital Discharge	Repeat Ablation in Blanking	6 Week Phone Call	3 Month Visit	6 and 12 Month Visit	Repeat Ablation Out of Blanking	Unscheduled Visit	Exit
Consent	X									
Inclusion/Exclusion Criteria	X									
Medical History	X									
Physical Examination	X[i]									
Review Medications	X		X		X	X	X		X	
Pregnancy Screen (if applicable)[ii]	X									
12-Lead ECG	X[i]		X			X	X		X	
Trans-thoracic Echocardiogram (TTE)[iii]	X									
SF-12 Health Survey and AFEQT Questionnaire	X						X			
Trans-esophageal Echocardiogram (TEE)[iv]	X			X						
Sub-study CardioInsight mapping system[v]	X					Upon recurrence of AF				
Ablation Procedure Data		X		X				X		
24h Continuous Monitoring with Holter							X			
Trans-telephonic monitoring						Weekly and upon symptoms				

Review symptoms suggestive of recurrent AF/AT/AFL					X	X	X		X	
Device Deficiencies	As they occur									
Adverse Events (incl. AE with outcome of death)	As they occur									
Study Deviation	As they occur									
Study Exit Information										X[vi]

[i] Only required if data not available from within prior 30 days from consent date.
[ii] Female subjects of childbearing potential only.
[iii] Only required if data not available from within prior 6 months from consent date.
[iv] TEE to assess for LA thrombus as indicated by the 2012 HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation.
[v] Subjects need to sign the sub-study patient informed consent form before mapping. Mapping will be performed before the initial cryoablation procedure and when the subject has a recurrence of AF outside of the 90 day post-procedure blanking period.
[vi] A review of medications, adverse event assessment and a 12-lead ECG should be attempted if the subject exits the study of a study visit.

3. Study Endpoints

The endpoints for the study were as follows:

Primary Effectiveness Endpoint

The primary effectiveness endpoint was the proportion of subjects free of treatment failure at 12 months after the pulmonary vein isolation (PVI) ablation procedure.

Treatment success was defined as freedom from treatment failure. Treatment failure was defined as any of the following components:

- Acute procedural failure
- Documented AF/AT/ AFL on Holter/TTM/12-lead ECG after the 90-day blanking period
    - Minimum of 30 seconds on Holter/TTM and 10 seconds on 12-lead ECG
- A reablation for the treatment of recurrent AF/AT/AFL after the 90-day blanking period
- Class I or III antiarrhythmic drug (AAD) dose increase from the historic maximum ineffective dose (prior to the ablation procedure) or initiation of a new Class I or III AAD after the 90-day blanking period.

Note: remaining on the same pre-ablation dose or decreased dose, or re-initiation of a previously failed or not tolerated Class I or III AAD after the 90-day blanking was not considered a failure. Subjects were allowed to remain on Class I or III antiarrhythmic medications at the historic maximum ineffective dose (on prior to the ablation procedure) after the 90-day post-procedure blanking period.

- Ablation using RF in the left atrium

Blanking period was defined as the first 90 days after the index ablation procedure.

Recurrences of atrial arrhythmias during the blanking period were not counted in the determination of the first clinical failure for the primary endpoint. Within the blanking period, recurrent arrhythmias could be managed with antiarrhythmic drugs, cardioversion or one cryo re-ablation procedure of the pulmonary veins. Titration of Class I and III antiarrhythmic medications was allowed during the blanking period.

The following hypothesis was tested at a one-sided significance level of 0.025 for the primary effectiveness endpoint:

Ho: $\pi_s \leq 40\%$
Ha: $\pi_s > 40\%$

Where π_s was the treatment success rate at 12 months.

The primary analysis cohort for the primary effectiveness endpoint included all subjects who had an Arctic Front Advance Catheter inserted into the vasculature. In total, 150 subjects met these criteria, and all 150 subjects were treated with cryoablation.

The primary effectiveness success rate at 12 months (365 days) was estimated using survival analysis, the Kaplan-Meier method. The standard error was approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the primary treatment success rate was constructed. If the lower bound of the 95% confidence interval at 12 months was greater than the performance goal of 40%, the primary effectiveness endpoint was considered met.

The effectiveness performance goal of 40% was derived from the minimum chronic acceptable success rate recommended in the Heart Rhythm Society Expert Consensus Statement on Catheter and Surgical Ablation of AF and a meta-analysis of published literature of persistent AF ablation using a cryoballoon catheter (Calkins, et al., 2012).

Primary Safety Endpoint

The primary safety endpoint was the proportion of subjects experiencing one or more primary safety event.

A primary safety event was defined as a serious procedure-related or serious system-related adverse event including the following:

- Transient ischemic attack (within 7 days of ablation procedure)
- Cerebrovascular accident (within 7 days of ablation procedure)
- Major bleeding that requires transfusion (within 7 days of ablation procedure)
- Cardiac perforation, tamponade or pericardial effusion (within 7 days of ablation procedure)
- Pulmonary vein stenosis (>75% reduction within 12-months of ablation procedure)
- Myocardial infarction (within 7 days of ablation procedure)
- Phrenic nerve injury (unresolved at 12-months)
- Atrio-esophageal fistula (within 12-months of ablation procedure)
- Death (within 7 days of ablation procedure)

The following hypothesis was tested at a one-sided significance level of 0.025 for the primary safety endpoint:

Ho: PS $\geq$ 13%
Ha: PS < 13%

Where PS was the primary safety event rate through 12 months.

The primary analysis cohort for the primary safety endpoint included all subjects who had an Arctic Front Advance Catheter inserted into the vasculature. In total, 150 subjects met these criteria, and all 150 subjects were treated with cryoablation.

The primary safety event rate at 12 months (365 days) was estimated using survival analysis, the Kaplan-Meier method. The standard error was approximated using Greenwood's formula. A two-sided 95% log-log confidence interval for the primary safety event rate was constructed. If the upper bound of the 95% confidence interval at 12 months was less than the performance goal of 13%, the primary safety endpoint was considered met.

The safety performance goal of 13% was derived from an estimated safety rate of 5% and a margin of indifference of 8%.

Secondary Endpoint

The secondary endpoint of the study was improvement in quality of life between baseline and 12 months post procedure as measured by the Atrial Fibrillation Effect on QualiTy-of-life (AFEQT) and SF-12 questionnaires.

Ancillary Endpoints included the following:

- **Acute Procedural Success** was the opposite of acute procedural failure.

  Acute procedural failure was defined as:

  - Inability to isolate all accessible targeted pulmonary veins (minimally assessed for entrance block and, where assessable, exit block) during the index procedure; OR
  - Left atrial non-PVI ablations including but not limited to, ablation of linear lesions, complex fractionated electrograms or non-PV triggers

- **12-month single procedure success**

  The same definition as the primary effectiveness endpoint was utilized for 12-month single procedure success, with the additional component that if an ablation occurred during the blanking period, those subjects were set to treatment failure at the date of the blanking period ablation.

- **Procedure measurements** included total procedure time, left atrial dwell time, fluoroscopy time, and application duration.

- **Treatment success in subjects off Class I and III AADs**

  This ancillary endpoint compared treatment success in subjects on vs. those off Class I and Class III AADs on day 90 post procedure. The same definition as the primary effectiveness endpoint was utilized for treatment failure.

- **Atrial arrhythmias present and/or treated** during the cryoablation procedure.

- **All Adverse Events**

4. **Sample Size**

The study was adequately powered for both the primary safety and primary effectiveness endpoints.

For the primary analysis cohort, 150 treated subjects afforded 90% power to perform hypothesis test for the primary effectiveness endpoint based on the following assumptions:

- One analysis at 12 months
- 12-month effectiveness rate = 54%
- Performance Goal = 40% at 12 months
- alpha = 0.025, one-sided
- 10% attrition through 12 months
- Binomial exact method

For the primary analysis cohort, 150 treated subjects afforded 86% power to assess the primary safety endpoint at 12 months based on the following assumptions:

- One analysis at 12 months
- 12-month safety rate = 5%
- Performance goal = 13%
- alpha = 0.025, one-sided
- 10% attrition
- Binomial exact method

5. Study Success Criteria

The study would be considered successful if the pre-defined performance goals for the primary safety and effectiveness endpoints are met.

6. Independent Events Committee and Core Lab

An independent Clinical Events Committee (CEC) was utilized to review and adjudicate all reported study safety data. The CEC reviewed all reported adverse events, including all system related and all procedure related adverse events, as well as all deaths and provided a final adjudication and death classification. The CEC also reviewed and classified all primary safety endpoint events.

