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1. Clinical Summary

Study Title:	STOP AF First
Number of Centers:	24 sites in the United States
Number of Subjects:	225 subjects enrolled in the study and 210 subjects were randomized 1:1 to either AAD therapy (control arm) or cryoablation (treatment arm)

2. Study Purpose

The purpose of the STOP AF First study was to establish a reasonable assurance of safety and effectiveness of pulmonary vein isolation with the Arctic Front Advance™ Cardiac CryoAblation Catheter for antiarrhythmic drug (AAD) naïve patients with recurrent symptomatic paroxysmal atrial fibrillation (AF).

3. Study Design

The STOP AF First study was a prospective, multi-center, randomized, controlled, unblinded pivotal study. The study enrolled adult patients (age 18-80) with recurrent symptomatic paroxysmal AF who had not previously received rhythm control therapy using class I or III antiarrhythmic drugs (AADs) at 24 sites in the United States. The first subject enrollment occurred in June 2017. There were 225 subjects enrolled in the study and 210 subjects were randomized 1:1 to either AAD therapy (control arm) or cryoablation (treatment arm). Subjects in the treatment arm underwent a pulmonary vein isolation (PVI) ablation procedure with the Arctic Front Advance™ Cardiac Cryoablation Catheter. Subjects in the control arm were treated with a class I or III AAD as prescribed by the study investigator. Crossover from AAD therapy to cryoablation was permitted only when a subject in the control arm was deemed a treatment failure.

An independent core lab was utilized to review and adjudicate all 24-hour ambulatory ECG monitoring, patient-activated ambulatory monitoring, and 12-lead ECG recordings. Additionally, a contract research organization was utilized for site monitoring activities, Clinical Events Committee (CEC) management,

clinical safety management and potential complaint reporting, database development, data review, and SAS programming.

An independent CEC reviewed all adverse events and deaths (if any had occurred) and provided a final adjudication of all device-related and procedure-related events for the primary safety endpoint evaluation.

3.1. Cryoablation (Treatment Arm)

Subjects allocated to the treatment arm underwent pulmonary vein isolation within 30 days of randomization. A second-generation cryoballoon (Arctic Front Advance Cardiac Cryoablation Catheter, Medtronic) was inserted using a trans-septal puncture and an over-the-wire delivery technique. Two cryoballoon applications, each three minutes in duration, were recommended for each pulmonary vein. Acute pulmonary vein isolation was confirmed by entrance block (and where assessable, exit block). Continuous phrenic nerve pacing with abdominal palpitation was performed for all right-sided pulmonary vein cryoablations. Electrical or pharmacological cardioversion was attempted following pulmonary vein isolation if sinus rhythm was not restored in patients who presented to the electrophysiology lab in AF. Class I and III antiarrhythmic drugs (excluding amiodarone) were permitted for up to 80 days post-procedure to allow complete washout by the end of the 90-day blanking period and to decrease the risk of protocol violation. Anticoagulation was administered for at least two months post ablation.

3.2. Drug Therapy (Control Arm)

A class I or III AAD was initiated within 30 days of randomization with a target of starting therapy within 14 days in subjects allocated to the control arm. 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 were consulted for AAD prescriptions. Modifications to AADs (type or dosage increase) were allowed for 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. Use of beta blockers and/or calcium channel blockers was permitted in both study arms.

3.3. 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

3.4. Study Follow-Up

All randomized subjects were followed from the time of consent through 12-months post-treatment initiation. The visit schedule and data collection requirements are summarized in the table below.

Table 1: 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
Trans-thoracic Echocardiogram (TTE)[2]	X							
Trans-esophageal 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 was detected during the procedure, the subject was 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 prior 6 months from consent date.

[3] TEE was required in all subjects who presented to the ablation procedure in atrial fibrillation 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. TEE was required if subjects had a CHA2DS2-VASc ≥2 and presented to the procedure with a sub-therapeutic INR (<2.0) or if the subject had a significant interruption of a novel oral anticoagulant (NOAC). A significant interruption of NOAC was defined as any missed dose within 21 days prior to the ablation procedure.

[4] Subjects were required to submit ECG transmissions weekly and whenever symptoms occurred after the AAD optimization/post-ablation blanking periods through 12-month follow-up.

In summary, follow up visits occurred at 1, 3, 6, and 12 months with a hospital discharge visit for the cryoablation subjects. Arrhythmia monitoring included a 12-lead ECG at baseline, 1, 3, 6, and 12 months, weekly and symptom-driven patient-activated ambulatory monitoring during months 3 through 12, and 24-hour ambulatory monitoring at 6 and 12 months. Subjects were exited from the study at the 12-month follow-up visit. The last subject visit occurred in June 2020.

