

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Cardiac Cryoablation Catheter

Device Trade Name: Freezor[®] *Xtra* Cardiac CryoAblation Catheter

Applicant's Name and Address: Medtronic Inc.
8200 Coral Sea Street
Minneapolis, MN 55112

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P020045/S073

Date of FDA Notice of Approval: 08/31/2016

Expedited: Not applicable

The original PMA (P020045) was approved on April 17, 2003 and is indicated for the cryoablation of the conducting tissues of the heart in the treatment of patients with atrioventricular nodal reentrant tachycardia (AVNRT). 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 Freezor *Xtra* Cardiac Cryoablation Catheter.

II. INDICATIONS FOR USE

The Freezor *Xtra* Cardiac CryoAblation Catheter, CryoConsole system, and related accessories are indicated for the cryoablation of the conducting tissues of the heart in the treatment of patients with atrioventricular nodal reentrant tachycardia (AVNRT). The Freezor *Xtra* catheter is also intended for minimally invasive cardiac surgery procedures, including surgical treatment of cardiac arrhythmias. The Freezor *Xtra* catheter freezes the target tissue and blocks the electrical conduction by creating an inflammatory response or cryonecrosis.

III. **CONTRAINDICATIONS**

The Freezor *Xtra* 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)

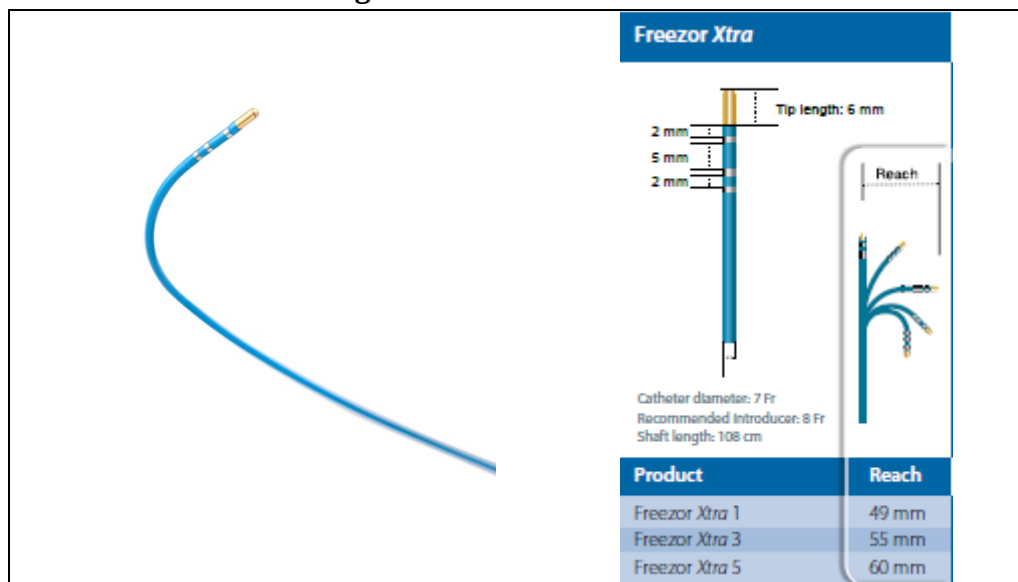
IV. **WARNINGS AND PRECAUTIONS**

The warnings and precautions can be found in the Freezor *Xtra* Cardiac CryoAblation Catheter labeling.

V. **DEVICE DESCRIPTION**

The Freezor *Xtra* Cardiac CryoAblation Catheter is a single use, disposable, 7F steerable deflectable catheter. The distal section is deflectable by a control level on the handle. There are three different deflection lengths or “reaches” available, as depicted in **Figure 1**. The catheter has a cooling segment (tip) 6mm in length at the distal end and 3 closely spaced electrode bands. The electrode tip and the 3 electrode bands can capture ECG signals. The tip can also read temperature. When liquid refrigerant is introduced into the Freezor *Xtra* Catheter, the catheter tip is cooled below freezing, resulting in tissue freezing at the point of contact and subsequent tissue necrosis.