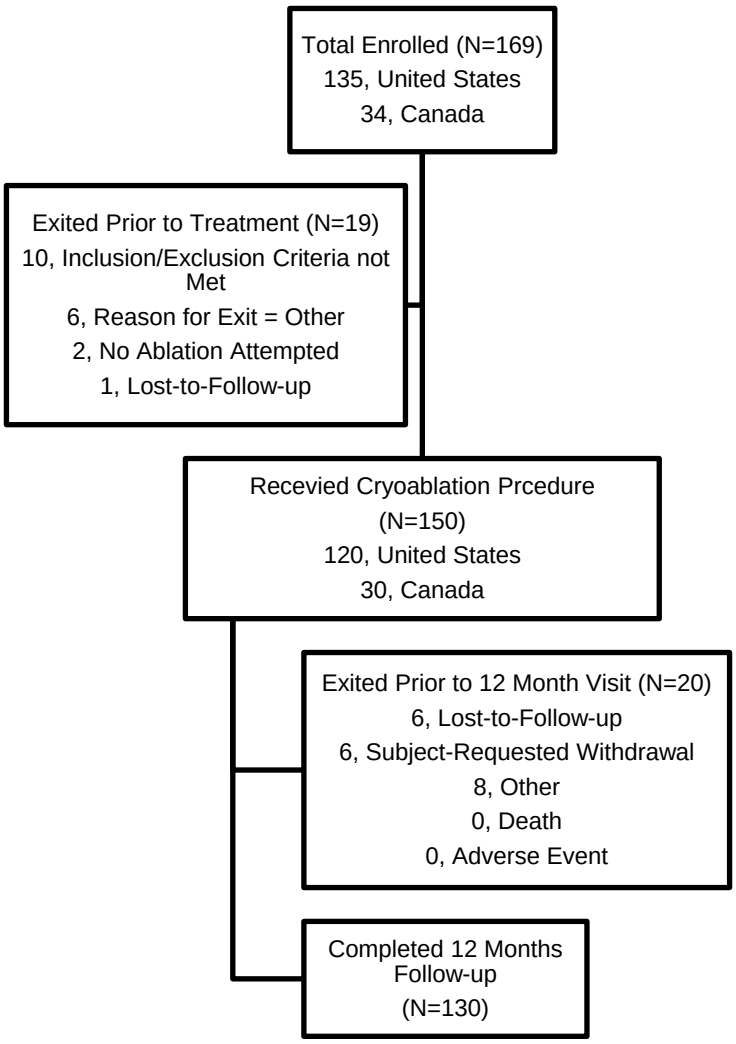
An independent core lab was utilized to review ECGs, Holters and TTMs for adjudication of all atrial arrythmias for the evaluation of the primary effectiveness endpoint.

B. Accountability of PMA Cohort

A total of 169 subjects signed a study informed consent form and were therefore considered enrolled in the PMA study in the US and Canada, of which 150 underwent a cryoablation procedure. Of the 150 treated patients, 20 subjects (13.3%) exited the

study without completing the 12 months follow-up visit, and 130 (86.7%) completed the 12 months follow-up visit. No subjects exited the study due to death or adverse events. All 150 treated subjects were included for analysis of study endpoints (**Error! Reference source not found.**).

Figure 3: Subject Flow from Enrollment to 12 Month Follow-up Visit



C. Study Population Demographics and Baseline Parameters

The demographics of the 150 treated subjects showed in Table 3 were typical for a persistent AF ablation study performed in the US.

Table 3: Demographic Characteristics

Demographics	**Subjects with Index Procedures (N=150)**
Age, years	

Mean ± SD	65 ± 9
Median	66
25th Percentile – 75th Percentile	59 – 72
Min, Max	38 – 88
Sex, n (%)	
Male	105 (70.0%)
Female	45 (30.0%)
Race/Ethnic Origin, n (%)	
Black	2 (1.3%)
Filipino	1 (0.7%)
Other Asian	1 (0.7%)
Prefer not to say	4 (2.7%)
White or Caucasian	142 (94.7%)

Table 4 summarizes baseline characteristics for subjects who underwent an index procedure in the trial.

Table 4: Baseline Characteristics

Baseline Characteristics	**Subjects with Index Procedures (N=150)**
Baseline BMI (kg/m^2)	
Mean ± Standard Deviation	31 ± 6
Median	30
25^{th} Percentile – 75^{th} Percentile	27 - 35
Min, Max	17 - 61
Baseline SBP (mmHg)	
Mean ± Standard Deviation	130 ± 18
Median	127
25^{th} Percentile – 75^{th} Percentile	117 - 140
Min, Max	97 - 183
Baseline DBP (mmHg)	
Mean ± Standard Deviation	80 ± 11
Median	80
25^{th} Percentile – 75^{th} Percentile	73 - 86
Min, Max	41 - 114
Time from First Diagnosis of Persistent AF[i] (years)	
Mean ± Standard Deviation	0.6 ± 1.4

Median	0.2
25th Percentile - 75th Percentile	0.1 - 0.5
Minimum – Maximum	0.0 - 9.9
Duration of Longest Persistent AF Episode (days)	
Mean ± Standard Deviation	70.9 ± 49.7
Median	60.9
25th Percentile - 75th Percentile	30.0 - 95.0
Minimum – Maximum	7.0 - 182.6
Cardioversion Prior to Enrollment	
N (%)	121 (80.7%)
Electrical	120 (80.0%)
Pharmacological	15 (10.0%)
Number of Prior Cardioversions	
Mean ± Standard Deviation	2.1 ± 2.3
Median	2.0
25th Percentile - 75th Percentile	1.0 - 3.0
Minimum – Maximum	0.0 - 21.0
Number of Failed Class I/III AADs	
Mean ± Standard Deviation	1.2 ± 0.6
Median	1.0
25th Percentile - 75th Percentile	1.0 - 1.0
Minimum - Maximum	0.0 - 3.0
History of Atrial Flutter (N,%)	
Yes	28 (18.7%)
No	122 (81.3%)
History of Atrial Tachycardia (N,%)	
Yes	3 (2.0%)
No	147 (98.0%)
Left Ventricular Ejection Fraction (%)	
Mean ± Standard Deviation	56 ± 6
Median	55
25th Percentile - 75th Percentile	54 - 60
Minimum - Maximum	36 - 71
Left Atrial Diameter (cm)	
Mean ± Standard Deviation	4.2 ± 0.6
Median	4.4

25th Percentile - 75th Percentile	3.8 - 4.7
Minimum - Maximum	2.4 - 5.0
Not reported at time of report (%)	3 (2.0%)
AFEQT Summary Score	
Mean ± Standard Deviation	61.1 ± 20.8
Not reported (%)	2 (1.3%)
SF-12 Physical Component Summary Score	
Mean ± Standard Deviation	43.5 ± 10.5
Not reported (%)	2 (1.3%)
SF-12 Mental Component Summary Score	
Mean ± Standard Deviation	48.5 ± 10.1
Not reported (%)	2 (1.3%)
NYHA Class	
Classification not available	12 (8.0%)
No heart failure	107 (71.3%)
Class I	8 (5.3%)
Class II	22 (14.7%)
Class III	1 (0.7%)
Class IV	0 (0.0%)
Medical History	
Coronary Artery Disease	18 (12.0%)
Myocardial Infarction	7 (4.7%)
Hypertension	93 (62.0%)
Prior Cardiac Valvular Surgery	1 (0.7%)
Diabetes	19 (12.7%)
Congestive Heart Failure	31 (20.7%)
Stroke or TIA	6 (4.0%)
Renal Insufficiency	8 (5.3%)
Sleep Apnea	52 (34.7%)
Chronic Obstructive Pulmonary Disease	10 (6.7%)
CHA_2DS_2-VASc Score	
Mean ± Standard Deviation	2.2 ± 1.4
Median	2
25th Percentile - 75th Percentile	1 – 3
Minimum - Maximum	0 – 6
>= 2	101 (67.3%)

Not reported (%)	6 (4.0%)
Baseline Medications	
Beta-blocker	40 (26.7%)
Calcium-channel blocker	32 (21.3%)
Anticoagulant	134 (89.3%)
Aspirin	7 (4.7%)
Class I/III AAD	91 (60.7%)
Amiodarone	32 (21.3%)
Dofetilide	4 (2.7%)
Dronedarone	7 (4.7%)
Flecainide	24 (16.0%)
Propafenone	12 (8.0%)
Sotalol	16 (10.7%)
Rhythm on baseline ECG	
Sinus Rhythm	27 (18.0%)
Atrial fibrillation	121 (80.7%)
Atrial flutter	2 (1.3%)

[i] Time from first diagnosis of persistent AF was defined as enrollment date minus diagnosis date of persistent AF provided by the clinician on study CRFs. All subjects reported AF episodes of 7 days or longer and less than 6 months to meet major inclusion criteria. The study CIP did not provide a definition for persistent AF diagnosis date, which has been reported as enrollment date in 11 subjects.