4. Study Endpoints

4.1. Primary Endpoints

4.1.1. 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 components:

- Acute procedural failure (treatment arm only).
- Documented atrial fibrillation (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 be 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: π cryo $\neq$ π AAD,

where πcryo 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.

4.1.2. Primary Safety Endpoint

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

- Transient ischemic attack (TIA) within 7 days of the ablation procedure.
- Cerebrovascular accident within 7 days of the ablation procedure.
- Major bleeding that required transfusion or results in a 20% or greater fall in hematocrit (HCT) within 7 days of the ablation procedure.
- Development of a significant pericardial effusion within 30 days of the ablation procedure. A significant pericardial effusion is one that results in hemodynamic compromise, requires elective or urgent pericardiocentesis, or results in a 1-cm or more pericardial effusion as documented by echocardiography.
- 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 (MI) within 7 days of the ablation procedure.

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

Hypothesis

To demonstrate an acceptable safety profile of the cryoablation procedure in the study population, the primary safety endpoint was compared against a performance goal of 12%, which was 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.

4.2. Secondary Endpoints

Secondary endpoints included:

- Change in the composite score from the Atrial Fibrillation Effect on QualiTy of life (AFEQT) questionnaire taken at the baseline and 12-month visits in the cryoablation arm;
- Change in the composite score for the European Quality of Life–5 Dimensions (EQ-5D) questionnaire taken at baseline and 12-month visits in the cryoablation arm.
- 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).

Analysis Methods

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

4.3. Ancillary Endpoints

4.3.1. All reported Adverse Events.

All adverse events were summarized.

4.3.2. Composite Adverse Event Rate over 12 Months.

The following composite adverse event list was used and applied to both treatment arms:

- Cerebrovascular accident
- TIA
- Major bleeding that requires 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
- MI
- PNI unresolved at 12 months
- Atrio-esophageal fistula
- Cardiovascular deaths
- 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.

4.3.3. Acute Procedural Failure.

Acute procedural failure was 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.

Acute procedural success is the opposite of acute procedural failure.

4.3.4. Cryoablation Procedure Parameters.

Total procedural time, left atrial dwell time, fluoroscopy time, and application duration were summarized.

4.3.5. Atrial Arrhythmias Present During the Index Ablation Procedure and their Treatment.

All atrial arrhythmias present and/or treated during the index cryoablation procedure were summarized.

4.4. 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.

4.5. Study Success Criteria

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

5. Study Subjects

5.1. Study Populations for Analysis

The **Full Analysis Set** consisted of all enrolled subjects. The full analysis set was used for AE reporting in general and summary of all adverse events. There were 225 subjects in the Full Analysis Set.