Figure 1: Freezor *Xtra* Catheter



The Freezor *Xtra* Catheter was approved under P020045 and there is no difference in the design from the commercially available device.

Please refer to the Freezor *Xtra* Cardiac CryoAblation Catheter Technical Manual 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 alternatives for the treatment of AVNRT, including the following: antiarrhythmic drugs, anti-arrhythmic pacing therapies, vagal maneuvers, surgical ablation, catheter ablation with a different approved catheter (including radiofrequency catheter ablation), implantable pacemaker or implantable cardioverter defibrillators (ICD). 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 Freezor *Xtra* Catheter has been marketed internationally since 2002 including European Union, Australia, Canada and other countries in the world for cardiac arrhythmias. Freezor *Xtra* Catheter has been marketed in the United States since 2004 for minimally invasive cardiac surgery procedures. The device has not been withdrawn from market in any country for any reason related to safety and 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 device:

Table 1: List of Adverse Events

- Access site complications (e.g., hematoma, infection, thrombosis, ecchymosis, AV fistula, bleeding from puncture site, hemorrhage)
- Arrhythmia (including new or worsening or existing arrhythmias)
- Cardiac arrest
- Cardiac tamponade / perforation
- Catheter entrapment in cardiac structures requiring surgical intervention
- Chest discomfort, pain or pressure
- Coronary artery spasm, dissection, thrombosis

- Damage to adjacent organs/structures
- Death
- Endocarditis
- Heart block, partial or complete, potentially requiring permanent pacemaker
- Hematoma
- Hemothorax
- Infection /sepsis
- Myocardial infarction
- Pericardial effusion
- Pericarditis
- Pleural effusion
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary embolism
- Stroke/transient ischemic attack/embolism
- Thrombosis
- Valvular damage
- Vascular complication (e.g., stenosis)
- Vasovagal reaction

IX. **SUMMARY OF PRECLINICAL STUDIES**

A series of non-clinical laboratory studies related to the Freezor *Xtra* Catheter was performed and the pertinent data is being leveraged from the previously approved PMA P020045.

Additional biocompatibility and animal study testing was conducted in support of the Freezor *Xtra* Cardiac CryoAblation Catheter for an indication of AVNRT.

A. BIOCOMPATIBILITY TESTING

New biocompatibility testing was conducted for Freezor *Xtra* Catheter taking into account the proposed AVNRT indication in accordance with ISO 10993 Standard: Biological Evaluation of Medical Devices, Part I: Evaluation and Testing (2010) and Part IV: Selection of Tests for Interactions with Blood (2006). Per FDA's request, direct and indirect hemolysis, direct complement activation with C3a and SC5b-9, and *in vivo* thrombogenicity (4 hour canine venous, unheparinized model) were included in the testing.

The 7F Freezor *Xtra* Catheter is an externally communicating device that contacts circulating blood for a limited duration (less than 24 hours).

Biocompatibility results are summarized in **Table 1**.

Table 1: Biocompatibility Testing Summary

Category & Standard	Test Description	Results
Cytotoxicity ISO 10993-5 (2009)	L929 MEM Cytotoxicity	Pass
	L929 MTT Cytotoxicity (24 hr)	Pass
Sensitization ISO 10993-10 (2010)	Kligman Maximization - ISO	Pass
Irritation or Intracutaneous Reactivity ISO 10993-10 (2010)	Intracutaneous Injection Test - ISO	Pass
Systemic Toxicity (acute) ISO 10993-11 (2006)	Systemic Injection Test – ISO	Pass
	Rabbit Pyrogen Test (Material Mediated) - ISO	Pass
Haemocompatibility ISO 10993-4 (2002)	<i>In Vitro</i> Haemocompatibility	Pass
Thrombosis	<i>In vivo</i> Thrombogenicity Study in Dogs - ISO	Pass
Coagulation	Prothrombin Time Assay – ISO	Pass
Coagulation (continued)	Unactivated Partial Thromboplastin Time Assay - ISO	Pass
Haematology ASTM F756-08 (2008) ASTM F619-03 (2008)	ASTM Hemolysis Method (Direct Contact)	Pass
	ASTM Hemolysis Method (Indirect Contact)	Pass
Complement System	Complement Activation (C3a and Sc5b-9) (Indirect Contact)	Pass
Complement System (continued)	Complement Activation (C3a and Sc5b-9) (Direct Contact)	Pass