D. Index Ablation Procedure

Table 5 summarizes ablations performed during the index ablation procedure and the device(s) used. In addition to PVI, the study protocol required ablation of the cavotricuspid isthmus (CTI) for subjects with a history of typical AFL or inducible CTI-dependent AFL. Additionally, other right atrial ablations were allowed during the index procedure if clinically necessary.

Table 5: Ablations Performed during Index Procedure

Procedural Characteristics	**Subjects with Index Procedures (N = 150)**
Cryoballoon Pulmonary Vein Ablation	**150 (100.0%)**
23 mm balloon size	1 (0.7%)
28 mm balloon size	141 (94.0%)
23 and 28 mm balloon size	8 (5.3%)
Focal Ablation (Freezor *MAX*) on Pulmonary Vein	**3 (2.0%)**

Focal Ablation (Radiofrequency [RF]) on Pulmonary Vein	**0 (0.0%)**
Cavo-tricuspid Isthmus (CTI) Ablation	**40 (26.7%)**
Focal Cryo	0 (0.0%)
Focal RF	40 (26.7%)
Other Right Atrial Ablations	**3[i] (2.0%)**

[i] Two were atrial tachycardia ablations and one was AVNRT ablation

E. Peri-Procedure and 3 months Rhythm Status

Table 6 summarizes rhythm status peri-procedure and at the 3-month visit. About 60% of the subjects presented in AF at the time of the index ablation procedure. At the completion of the procedure, all but two subjects were in sinus rhythm. Cardioversion was required to restore sinus rhythm in 98 subjects at the end of the procedure after all ablations were performed. Sinus rhythm was the rhythm on the discharge ECG and 3 months ECG in the vast majority of the subjects.

Table 6: Peri-Procedure and 3 Months Post Procedure Rhythm Status

Rhythm Status	Ablation procedure onset (N=150)	Ablation procedure completion (N=150[i])	Discharge ECG (N=141[ii])	3 months ECG (N=144[iii])
Sinus Rhythm	58 (38.7%)	148 (98.7%)	133 (94.3%)	133 (92.4%)
Atrial Fibrillation	89 (59.3%)	1 (0.7%)	5 (3.5%)	8 (5.6%)
Atrial Flutter	2 (1.3%)	1 (0.7%)	3 (2.1%)	3 (2.1%)
Atrial Tachycardia	1 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

[i] 98 subjects received cardioversion at end of procedure.
[ii] 141 of 150 subjects completed a 12-lead ECG at hospital discharge.
[iii] 144 of 150 patients completed a 3-month visit. All 144 subjects completed an ECG at the visit.

F. Post-ablation AAD therapy

The study did not employ a standardized protocol for AAD therapy post-ablation. The use of class I and III AADs and cardioversion for AF during the 90-day post-ablation blanking period were at the discretion of the investigators. Titration of Class I and III AADs was allowed during the blanking period.

The study protocol recommended discontinuation of Class I and III AADs by the end of the blanking period. However, subjects were allowed to remain on Class I or III AADs at the historic maximum ineffective dose after the blanking period.

As indicated in Table 7, the majority of the 150 treated subjects were on a Class I or III AAD at discharge and about half of the subjects remained on a Class I or III AAD at 3 months post-ablation. More than 30% of the subjects were taking a Class I or III AAD at 6 months and 12 months post procedure.

Table 7: Class I/III AAD use at discharge, and 3, 6, and 12 months post procedure

Class I/III AAD[i]	N (%) on AAD at Discharge (n=150)	N (%) on AAD at 3 Months[ii] (n=147)	N (%) on AAD at 6 Months (n=142)	N (%) on AAD at 12 Months (n=133)
Number of Subjects on AAD[iii]	**98 (65.3%)**	**67 (45.6%)**	**49 (34.5%)**	**40 (30.1%)**
Amiodarone	33 (22.0%)	18 (12.2%)	13 (9.2%)	12 (9.0%)
Dofetilide	5 (3.3%)	4 (2.7%)	3 (2.1%)	3 (2.3%)
Dronedarone	7 (4.7%)	5 (3.3%)	5 (3.5%)	5 (3.8%)
Flecainide	30 (20.0%)	17 (11.5%)	9 (6.3%)	5 (3.8%)
Propafenone	12 (8.0%)	9 (6.1%)	7 (4.9%)	6 (4.5%)
Sotalol	17 (11.3%)	16 (10.8%)	14 (9.8%)	11 (8.3%)

[i] In this analysis, at months m = 3, 6, and 12, subjects with exit dates prior to month m (or in rare cases, with unknown AAD status) are not included.
[ii] Two subjects had exited the study during the blanking period, and one subject had no date specified for the discontinuation of amiodarone at a dose less than the pre-ablation maximum, leading to a status at day 90 that could not be determined.
[iii] Medications and medication changes were captured on a Medication Log CRF. Centers were instructed to update medication log as prescriptions changes. For analysis, the time for 3 months was defined as day 90, similarly 6 months and 12 months were defined as day 180 and day 365. Prescription data included through study exit.

G. Repeat ablation during the blanking period

The study allowed one repeat ablation during the 90-day post-procedure blanking period. Ablations other than PV isolation ablation using the study device and ablation in the right atrium would result in a subject being classified as a treatment failure.

As shown in Table 8, 7 (4.7%) subjects underwent a repeat ablation procedure within the 90-day blanking period. Of these 7 subjects, 2 were classified as treatment failures, one due to cryoablation in the left atrium outside of the PVs and one due to RF ablation for PVI.

Table 8: Details of Repeat Ablations within 90-Day Blanking Period

Subject	Catheter Type	Type of Ablation	Days from Index Procedure	Number of PVs Re-treated	Primary Effectiveness Endpoint Failure?

M100001005	Cryoballoon	PVI	74	4	No
M100001010	Cryoballoon	Left atrial roof line/Left atrial posterior wall	82	0	Yes
M100001011	Cryoballoon	PVI	90	4	No
M100011004	Focal RF	Cavotricuspid Isthmus (CTI line)	42	0	No
M100011007	Focal RF	Cavotricuspid Isthmus (CTI line)	48	0	No
M134170002	Focal RF	Cavotricuspid Isthmus (CTI line)	14	0	No
M200001002	Focal RF	PVI	89	1	Yes

H. Rhythm monitoring compliance

Table 9 displays data on compliance to the required 12-lead ECG and 24-Hour Holter during follow-up. A total of 408 completed visits required a 12-lead ECGs, of which 408 (100%) were completed. The study protocol did not require Holter monitoring at the 3-month or unscheduled visits; 233 of the 264 required Holters were completed, resulting in an overall compliance rate of 88.3%.

Table 9: Rhythm Monitoring Compliance in Subjects with Index Procedures

Visit Name	Completed Visits	12-lead ECG Completion	24-Hour Holter Completion
3 Month Follow-Up	144	144 (100.0%)	24-Hour Holter not required
6 Month Follow-Up	134	134 (100.0%)	121 (90.3%)
12 Month Follow-Up	130	130 (100.0%)	112 (86.2%)
Total	408	408 (100.0%)	233 (88.3%)

Error! Reference source not found. displays compliance to the required weekly t ransmissions of trans-telephonic monitoring (TTM). Study subjects were instructed to perform TTM weekly, beginning one week after the 3-month visit. Subjects were followed for a total of 5225 weeks post 3 months, of which a total of 3772 weekly transmissions were received, resulting in an overall compliance rate of 72.2%, as shown in Table 10.