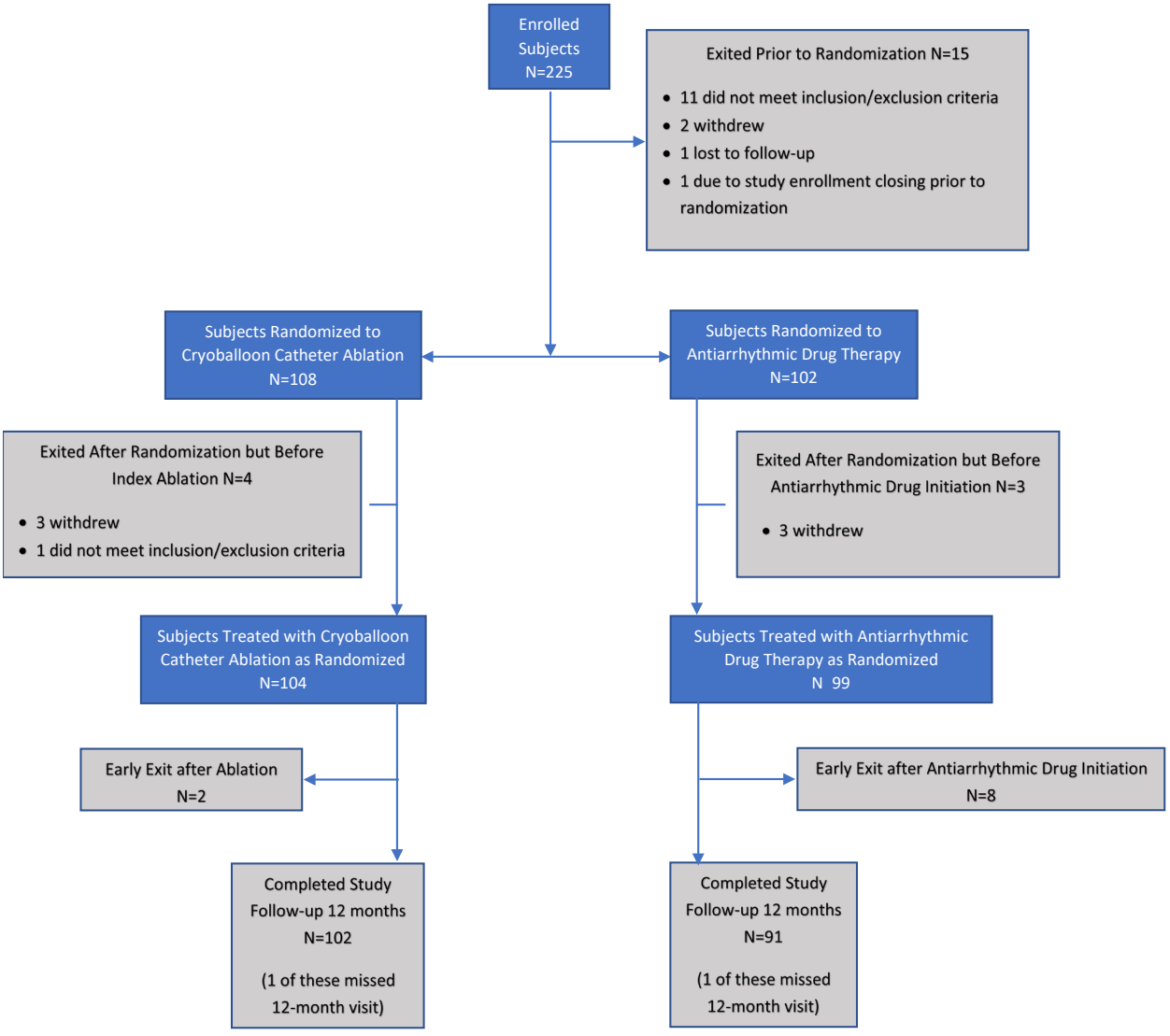
The **Modified Intention-to-Treat** (mITT) cohort was the subset of subjects who maintained informed consent at least until the initiation of a cryoablation procedure or commencement of AAD treatment. For analysis in this group of subjects, the standard intention-to-treat protocol applied immediately upon first receipt of a treatment (regardless of whether the assigned treatment was actually received). There were 104 cryoablation subjects and 99 AAD subjects in the mITT cohort.

5.2. Subject Accountability

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. A total of 225 subjects were enrolled of which 210 were randomized at 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



5.3. Subject Baseline Characteristics and Demographics

The following tables summarize demographics and clinical characteristics at baseline for the mITT cohort of subjects. The baseline characteristics were similar between the two study arms.

Table 2: 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 3: 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	

Subject Characteristics	Cryoablation (n = 104)	AAD Therapy (n = 99)	Total (n = 203)	P-value*
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)				
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
Atrial Arrhythmia History				
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
Baseline Quality of Life Scores				
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	

Subject Characteristics	Cryoablation (n = 104)	AAD Therapy (n = 99)	Total (n = 203)	P-value*
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
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.

6. Results

6.1. Treatment Characteristics

6.1.1. 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.

Table 4: 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%)
Other: PV tachycardia	1 (1.0%)	0 (0.0%)
Other: 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 5: 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

6.1.2. AAD Therapy in the Control Arm

All 99 mITT control subjects received a class I or III 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 6: 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 I or III 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).

6.1.3. 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 6.3.4.

6.1.4. Post-Ablation AAD Therapy in the Cryoablation Arm

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

Of the 104 mITT cryoablation subjects, 9 received AAD therapy during the 90-day blanking period. All these 9 subjects remained in the study through 12 months post-ablation, with 4 failing the primary effectiveness endpoint. Three of the 4 failures were due to AAD use after the 90-day post-ablation blanking period. None of these 3 subjects had documented atrial tachyarrhythmia after the blanking period.