B. ANIMAL STUDIES

Animal studies previously submitted in PMA020045 took place between 2000 and 2004 and did not fully meet the most current animal study guidance in 2010. Therefore, Medtronic opted to complete a new animal study designed to compare/confirm the lesion characteristics of the 4 mm tip Freezor Catheter, the 6 mm tip Freezor *Xtra* Catheter, and the 8 mm tip Freezor *MAX* Catheter in a single study. Included in this study were lesions made using the 4mm tip RF Mariner catheter. Overall, no pathognomonic features that allowed for the distinction of lesion origin (cryogenic or heat) were observed. Based on analysis of semiquantitative scoring, a higher percentage of RF lesions had thrombus deposits, subendocardial hemorrhage and resulted in a narrower rim of fibrovascular tissue and a larger core of sequestered myocardium as compared to the cryolesions created with Freezor and Freezor *Xtra* Catheters. Sequesters and the rim of fibrovascular tissue observed for Freezor *MAX* were intermediate. Despite the fact that most of the RF lesions were transmural, they were comparable in size (volume) to the Freezor *Xtra* cryolesions, and somewhat smaller than those created with Freezor *MAX*.

Animal Study results are summarized in **Table 2**.

Table 2: Animal Study Testing Summary

Study Type	Number of Animals	Follow-up Duration	Relevant Findings
GLP Porcine Study	12 (40-50kg)	Subacute (7 ± 1 days)	The purpose was to compare endocardial lesion characteristics between Freezor[®] (7Fr, 4mm tip), Freezor[®] Xtra (7Fr, 6mm tip), and Freezor[®] MAX (9Fr, 8mm tip) Cryocatheters. A general comparison of cryolesion size and lesion characteristics with an RF catheter (Marinr MC, 4mm tip) composed a secondary objective. The study had no safety objectives. - Procedures: - One RF lesion placed in the RV in each animal. - Four Cryolesions placed at 4 distinct locations in the RV and four cryolesions in the LV, avoiding areas of high flow such as the outflow tract regions, for 4min at the coldest attainable temperature. - One model of cryoablation catheter was used per chamber. - An <i>a priori</i> randomized factorial design was followed with the randomized unit the cardiac chamber (RV or LV). - Each cryoablation catheter was used in each chamber (RV or LV) for a total of 9 lesions per pig (1 RF + 8 Cryo). - At study endpoint animals were euthanized and lesions evaluated (gross and histology). - Results: - Lesion size by catheter -- all lesions - Freezor[®]: 6.19 ± 1.66mm wide, 4.15 ± 1.74mm deep, 8.51 ± 2.13mm long, 119.08 ± 62.19mm³ volume - Freezor[®] Xtra: 6.47 ± 1.56mm wide, 5.05 ± 1.74mm deep, 9.34 ± 2.1mm long, 165 ± 94.55mm³ volume - Freezor[®] MAX: 6.92 ± 1.58mm wide, 4.97 ± 1.66mm deep, 10.77 ± 3.1mm long, 211.9 ± 113.4mm³ volume - Marinr MC: 6.51 ± 1.67mm wide, 4.31 ± 1.72mm deep, 9.37 ± 2.14mm long, 154.79 ± 97.07 mm³ volume - Freezor[®] Xtra created significantly deeper lesions than those by Freezor[®]: 21.7% increase in depth (p = 0.0014) and lesion volume was significantly larger with a 33.4% increase in volume compared to Freezor[®] (p=0.0014). - Freezor[®] MAX lesion volume showed a 27.2% increase relative to the Freezor[®] Xtra (p = 0.0052) and a 69.6% increase relative to the Freezor[®] (p < 0.0001). - Gross and Histologic Characteristics of lesions: - All lesions easily identified on the endocardial surfaces, as well-demarcated red-beige foci, slightly sunken; - Cross-sections through lesion center: ➤ 22/92 (23.91%) cryolesions were transmural. ➤ 10/12 (83.33%) RF lesions were transmural. ➤ Overall there was no feature that distinguished lesion origin (cryogenic or RF) but a higher percentage of RF lesions had mild thrombus deposits, focal subendocardial hemorrhage, and a larger core of sequestered myocardium compared to cryo lesions. - Adverse Events, RF Catheter: - Focal thermal damage of abutting lung to the RF lesion, 2 animals. - Focal thermal damage of intercostal muscle near the RF lesion, 1 animal. - A “larger epicardial blood vessel” was included in the RF lesion and