Figure 4: Weekly Trans-Telephonic Monitoring (TTM) Compliance

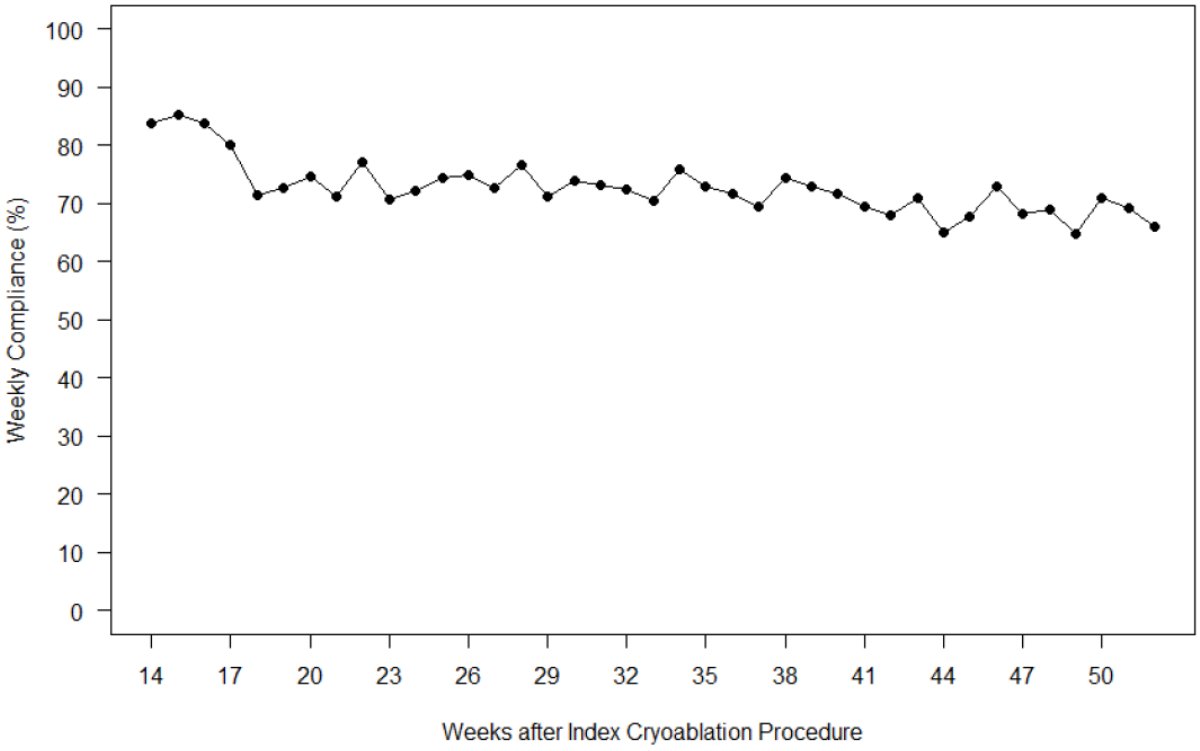


Table 10: Overall TTM Compliance

Number of total weeks of follow up[i,ii]	5225
Number of weeks with reported TTM	3772
Overall TTM compliance	72.2%

[i] TTM transmissions are expected starting 7 days after the 3-month visit. If subject missed 3-month visit, TTM compliance calculations assume transmissions after day 121 (end of 3 month visit window).
[ii] This includes eligible weeks between 13- and 52-weeks post ablation, so the maximum number of expected weeks per subject is 40. Week 13 post ablation is not included in the plot, as only subjects receiving TTM equipment at out-of-window early 3-month follow-up visits had expected TTM transmissions in week 13.

In addition to the required weekly TTM transmissions and required study visits, subjects were trained to complete TTM transmissions upon symptoms. In total, 509 additional TTM transmissions were received. Also, when a subject attended the clinic for an unscheduled visit, the study required an Unscheduled Visit CRF to be completed which included collection of an ECG. A total of 34 ECGs from unscheduled visits were reported over the duration of the study.

I. Study Results

1. Safety Results

Primary Safety Endpoint

The analysis of primary safety endpoint was based on the cohort of 150 patients who underwent a cryoablation procedure. The components of the primary safety endpoint and associated event rate are reported in Table 11. Of the 150 subjects, one subject (0.7%) had a CEC adjudicated primary safety event through 12 months of follow-up. The single primary safety event observed was an aortic root perforation during transseptal puncture that occurred during a planned radiofrequency repeat ablation 163 days following the index procedure. The event met the primary safety endpoint component of cardiac perforation. The Kaplan-Meier estimate of the primary safety event rate and corresponding 95% confidence interval was 0.7% (95% CI: 0.1% – 4.9%). Because the upper bound of the 95% confidence interval was lower than the predefined performance goal of 13%, the primary safety endpoint was met.

Table 11: Summary of CEC Adjudicated Adverse Events Contributing to the Primary Safety Endpoint

Adverse Events Included in the Primary Safety Endpoint Definition	**Number of Subjects with Event (%) (N=150)**
Atrio-esophageal fistula (within 12 months of ablation procedure)	0 (0.0%)
Cardiac perforation, tamponade or pericardial effusion (within 7 days of ablation procedure)	1 (0.7%)
Cerebrovascular accident (within 7 days of ablation procedure)	0 (0.0%)
Death (within 7 days of ablation procedure)	0 (0.0%)
Major bleeding that requires transfusion (within 7 days of ablation procedure)	0 (0.0%)
Myocardial infarction (within 7 days of ablation procedure)	0 (0.0%)
Phrenic nerve injury (unresolved at 12 months)	0 (0.0%)
Pulmonary vein stenosis (>75% reduction within 12 months of ablation procedure)	0 (0.0%)
Transient ischemic attack (within 7 days of ablation procedure)	0 (0.0%)

Summary of All Adverse Events

Subjects were monitored for adverse events that occurred during the study. There were no Unanticipated Adverse Device Effects or deaths reported in the trial.

Table 12 summarizes all adverse events that occurred during or after the index ablation procedure in the 150 treated subjects by seriousness and relatedness to the cryoablation system or procedure. There were a total of 198 adverse events reported in 88 (58.7%) of the 150 subjects. Of the 198 adverse events, 43 were adjudicated as serious adverse events (SAEs); 25 adjudicated as related to the cryoablation system, of which 3 were SAEs; and 42 adjudicated as related to a cryoablation procedure, of which 7 were SAEs.

Table 12: Summary of Adverse Event Reported during or after Index Ablation Procedure

	Number of Events (Number of Subjects, % of Subjects) Total subjects: N=150	
Adverse Event Classifications	**All Adverse Events**	**Serious Adverse Events**
Total Adverse Events	198 (88, 58.7%)	43 (27, 18.0%)
Relationship to Index CryoAblation Procedure		
Not related	154 (77, 51.3%)	36 (24, 16.0%)
Related	39 (32, 21.3%)	5 (4, 2.7%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)
Relationship to Repeat CryoAblation Procedure (Number of Repeat CryoAblation procedures = 3)		
Not related	2 (2, 66.7%)	0 (0, 0.0%)
Related	3 (2, 66.7%)	2 (2, 66.7%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)
Relationship to CryoAblation System		
Not related	172 (82, 54.7%)	40 (25, 16.7%)
Related	25 (22, 14.7%)	3 (3, 2.0%)
Unknown	1 (1, 0.7%)	0 (0, 0.0%)
Relationship to Other Devices		
Not related	196 (87, 58.0%)	42 (27, 18.0%)
Related	2 (2, 1.3%)	1 (1, 0.7%)

Unknown	0 (0, 0.0%)	0 (0, 0.0%)
Relationship to Other Procedure		
Not related	197 (88, 58.7%)	42 (27, 18.0%)
Related	1[i] (1, 0.7%)	1 (1, 0.7%)
Unknown	0 (0, 0.0%)	0 (0, 0.0%)

[i] The single AE related to an 'other' procedure was an aortic perforation during transseptal puncture for subject M200001009. This AE was determined by the CEC to meet the criteria for the primary safety endpoint.

Cryoablation system or procedure related serious adverse events

Table 13 summarizes the seven (7) cryoablation system or procedure related SAEs reported in 6 (4%) of the 150 treated subjects.

Table 13: Cryoablation system or procedure related serious adverse events

Serious Adverse Events	Number of Events (Number of Subjects, % of Subjects) Total subjects: N=150
Atrial tachycardia	1 (1, 0.7%)
Pericarditis	1 (1, 0.7%)
Heart failure	1 (1, 0.7%)
Respiratory failure	1 (1, 0.7%)
Pseudoaneurysm requiring thrombin injection	1 (1, 0.7%)
Urinary tract infection	1 (1, 0.7%)
Postoperative ileus	1 (1, 0.7%)
Total	**7 (6, 4%)**

Phrenic Nerve Injury

Phrenic nerve injury resulting in diaphragmatic paralysis occurred in three (3) of 150 subjects (2%) who underwent a cryoballoon ablation procedure. None of the 3 occurrences of diaphragmatic paralysis was classified by the CEC as a SAE. Two of these occurrences resolved prior to discharge from the index ablation. The third persisted for at least 6 months and its recovery was not confirmed on chest x-ray until 15 months post ablation prior to subject's exit from the study. Since this occurrence of diaphragmatic paralysis was not classified as a SAE, the adverse event did not count towards the primary safety endpoint.

Adverse Events Related to Concomitant Anti-Arrhythmic Drug Therapy

Two adverse events that were related to the use of Class I/III AAD post procedure occurred in two (1.3%) of the 150 treated subjects. One was an episode of non-sustained ventricular tachycardia (VT) recorded on telemetry after initiation of flecainide. The other was QT prolongation resulting in reduction of flecainide dose. Neither of them was adjudicated as a SAE.