6.1.5. 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 7: 24-Hour Ambulatory 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 8: 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%)

	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
Total	N/A	309	279 (90.3%)	N/A	282	250 (88.7%)

6.2. Safety Results

6.2.1. Primary Safety Endpoint Results

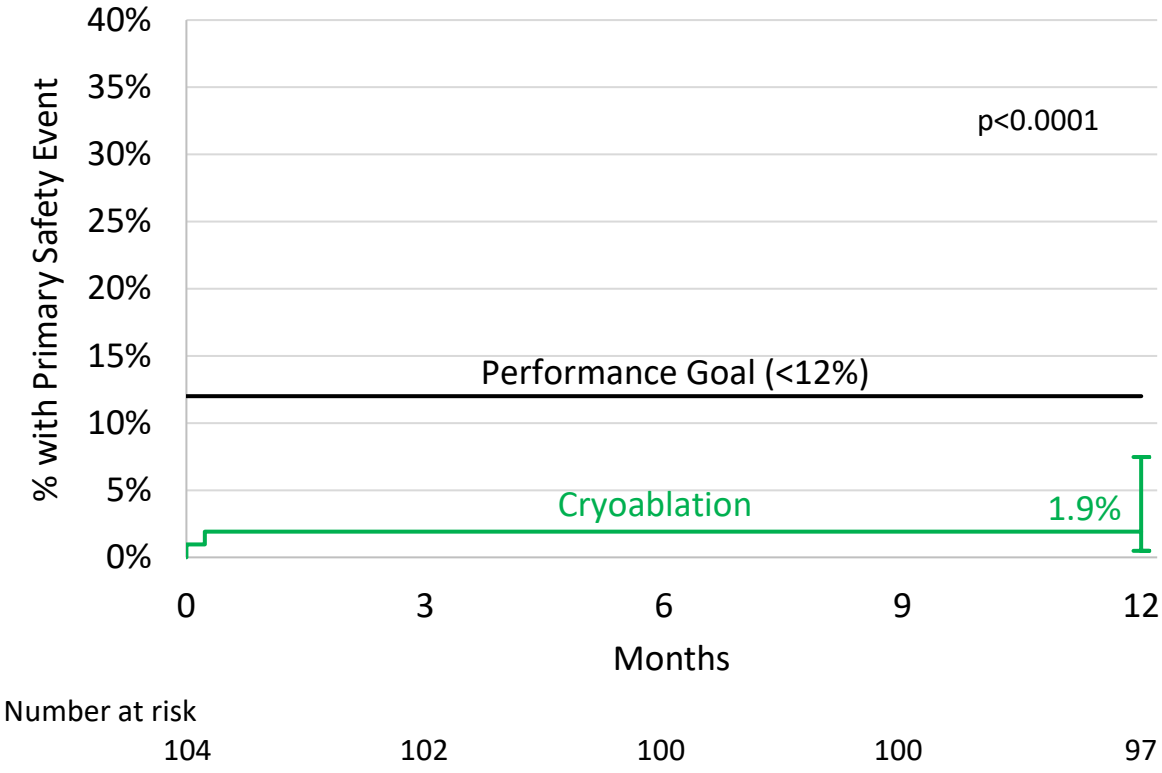
Of the 104 mITT cryoablation subjects two subjects reported a primary safety event through 12 months of follow-up. The two primary safety events were the following:

- 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.

The figure below displays the Kaplan-Meier curve for the primary safety event rate through 12-months post-procedure. The rate of primary safety events 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 at 12 Months



6.2.2. 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 9: 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%)

Adverse Event Classifications	Cryoablation (n=104)	AAD Therapy (n=99)
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)

6.2.3. 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 10: 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, 6 SAEs (occurred in 5/104 or 4.8% of cryoablation subjects) were adjudicated as device or cryoablation procedure-related, and 13 were related to the cardiovascular system. Among the 16 SAEs in the control arm, 1 SAE (occurred in 1/99 or 1% of control subjects) was adjudicated as related to AAD, 3 were adjudicated as device or cryoablation procedure-related (due to crossover ablation), and 9 were related to the cardiovascular system.

6.2.4. Device or Cryoablation Procedure-Related SAEs

A total of 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 9 device or cryoablation procedure-related SAEs.

Table 11: 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%)

Serious Adverse Events	Number of Events (Number of Subjects, % of Subjects) Total subjects: N=138
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%)**

6.2.5. 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 I or III 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.

6.2.6. Phrenic Nerve Palsy

Phrenic nerve palsy, a common complication associated with cryoballoon ablation of AF occurred in 2 (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.