Study Type	Number of Animals	Follow-up Duration	Relevant Findings
			was thrombosed. Adverse Events, Cryo Catheters: None observed The depth and surface area of cryolesions made by the 3 cryocatheters were not significantly different although a positive correlation between tip size and lesion volume was seen. Cardiac lesions created by RF or cryo energy were not statistically different.

X. SUMMARY OF PRIMARY CLINICAL STUDY

ICY-AVNRT was a prospective, multi-center, non-randomized, single-arm, unblinded investigational clinical study in the United States and Canada, with a goal of demonstrating the effectiveness and safety of the Freezor *Xtra* Catheter for the cryoablation of the conducting tissues of the heart in the treatment of patients with AVNRT using an endocardial approach, under IDE# G100272. Data from this clinical study were the basis for the PMA-S approval decision. A summary of the clinical study is presented below.

A. STUDY DESIGN

The first study subject enrollment occurred on May 14, 2012, and the last subject enrollment occurred on February 25, 2015. The database for this PMA supplement reflect data collected by centers for visits occurring on or before September 18, 2015 and received in the database by October 8, 2015. Data from both geographies (29 U.S. centers and 8 Canadian centers) are included in this summary.

ICY-AVNRT was a prospective, multi-center, non-randomized, single-arm, unblinded, North American investigational clinical study. The study will be closed after PMA-S approval. The analysis of the primary and key secondary objectives took place once subjects with a study cryoablation procedure attempt reached 6 months of follow-up.

Primary Effectiveness Endpoint

The primary effectiveness endpoint is a chronic clinical success/failure measure for each subject through 6 months following the study cryoablation procedure. The subject is considered a chronic success at 6 months if there is no documented evidence of AVNRT recurrence through 6 months of follow-up and the subject's study cryoablation procedure was an acute success.

The following hypothesis was tested at a one-sided 0.025 significance level.

$$H_0: P_E \leq 0.83$$

$$H_a: P_E > 0.83,$$

Where P_E is the probability of a subject achieving chronic effectiveness success at the 6-month follow-up and 0.83 is the pre-specified performance goal.

Kaplan-Meier methods were utilized to calculate a two-sided 95% log-log confidence interval for the probability at 6 months. If the lower bound of the 95% log-log confidence interval at 6 months is greater than the performance goal of 0.83, the primary effectiveness objective is met.

Primary Safety Endpoint

The primary safety endpoint is a documented safety event. Subjects who have at least one safety event during or after their cryoablation procedure, through 6 months of follow-up, are considered a primary safety failure.

A safety event is defined as the occurrence of any adverse event that is adjudicated by the Adverse Events Adjudication Committee (AEAC) as being serious and study ablation procedure-related and/or Freezor *Xtra* Catheter-related that:

- Results in death

- Results in a life-threatening illness or injury
- Results in permanent impairment of a body function or permanent damage to a body structure
- Necessitates significant intervention, such as major surgery or even intravenous medical therapy (e.g. vasopressors), to prevent permanent impairment of a body function or permanent damage to a body structure
- Requires in-patient hospitalization or a prolongation of an existing hospital stay

The following hypothesis was tested at a one-sided 0.025 significance level.

$$H_0: P_s \geq 0.07$$

$$H_a: P_s < 0.07,$$

Where P_s is the probability of a subject experiencing at least one safety event through 6 months with a 0.07 pre-specified performance goal.