There was no class I/III AAD-related bradycardia, Torsades des pointes, hypotension, heart failure, pulmonary toxicity, liver injury/failure, hyper-or hypothyroidism, renal failure, or blindness reported in the 150 treated subjects.

Other adverse events

Other notable adverse events included a non-ST-segment elevation myocardial infarction that occurred in a subject on day 118 post ablation and a TIA that occurred in another subject on day 309 post ablation. Neither of the two adverse events was adjudicated as related to the cryoablation system or procedure.

There was no stroke, cardiac arrest, systemic embolism or death reported in the study.

2. Effectiveness Results

Acute Procedural Success

All 150 treated subjects had acute procedural success (100%) with a total of 588 pulmonary veins (23 LCPVs, 129 LSPVs, 129 LIPVs, 2 RCPVs, 148 RSPVs, 148 RIPVs, and 9 RMPVs) isolated using the study catheters at index ablation. A Freezor *MAX* CryoAblation Catheter was utilized for 4 (0.7%) of 588 pulmonary veins in 3 (2%) of 150 treated subjects to complete PV isolation.

Primary Effectiveness Endpoint

Primary Effectiveness Analysis

The analysis of primary effectiveness endpoint was based on the cohort of 150 subjects who underwent cryoablation procedure. Of the 150 subjects, 69 reported at least one primary effectiveness failure event through 12 months of follow-up. The distribution of first primary effectiveness failure events observed in these 69 subjects is summarized below:

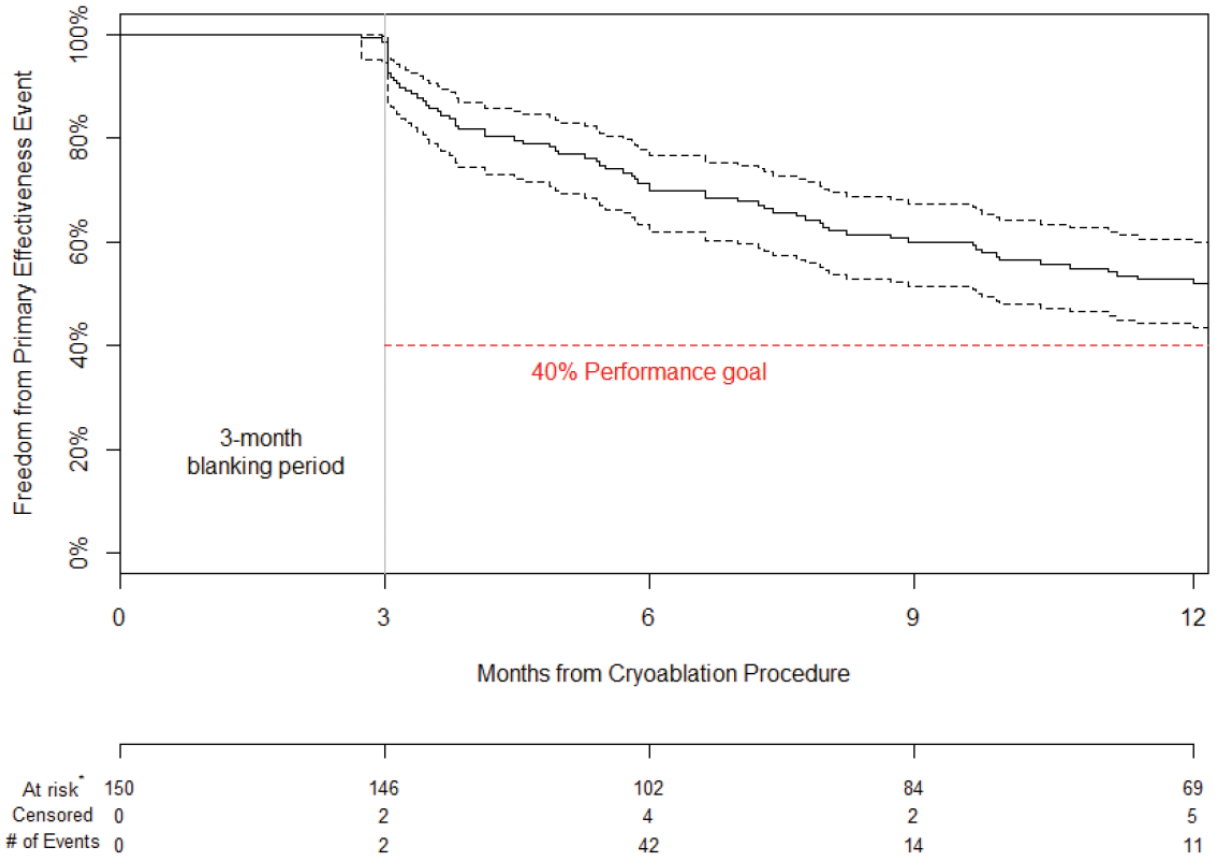
- 0 with acute procedure failure

- 2 with additional interventions in the left atrium within the 90-day blanking period
- 57 with AF/AT/AFL recurrences post blanking period
  - 44 with atrial fibrillation (AF)
  - 9 with atrial flutter (AFL)
  - 1 with atrial fibrillation and atrial flutter
  - 3 with atrial tachycardia (AT)
- 10 with Class I/III AAD dose greater than pre-ablation maximum

The rate of freedom from primary effectiveness failure at 12 months was estimated to be 52.1% [95% CI: 43.6 - 59.9%] using the Kaplan-Meier method.

Figure 5 displays the Kaplan-Meier curve for freedom from primary effectiveness failure for the 150 treated subjects through 12 months post procedure. The solid line is the Kaplan-Meier estimate, and the dashed lines are the 95% confidence interval. Because the lower bound of 95% confidence interval was greater than the predefined performance goal of 40%, the primary effectiveness endpoint was met.

Figure 5: Freedom from Primary Effectiveness Failure at 12 Months



* The number at risk, number censored, and number of events are included per Kaplan-Meier analysis methods: at risk equals the number of patients at risk up to months 3, 6, 9, and 12; number censored equals the number of patients censored up to months 3, 6, 9, and 12; number of events equals the number of events through the end of the intervals.

Sensitivity analyses of primary effectiveness endpoint

Of the 150 treated subjects, 20 exited the study without completing the 12-month visit. Of those 20 subjects, 5 had experienced a primary effectiveness failure event prior to study exit and 15 had not experienced a primary effectiveness failure event prior to study exit. Sensitivity analyses were performed to assess the impact of these 15 subjects with an unknown primary effectiveness outcome due to incomplete follow-up on the primary effectiveness results. The results of the sensitivity analysis are shown in Table 14 below. Each row corresponds to the re-estimated primary effectiveness success rate as each subject with an unknown primary effectiveness outcome is assumed to be an additional primary effectiveness failure. The tipping point, the point at which the primary effectiveness endpoint would not be met occurs when 9 (60%) of the 15 subjects with an unknown primary effectiveness outcome are assumed to be additional failures. The sensitivity analyses were considered supportive of the primary effectiveness endpoint conclusion.

Table 14: Sensitivity Analysis – Primary Effectiveness Success at 12 Months

Analysis	Additional Number of Subjects with Early Exit and Counted as Failures	Total Number of Failures	Total Number of Successes	Estimate (95% CI)
Primary	0	69	81	52.1% (43.6% - 59.9%)
Tipping Point Analysis	1	70	80	51.7% (43.3% - 59.5%)
	2	71	79	51.4% (43.0% - 59.2%)
	3	72	78	51.0% (42.6% - 58.8%)
	4	73	77	50.5% (42.2% - 58.3%)
	5	74	76	50.1% (41.8% - 57.8%)
	6	75	75	49.6% (41.3% - 57.3%)
	7	76	74	49.1% (40.9% - 56.8%)
	8	77	73	48.6% (40.4% - 56.3%)
	9	78	72	48.0% (39.8% - 55.7%)

Class I/III AAD use in subjects without a primary effectiveness failure event

Data on Class I and III AAD use was collected at each follow-up visit. The study allowed subjects to remain on a Class I or III AAD at the historic maximum ineffective dose after the blanking period. Per study protocol, such subjects were not classified as primary effectiveness failures for taking a Class I or III AAD during the 9-month effectiveness evaluation period (days 91-365 post procedure).

Among the 150 treated subjects, 69 were classified as primary effectiveness failures and 81 had not experienced a primary effectiveness failure event. Table 15 summarizes Class I/III AAD use in the 81 subjects without a primary effectiveness failure event. As indicated in Table 15, approximately 40% of the subjects without a primary effectiveness failure event remained on a Class I or III AAD at 3 months post procedure. The proportion of the subjects without a primary effectiveness failure event taking a previously ineffective Class I or III AAD decreased during the course of 9-month effectiveness evaluation period to approximately 24% at 12 months post procedure.