6.2.7. 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 12: 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%)

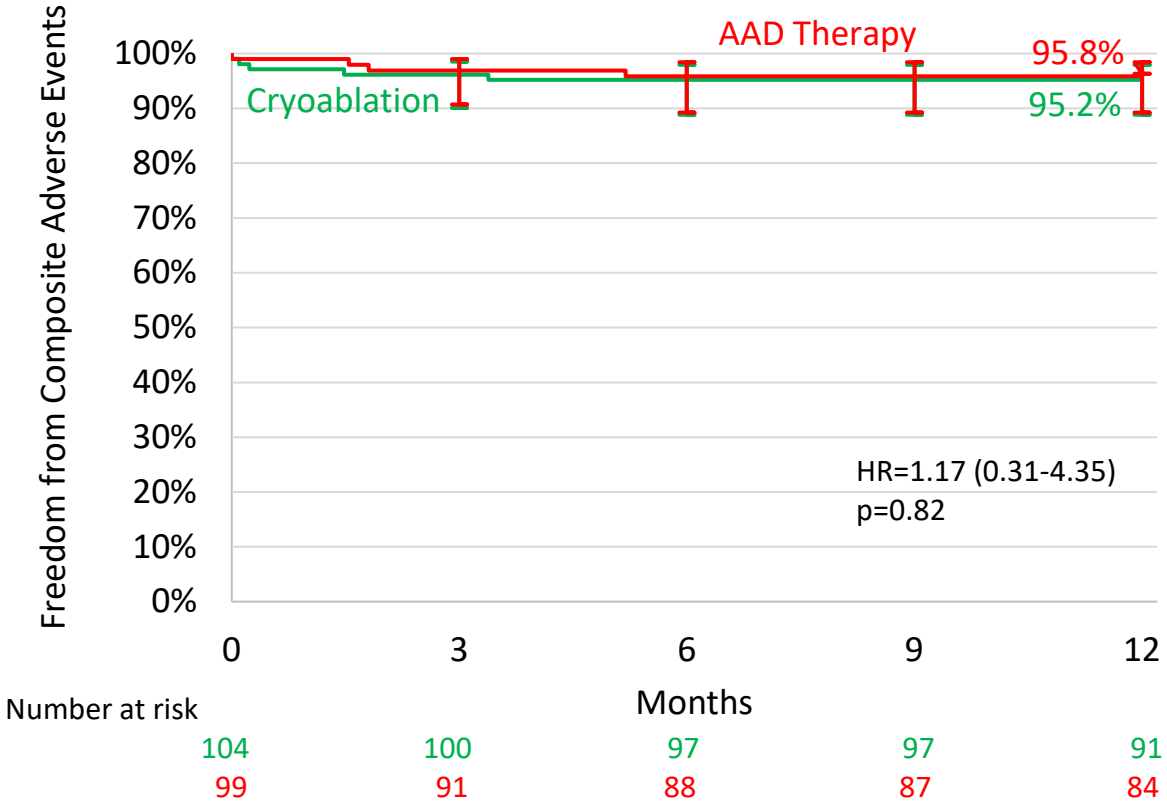
Adverse Event	Cryoablation (n=104)	AAD Therapy (n=99)
Cardiac perforation, tamponade, or pericardial effusion	1 (1.0%)	1 (1.0%)
Symptomatic PV stenosis within 12 months; accompanied by one of the following: 50%-70% reduction in diameter of the pulmonary vein, with symptoms not explained by other conditions; 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



6.3. Effectiveness Results

6.3.1. Summary of Primary Effectiveness Endpoint Analysis

Of the 203 subjects who were eligible for primary effectiveness analysis (mITT cohort), 27 of 104 cryoablation and 51 of 99 control subjects reported at least one primary effectiveness failure event through 12 months of follow-up. The distribution of first primary effectiveness events is shown in the table below.