Kaplan-Meier methods were utilized to calculate a two-sided 95% log-log confidence interval for the probability at 6 months was constructed. If the upper bound of the 95% log-log confidence interval at 6 months is less than the performance goal 0.07, the primary safety objective is met.

Sample Size Rationale

The sample size was calculated to simultaneously power for the primary effectiveness and primary safety endpoints by comparing to the pre-specified Objective Performance Criteria (OPC). In order to adequately power for both primary effectiveness and primary safety hypotheses, a sample size of 353 mITT subjects completing the 6 month follow-up visit were required to provide 90% power. The dropout rate of mITT subjects was assumed to be 12%, giving a final sample size for the study of up to 400 subjects with procedure attempts.

Independent Evaluators and Core Lab

An independent Data Monitoring Committee (DMC) was utilized during the ICY-AVNRT study to assess the safety and monitor the overall conduct of the study. Closed sessions provided the DMC the opportunity to review the confidential statistical analysis of safety and effectiveness objectives and formulate recommendations to Medtronic.

An independent Adverse Event Adjudication Committee (AEAC) conducted medical review at regular intervals of all adverse events and deaths for subjects participating in the study. This committee also adjudicated events for endpoint considerations (chronic safety event assessment).

In addition, an independent core lab was responsible for reviewing ECGs, Holters and other telemetry strips in support of AEAC adjudication of recurrence of AVNRT.

Clinical Inclusion and Exclusion Criteria

Enrollment in the ICY-AVNRT study was limited to patients who met the following inclusion criteria and none of the following exclusion criteria:

1. Inclusion and Exclusion Criteria

Enrollment in the ICY-AVNRT study was limited to patients who met the following inclusion criteria and none of the following exclusion criteria:

1.1. Pre-EP Study Inclusion and Exclusion Criteria

1.1.1. Inclusion Criteria

- SVT compatible with AVNRT (Documented by electrocardiogram (ECG), transtelephonic monitoring (TTM), Holter or event monitor)

1.1.2. Exclusion Criteria

- History of sustained (≥ 30 seconds) ventricular tachycardia
- Atrial tachycardia or other arrhythmia that could be confused with AVNRT
- Reversible cause of SVT
- History of previous AVNRT ablation
- Therapy with amiodarone within last 90 days
- Unstable angina/myocardial infarction/open heart surgery in past 60 days
- NYHA Classification III or IV currently or within the past 90 days
- Implantable cardiac rhythm device
 - Pacemaker, Defibrillator, Cardiac resynchronization device
 - Implantable loop recorder
- Atrioventricular block (1° (PR interval ≥ 220 ms), 2° , 3°) or left bundle branch block
- Stroke or transient ischemic attack within the past 180 days
- Life expectancy less than 12 months
- Female known to be pregnant
 - If a pregnancy test needed to be completed, the subject had to give consent prior to the test
- Unable/unwilling to give informed consent
- Unable/unwilling to comply with follow-up visits and study requirements
- < 18 years of age
- Active systemic infection

- Cryoglobulinemia
- Other conditions where the manipulation of the catheter would be unsafe (for example, intracardiac mural thrombus)
- Participating in a concurrent clinical study that may confound the results of this study (Subject involvement in any concurrent clinical study requires the approval of the study manager or designee)

1.2. Post-Electrophysiology (EP) Study Inclusion and Exclusion Criteria

1.2.1. Inclusion Criteria

- Subject must have one EP Study-documented inducible sustained (≥ 15 seconds) supraventricular tachycardia that is classified as AVNRT.
- To be considered as AVNRT for this study at least ONE of the following must be documented:
 - Induction mode compatible with AVNRT: critically prolonged AH or HA required
 - Inability to reset the atrium from the ventricle with the HIS refractory
 - Inability to terminate in the ventricle with the HIS refractory
 - VAV or VAHA to right ventricular entrainment
 - Reproducible termination with an atrial electrogram with intravenous adenosine:
 - Lack of the presence of an accessory pathway in cases where a slow pathway is the retrograde limb of the circuit
 - Presence of linking during resetting of the tachycardia