Table 15: Class I/III AAD use in subjects without a primary effectiveness failure event

	Subjects without a Primary Effectiveness Failure Event (n=81)

Class I and III AADs[i]	N (%) on AAD at Baseline (n=81)	N (%) on AAD at Discharge[ii] (n=80)	N (%) on AAD at 3 Months[iii] (n=78)	N (%) on AAD at 6 Months (n=74)	N (%) on AAD at 12 Months (n=67)
Number of Subjects on AAD[iv]	**47 (58.0%)**	**50 (62.5%)**	**30 (38.5%)**	**21 (28.4%)**	**16 (23.9%)**
Amiodarone	18 (22.2%)	18 (22.5%)	9 (11.5%)	6 (8.1%)	5 (7.5%)
Dofetilide	3 (3.7%)	3 (3.7%)	1 (1.3%)	0	0
Dronedarone	4 (4.9%)	4 (4.9%)	2 (2.5%)	2 (2.7%)	2 (3.0%)
Flecainide	15 (18.5%)	18 (22.2%)	7 (8.9%)	3 (4.0%)	1 (1.5%)
Propafenone	6 (7.4%)	6 (7.4%)	6 (7.6%)	6 (8.0%)	4 (6.0%)
Sotalol	5 (6.2%)	6 (7.4%)	6 (7.6%)	5 (6.7%)	5 (7.5%)

[i] In this analysis, at months m = 3, 6, and 12, subjects with exit dates prior to month m (or in rare cases, with unknown AAD status) are not included.
[ii] One subject had no date specified for the discontinuation of amiodarone at a dose less than the pre-ablation maximum; therefore, the status at hospital discharge could not be determined.
[iii] Two subjects had exited the study during the blanking period, and one subject had no date specified for the discontinuation of amiodarone at a dose less than the pre-ablation maximum, leading to a status at day 90 that could not be determined.
[iv] Medications and medication changes were captured on a Medication Log CRF. Centers were instructed to update medication log as prescriptions changes. For analysis, the time for 3 months was defined as day 90, similarly 6 months and 12 months were defined as day 180 and day 365. Prescription data included through study exit.

Primary Effectiveness by Rhythm Monitoring Method

Post-hoc analyses were performed to explore the impact of rhythm monitoring method on primary effectiveness results. As shown in the Table 16, the primary effectiveness success rate would be estimated to be 71% at 12 months post procedure had only 12-lead ECG and Holter been used for detecting atrial tachyarrhythmia recurrence in the study. The primary effectiveness success rate at 12 months post procedure based on the findings of TTM only would be almost identical to that of the primary analysis based on ECG, Holter and TTM findings, indicating that the use of weekly and symptom-driven TTM significantly improved the detection of atrial tachyarrhythmia recurrence in the study subjects.

Table 16: Freedom from Primary Effectiveness Failure by Rhythm Monitoring Method

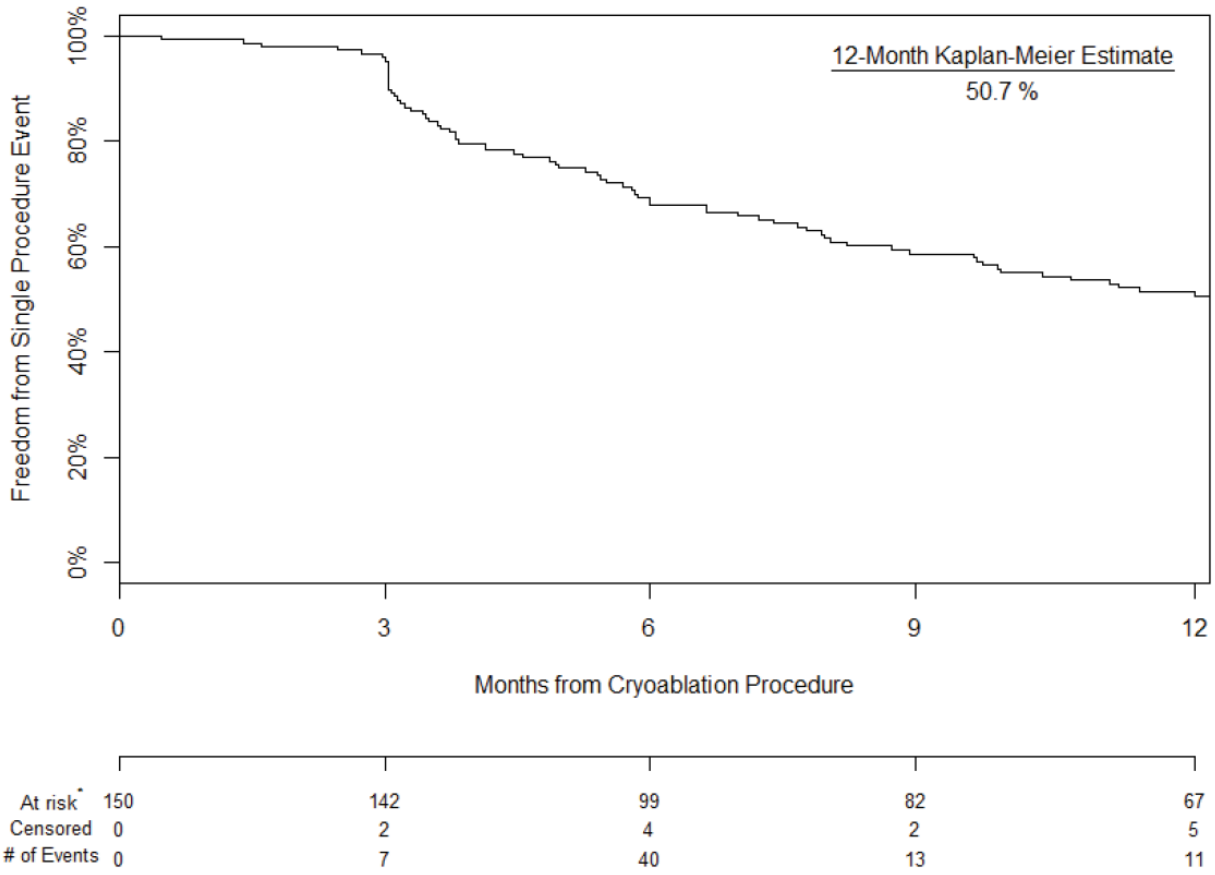
Rhythm Monitoring	Freedom from Primary Effectiveness Failure at 12 months Post Procedure
ECG/Holter/TTM	52.1%
ECG and Holter Only	71.0%

TTM only	52.8%

12-month Single Procedural Success

Seven (7) subjects (4.7%) had a repeat ablation within the 90-day blanking period. When these repeat ablations were counted as effectiveness failures, the single procedure success rate was estimated to be 50.7% based on the Kaplan-Meier curve shown in **Error! Reference source not found.**6.

Figure 6: Single Procedure Freedom from Primary Effectiveness Failure at 12 Months



* The number at risk, number censored, and number of events are included per Kaplan-Meier analysis methods: at risk equals the number of patients at risk up to months 3, 6, 9, and 12; number censored equals the number of patients censored up to months 3, 6, 9, and 12; number of events equals the number of events through the end of the intervals.

Treatment Success in subjects off Class I and III AADs

This ancillary endpoint compared treatment success in subjects on vs. those off Class I and III AADs on day 90 post procedure.

Of the 150 treated subjects, 145 were included in the analysis. Five (5) subjects were not included due to:

- Study exit prior to day 90 post procedure (n = 2);
- primary effectiveness failure prior to day 90 (n =2);
- unknown Class I/III AAD use status on day 90 post procedure (n = 1).

Of the 145 subjects included in the analysis, 79 were off Class I and III AADs, and 66 were on a Class I or III AAD on day 90 post procedure. As shown in Figure 7 and * The number at risk, number censored, and number of events are included per Kaplan-Meier analysis methods: at risk equals the number of patients at risk up to months 3, 6, 9, and 12; number censored equals the number of patients censored up to months 3, 6, 9, and 12; number of events equals the number of events through the end of the intervals.