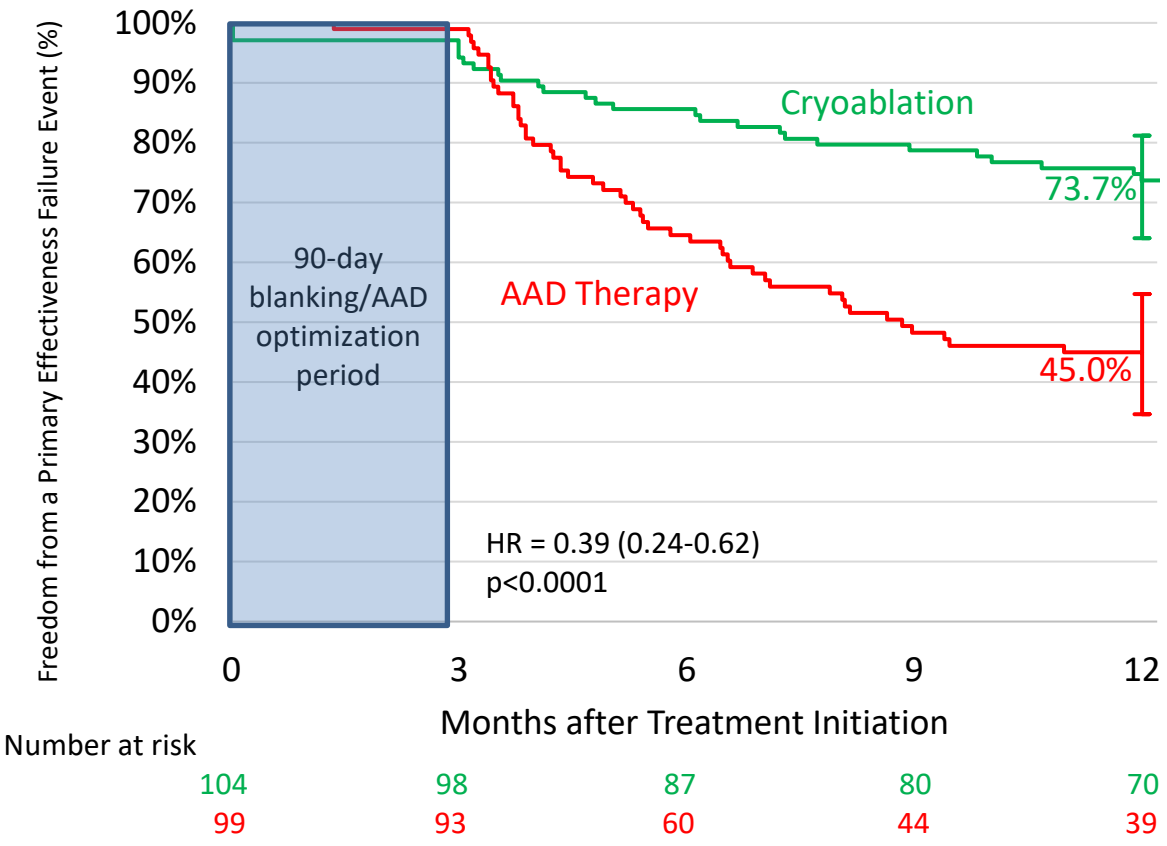
Table 13: First Primary Effectiveness Failure Events

	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

The figure below displays the Kaplan-Meier curve for freedom from primary effectiveness failure through 12-months post-treatment initiation. The 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 in the control arm, with a log-rank test p-value of <0.0001.

Figure 4: Freedom from Primary Effectiveness Failure at 12 Months



6.3.2. Primary Effectiveness endpoint results in the Cryoablation Arm

Among the 104 cryoablation subjects included in the primary effectiveness analysis, 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.

6.3.3. Primary Effectiveness endpoint results in the Control Arm

Among the 99 control subjects included in the primary effectiveness analysis, 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 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.

6.3.4. 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 I or III 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, the 2014 AHA/ACC/HRS Guideline for the Management of Patients with AF, Use of Flecainide for the Treatment of AF (Debra Echt and Jeremy Ruskin. Am J Cardio 2020), as well as FDA drug labels for Tambocor (flecainide acetate) and Betapace AF (sotalol HCl). 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

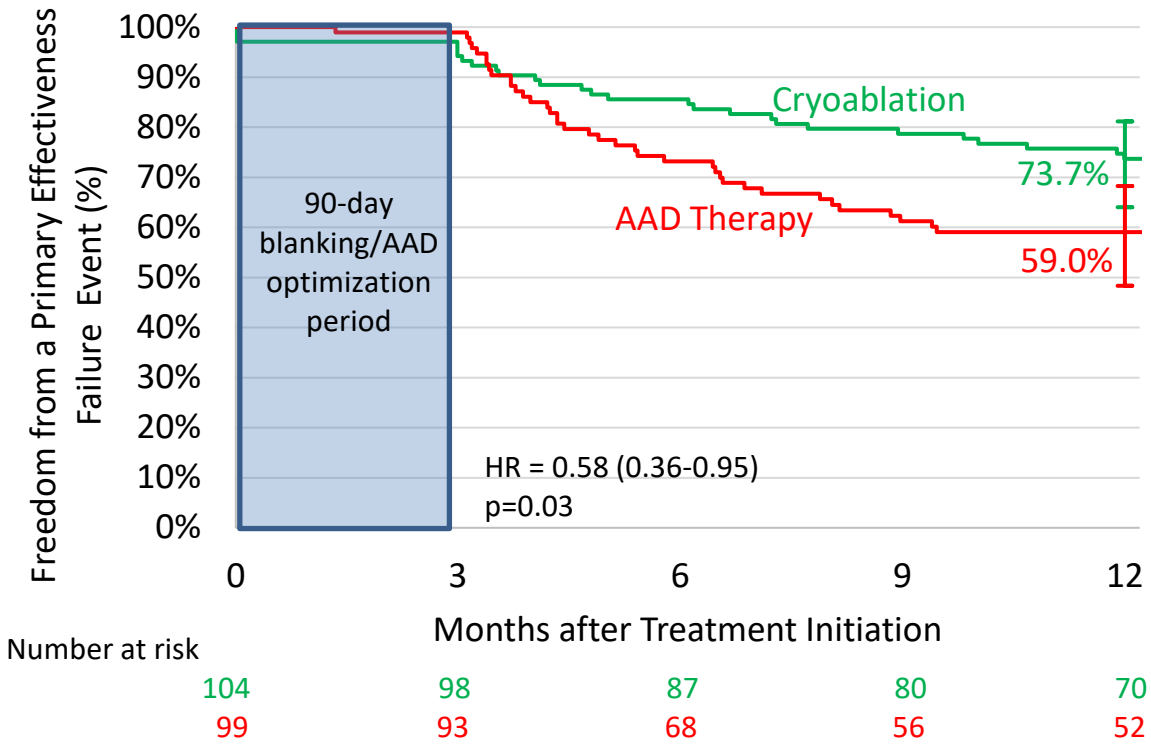
the absence of documented side effects during the AAD optimization period, or underwent crossover ablation without ECG-documented arrhythmia recurrence or documented AAD side effects.