1.2.2. Exclusion Criteria

- Presence of a second inducible arrhythmia that could be confused with AVNRT during follow-up or will likely result in ablation within the next 6 months
- Presence of inducible sustained ventricular tachycardia or fibrillation
- Presence of an accessory pathway
- Presence of abnormal conduction or refractoriness parameters of the atrioventricular conduction system.
- Indication for a pacemaker, defibrillator or CRT

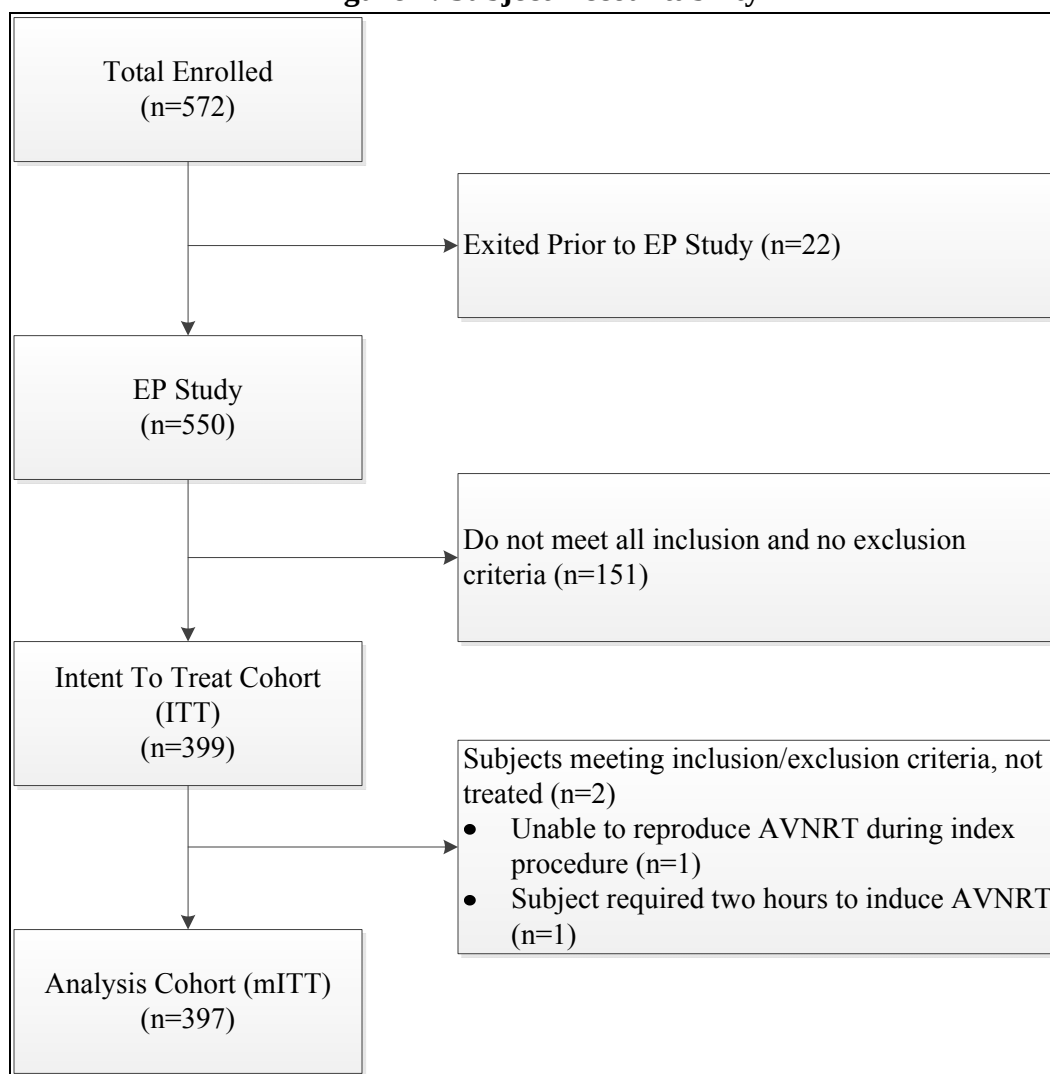
2. Follow-up Schedule

Clinical data were required to be collected at the following subject visit intervals: baseline/enrollment, during the EP study/procedure, at the pre-discharge visit, acute safety assessment (phone visit 8 days post-procedure), in-person visits at 1, 3, and 6 months, and phone visits at 1, 2, and 3 years. Adverse events and complications were recorded at all visits.