Figure 7: Freedom from Primary Effectiveness Failure at 12 Months by Class I/III AAD use on day 90 Post Procedure

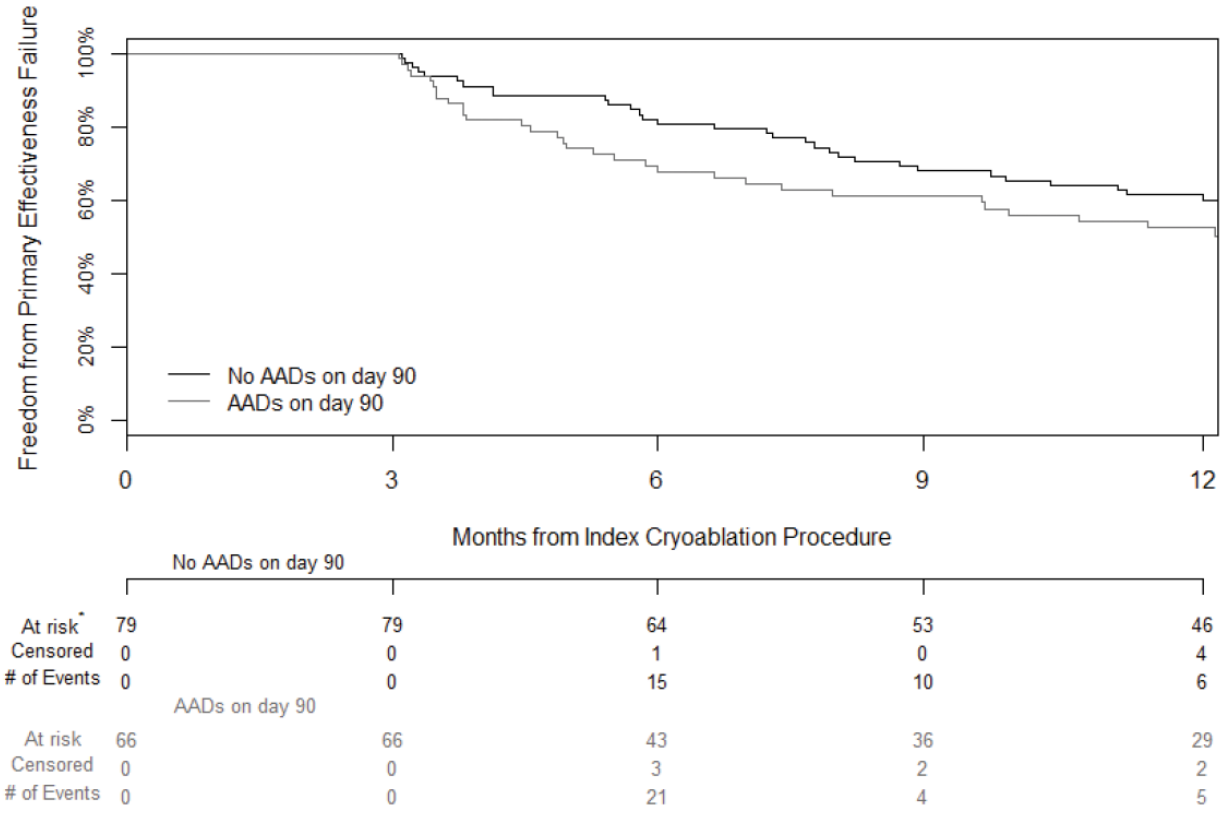


Table 17, the primary effectiveness success rate in subjects who were taking a Class I or III AAD on day 90 post-index ablation was approximately 10% lower than that in those who were not.

* The number at risk, number censored, and number of events are included per Kaplan-Meier analysis methods: at risk equals the number of patients at risk up to months 3, 6, 9, and 12; number censored equals the number of patients censored up to months 3, 6, 9, and 12; number of events equals the number of events through the end of the intervals.

Table 17: Primary Effectiveness Success at 12 Months by Class I/III AAD use on Day 90 Post Procedure

Subgroup	N	Kaplan-Meier Rate
On AAD on Day 90	66	50.4%
Off AAD on Day 90	79	60.2%

3. **Improvement in Quality of Life**

The secondary endpoint measurements of quality of life are summarized in Table 18. The AFEQT questionnaire and SF-12 questionnaire were used to evaluate changes in quality of life post ablation.

The AFEQT questionnaire is an AF specific health-related quality of life questionnaire to assess the impact of AF on a patient's life. The summary score ranges from 0 – 100, with 0 corresponding to complete disability and 100 corresponding to no disability. Two previous studies suggested 5 points (Holmes, et al., 2019) and 19 points (Dorian, et al., 2013), respectively, as a threshold for clinically important difference for the AFEQT summary score.

The SF-12 questionnaire is a health-related quality of life questionnaire to evaluate the patient's mental and physical performance. Physical and mental health component summary scores were calculated using responses to 12 questions with a response range from 0 – 100, with 0 corresponding to lowest level of health and 100 indicating highest level of health. A three-to-five point increase in physical component summary score or mental component summary score was considered clinically important in a previous AF ablation study (Essebag, et al., 2020).

According to the protocol, if both the primary safety endpoint and primary effectiveness endpoints are met, these three secondary endpoints can be tested to compare the change of scores from baseline to 12 months with 0. One-sample t-test was pre-specified for each hypothesis test with one-sided significance level of 0.025. A Hommel multiple testing procedure was utilized to maintain the overall Type I error rate at one-sided 0.025 for the three quality of life hypotheses tested.

As showed in Table 18, all three secondary endpoints statistically significantly improved from baseline to 12 months follow-up. Since the largest p-value among three tests was < 0.025 (all p-values were <0.0001), all three quality of life endpoints were met.

Table 18: Qualify of Life Endpoints Results

Quality of Life Measurement	N	Baseline Score (Mean ± SD)	12 Months Follow-up (Mean ± SD)	Difference (95% CI)	p-value[i]
AFEQT	126	62.4 ± 20.8	89.1 ± 14.3	26.7 (22.7 - 30.8)	<0.0001
SF-12 Physical Component	127	44.0 ± 9.5	49.1 ± 8.3	5.2 (3.7 - 6.7)	<0.0001
SF-12 Mental Component	127	49.1 ± 10.1	54.2 ± 7.7	5.1 (3.2 - 6.9)	<0.0001

[i] t-test assessing baseline to 12-month change

Post-hoc analyses were performed to explore changes in AFEQT summary score and SF-12 physical and mental summary scores from baseline through 6 months and 12 months post ablation. As indicated in the Table 19 and Table 20, all three summary scores increased at 6 months and the improvements persisted at 12 months post ablation. Of note, since the post-hoc analyses included all available data, the number of subjects included for the baseline scores was slightly different from that included in Table 18. However, the results were consistent with the paired analysis shown in Table 18.

Table 19: AFEQT Summary Score by Visit

Visit	N	Mean ± SD
Baseline	148	61.1 ± 20.8
6 Months	130	87.8 ± 15.4
12 Months	126	89.1 ± 14.3

Table 20: SF-12 Summary Scores by Visit

Visit	N	SF-12 Physical Component Mean ± SD	SF-12 Mental Component Mean ± SD
Baseline	148	43.5 ± 10.5	48.5 ± 10.1
6 Months	131	48.9 ± 8.8	53.9 ± 9.0
12 Months	128	48.9 ± 8.6	54.2 ± 7.7

4. Procedure Measurements

Table 21 summarizes the procedure data for the 150 index procedures. Of note, total procedure time and left atrial dwell time calculations ended at the time of last sheath removal.

Table 21: Procedure Measurements

	Subjects with Index Procedures (N = 150)
Total Procedure Time (mins)	
Mean ± Standard Deviation	122 ± 47
Median	113
25th Percentile - 75th Percentile	88 - 146
Minimum - Maximum	48 - 357
Not reported (%)	1 (1%)
Left Atrial Dwell Time (mins)	
Mean ± Standard Deviation	103 ± 42
Median	96
25th Percentile - 75th Percentile	75 - 117
Minimum - Maximum	43 - 346
Not reported (%)	1 (1%)
Study Device Left Atrial Dwell Time (mins)	
Mean ± Standard Deviation	67 ± 25
Median	65
25th Percentile - 75th Percentile	49 - 81
Minimum - Maximum	16 - 164
Not reported (%)	1 (1%)
Total Fluoroscopy Time (mins)	
Mean ± Standard Deviation	17.0 ± 13.1
Median	14.7
25th Percentile - 75th Percentile	6.8 - 23.9
Minimum - Maximum	0.1 - 65.9
Not reported (%)	3 (2.0%)
Application Duration (mins)	
Mean ± Standard Deviation	24.9 ± 8.0
Median	24.0
25th Percentile - 75th Percentile	19.2 - 28.5
Minimum - Maximum	13.0 - 51.8
Not reported (%)	(0.0%)

5. Atrial Arrythmias Present and/or Treated

Atrial arrhythmias in addition to AF present and/or treated during the index cryoablation procedure are summarized in Table 22. The most frequent additional atrial arrhythmia was cavo-tricuspid isthmus (CTI)-dependent atrial flutter.