6.3.5. 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 I or III 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 I or III 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



6.3.6. 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 I or III 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 I or III 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.

6.4. Additional Results

6.4.1. Quality of Life Results

Atrial Fibrillation Effect on Quality-of-Life (AFEQT)

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 14: 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

Euroqol EQ-5D

The Euroqol EQ-5D questionnaire (which consists of a 5-question survey and a visual analog scale [VAS]) 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 15: 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

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. Am Heart J. 2013;166(2):381-387 e388.) 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 16: 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)

		Cryoablation (n=104)	AAD Therapy (n=99)
	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.

6.4.2. Cardiovascular Healthcare Utilization Results

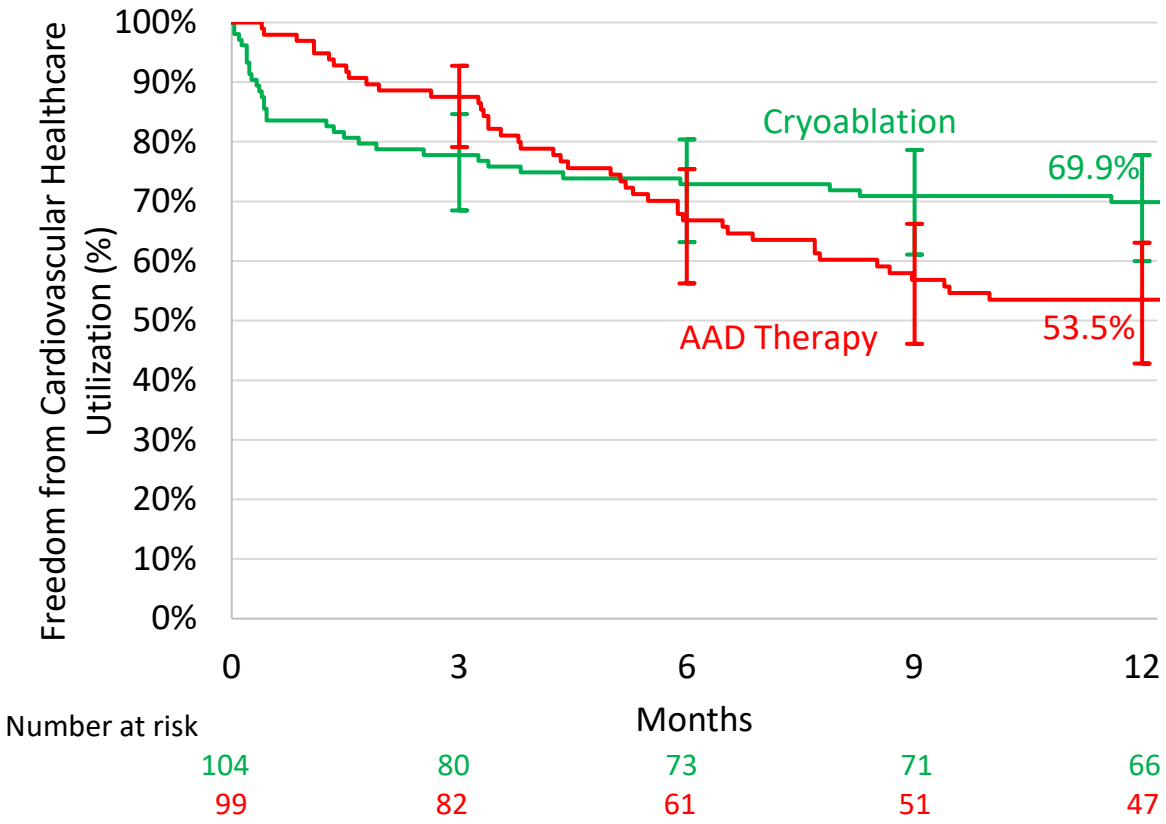
Of the 203 subjects who were eligible for analysis (mITT), 31 of 104 cryoablation (29.8%) and 43 of 99 AAD subjects (43.4%) reported at least one cardiovascular-related healthcare utilization through 12 months of follow-up. The distribution of healthcare utilizations is shown in the table below.