Table 22: Arrhythmias in addition to AF present and/or treated during the index cryoablation procedure

Arrhythmia	Number of subjects with arrhythmia present N (%) [95% CI]	Number of subjects with arrhythmia treated N (%)
Atrioventricular nodal reentrant tachycardia (AVNRT)	1 (0.7%) [0.0 - 3.7%]	1 (100.0%)
Cavo-tricuspid isthmus (CTI)-dependent Atrial Flutter	40 (26.7%) [19.8 - 34.5%]	40 (100.0%)
Other	4 (2.7%) [0.7 - 6.7%]	2[i] (50.0%)

[i] Both were right atrial tachycardia

6. Subgroup Analyses

Subgroup analyses were performed to assess the consistency of primary effectiveness outcome across the following preoperative characteristics: age, sex and race (Table 23).

There was no significant difference in the primary effectiveness outcome between predefined sex and race subgroups (all p>0.15).

Per study protocol, subgroup analysis on age was performed by dividing age into quartiles. The estimated primary effectiveness rate in age quartile of 66-71 years of age was much lower than the rates in other age quartiles, and this difference was statistically significant at an alpha level of 0.15 (p-value=0.133<0.15). This difference was likely caused by chance because there is no known biological basis for a lower success rate in this specific age group (66-71 years of age).

Table 23: Subgroup Analysis of Primary Effectiveness Endpoint

Covariate	Subgroup	N (%)	12-Month Primary Effectiveness Rate[i]	p-value[ii]
	Quartile 1 38 – 58	37 (24.7%)	59.5%	0.133

Predefined Subgroup: Age Quartile	Quartile 2 59 – 65	32 (21.3%)	61.6%	
	Quartile 3 66 – 71	43 (28.7%)	36.1%	
	Quartile 4 72 – 88	38 (25.3%)	54.2%	
Sex	Female	45 (30.0%)	53.3%	0.894
	Male	105 (70.0%)	51.4%	
Subgroup: Non-Hispanic White	Not reported	5 (3.3%)	40.0%	0.973
	No	7 (4.7%)	57.1%	
	Yes	138 (92.0%)	52.3%	

[i] Kaplan-Meier 12-month estimate
[ii] Log-rank test

7. Pediatric Extrapolation

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

J. 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 75 investigators of which 1 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 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 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 Persistent AF study demonstrated that the study catheters are effective for the treatment of symptomatic drug refractory recurrent persistent AF of less than 6 months duration.

The pivotal study met its primary effectiveness endpoint. Specifically, the rate of primary effectiveness success (defined as freedom from atrial tachyarrhythmia recurrence at one year post procedure off Class I and III AAD or on a previously ineffective Class I or III AAD) was estimated to be 52.1% (95% CI: 43.6%-59.9%). The 95% lower confidence bound of the primary effectiveness success rate exceeded the pre-defined performance goal of 40% derived from the minimum chronic acceptable success rate recommended in the Heart Rhythm Society Expert Consensus Statement on Catheter and Surgical Ablation of AF and published literature of persistent AF ablation using a cryoballoon catheter. Freedom from atrial tachyarrhythmia recurrence has been widely used in clinical trials 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 AF ablation (Calkins, et al., 2017).

The pivotal study also showed that ablation was associated with an improvement in quality of life scores. Although a placebo effect cannot be excluded in this unblinded single-arm study, the finding of sustained improvement in quality of life scores at one year post procedure and the magnitude of changes in quality of life sores were supportive of a quality of life treatment benefit in this group of symptomatic patients whose quality of life was impaired by AF.

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

1. The study did not include an active control arm. It is uncertain from the study results how catheter ablation using the study catheters compares with medical management or other devices in terms of treatment benefits such as reducing arrhythmia recurrence and improving quality of life in this patient population. Nevertheless, data from a previous controlled study suggested a much lower success rate with medical management in patients with drug refractory persistent AF (Hummel, et al., 2014). The primary effectiveness success rate reported in the pivotal study was largely in line with previous studies of catheter ablation of persistent AF that supported the professional society guideline recommendation for catheter ablation as a rhythm control strategy for patients with symptomatic drug refractory persistent AF, factoring in differences in effectiveness success definition and rhythm surveillance monitoring intensity (January, et al., 2014).

2. Fifteen (15) of the 150 treated subjects (10%) exited the study without completing the 12-month visit and had not experienced a primary effective failure event prior to study exit. This incomplete follow-up resulted in uncertainties in estimating treatment success, even though the sensitivity analyses were considered supportive of the primary effectiveness endpoint conclusion.

3. The study did not standardize a protocol for AAD withdrawal post ablation. A significant proportion of subjects free of arrhythmia recurrence were taking a previously ineffective Class I or III AAD during the effectiveness evaluation period. This precluded an accurate estimate of the treatment benefits purely from ablation using the study catheters. It is likely that the effectiveness results to some extent reflected the outcomes of a treatment strategy that combines PV isolation using the study catheters and AAD therapy using a previously ineffective Class I or III AAD.

4. The study was unblinded and did not have a sham control arm. It is known that catheter ablation of AF is subject to placebo effects. Therefore, it is uncertain how much improvement in quality of life scores was attributable to catheter ablation using the study catheters vs. a placebo effect.

B. Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above. One of the 150 treated subjects in the STOP AF Persistent AF study had a primary safety event which was a cardiac perforation related to a repeat RF ablation procedure, resulting in a primary safety event rate of 0.7% (95% CI: 0.1% - 4.9%). Since the 95% upper confidence bound of the primary safety event rate was less than the pre-defined safety performance goal of 13%, the study met its primary safety endpoint. There was no device or procedure-related death, cardiac tamponade, myocardial infarction, stroke, severe pulmonary stenosis, or atrio-esophageal fistula.

The results of the pivotal study showed that the incidence of complications associated with the study device or cryoablation procedure was low. The frequency, severity and nature of the procedural complications observed in the study were well in line with the published literature of cryoballoon ablation of AF.

A total of seven (7) study device and/or cryoablation procedure-related serious adverse events were reported in 6 subjects (4%). Phrenic nerve injury, a common complication associated with cryoballoon ablation of AF occurred in three (3) subjects (2%). None of the phrenic nerve injury events was adjudicated as a serious adverse event. Two of the three phrenic nerve injury events resolved prior to discharge and the third one persisted for at least 6 months and resolved prior to study exit.

Other adverse events reported in the study did not raise significant safety concerns either about the study device/procedure or concomitant medical management including AAD therapy a significant proportion of the study subjects received during follow-up.

C. Benefit-Risk Determination

Although there were uncertainties in the treatment benefits, the overall effectiveness and safety data reported in the STOP Persistent AF study supports the notion that the probable benefits outweigh the probable risks when the Arctic Front Advance and Freezor *MAX* Cardiac CryoAblation Catheters are used for the treatment of symptomatic drug refractory recurrent persistent AF of less than 6 months duration.

1. Patient Perspectives

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

D. Overall Conclusions

The results of the STOP Persistent AF study provided valid scientific evidence in support of effectiveness and safety of the study device for the treatment of symptomatic drug refractory recurrent persistent AF of less than 6 months duration.

This prospective multi-center non-randomized single-arm pivotal study was adequately powered to compare the primary effectiveness and safety endpoints to pre-defined performance goals. A total of 150 subjects with symptomatic drug refractory persistent AF of less than 6 months duration underwent a PV isolation procedure using the study catheters. Acute PV isolation was achieved in all 150 subjects. Repeat ablations were performed in 4.7% of the subjects. The primary effectiveness success rate was estimated to be 52.1% (95% CI: 43.6%-59.9%) at 12 months post procedure, meeting the pre-defined performance goal. The primary effectiveness success results

supported the treatment benefit of reducing atrial tachyarrhythmia recurrence. The study also showed that ablation was associated with an improvement in quality of life scores. Although a placebo effect cannot be excluded in this unblinded single-arm study, the finding of sustained improvement in quality of life scores at one year post procedure and the magnitude of changes in quality of life scores were supportive of a quality of life benefit offered by the study device in symptomatic persistent AF patients whose quality of life was impaired by AF.

One of the 150 treated subjects had a primary safety event which was a cardiac perforation related to a repeat RF ablation procedure, resulting in a primary safety event rate of 0.7% (95% CI: 0.1% - 4.9%). There was no study device or cryoablation procedure-related primary safety event. The frequency, severity and nature of the procedural complications observed in the study were well in line with the published literature of cryoballoon ablation for AF that showed a low risk of procedural complications.

Taken together, the results of the STOP Persistent AF 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 symptomatic drug refractory recurrent persistent AF of less than 6 months duration.

XIII. CDRH DECISION

CDRH issued an approval order on June 23, 2020.

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.

XV. REFERENCES

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