Table 17: 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

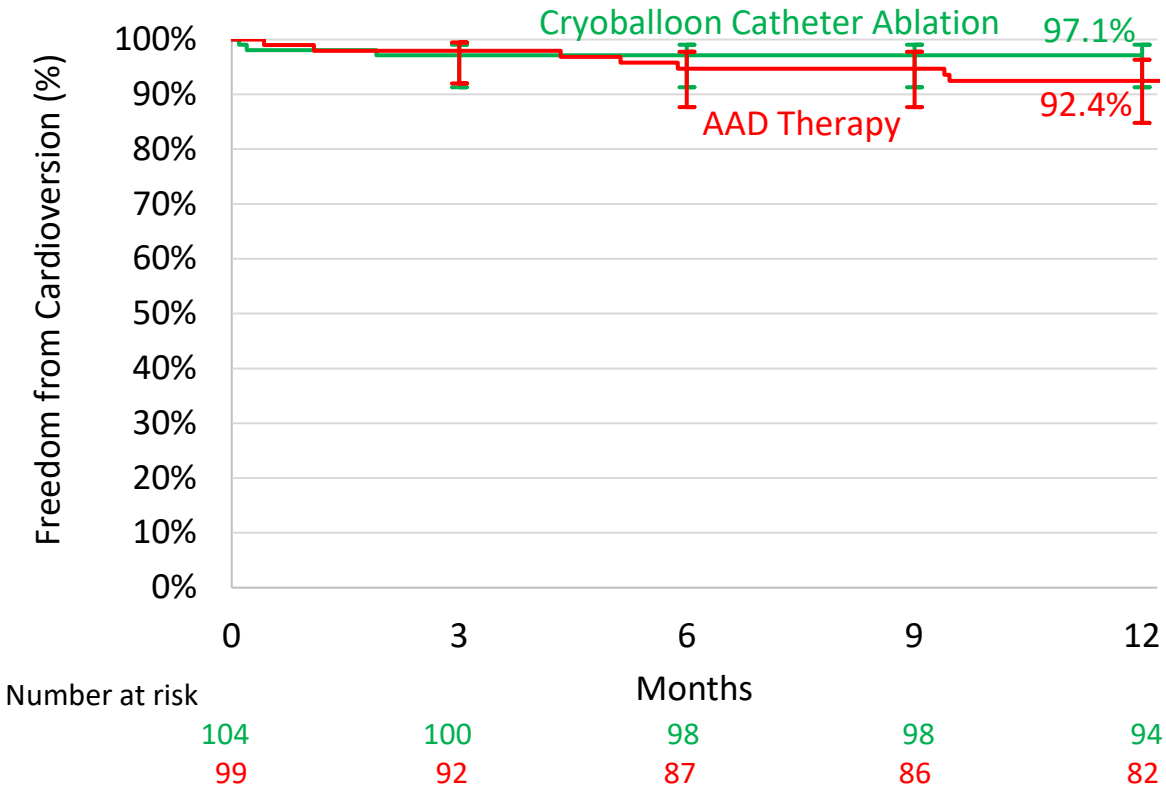


A review of limited data collected on the primary reason or diagnosis for cardiovascular HCU suggested that the difference in cardiovascular-related hospitalization (13 times in the cryoablation arm vs 32 times in the control arm) was largely driven by crossover ablations and the difference in cardiovascular-related 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.

6.4.3. Cardioversions

Of the 203 subjects who were eligible for analysis (mITT), 3 (of 104) cryoablation subjects had a total of 5 cardioversions (all electrical cardioversions) and 7 (of 99) AAD 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



6.5. 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 18: 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%)

7. Study Conclusions

In conclusion, 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 antiarrhythmic drug therapy as an initial rhythm control strategy.