B. ACCOUNTABILITY OF PMA COHORT

At the time of database freeze for the PMA-S, 572 patients were enrolled in the study. Three hundred and ninety nine (399) subjects were consented, diagnosed with AVNRT, and met all inclusion and no exclusion criteria after completion of the EP study to make up the Intent-to-Treat (ITT) analysis population. Three hundred and ninety seven (397) subjects met all post-EP inclusion and no exclusion criteria, and received cryoablation, comprising the modified Intent-to-Treat (mITT) analysis population. The resulting number of subjects in each analysis population is displayed in **Figure 2**.

Figure 2: Subject Accountability



C. STUDY POPULATION DEMOGRAPHICS AND BASELINE PARAMETERS

The demographics of the ICY-AVNRT study subject cohort provide an accurate representation of the intended AVNRT population.

The majority of subjects enrolled in the study were female (279/397; 70.3%) and of white or Caucasian race (353/397; 88.9%). The median age of subjects was 54 years, with 5 subjects (1.3%) between the ages of 18 and 21 at the time of consent.

Table 3: Subject Demographics

Subject Characteristics	mITT Subjects (N = 397)
Gender (N, %)	397 (100.0%)
Male	118 (29.7%)
Female	279 (70.3%)
Age (years)	
N	397 (100.0%)
Mean +/- Standard Deviation	52.6 +/- 13.9
Median	54.0
25th Percentile – 75th Percentile	44.0 - 62.0
Minimum – Maximum	18.0 - 84.0
Age > 18 and ≤ 21 (Years) (N, %)	5 (1.3%)
Race/ Ethnic Origin (N, %)	
Subject/physician chose not to provide information	10 (2.5%)
Not reportable per local laws or regulations	0 (0.0%)
American Indian or Alaska Native	1 (0.3%)
Asian	10 (2.5%)
Black or African American	16 (4.0%)
Hispanic or Latino	4 (1.0%)
Native Hawaiian or Pacific Islander	0 (0.0%)
White or Caucasian	353 (88.9%)
Two or more races	1 (0.3%)
Other race	2 (0.5%)

The rhythm at the baseline visit for the study was documented by a 12-lead ECG for each subject. One hundred forty three (143/397; 36.0%) had an abnormal rhythm while the remaining subjects (254/397; 64.0%) were in sinus rhythm for the baseline ECG assessment (4). Heart rates (average of 74.4 ± 25.5 bpm) and AV node function (average PR interval of 151.9 ± 38.5 ms) captured by the 12-lead ECGs were in the normal range for most subjects.

Table 4: 12-Lead ECG at Baseline

Subject Characteristics	mITT Subjects (N = 397)
Heart Rate (bpm)	
N	397 (100.0%)
Mean +/- Standard Deviation	74.4 +/- 25.5
Median	68.0
25th Percentile – 75th Percentile	61.0 - 80.0
Minimum – Maximum	42.0 - 206.0
PR Interval (ms)	
N	392 (98.7%)
Mean +/- Standard Deviation	151.9 +/- 38.5
Median	150.0
25th Percentile – 75th Percentile	135.5 - 166.0
Minimum – Maximum	0.0 - 674.0
QRS duration (ms)	
N	397 (100.0%)
Mean +/- Standard Deviation	87.6 +/- 13.8
Median	86.0
25th Percentile – 75th Percentile	80.0 - 94.0
Minimum – Maximum	53.0 - 172.0
ECG interpretation	
Sinus Rhythm	254 (64.0%)
Abnormal	143 (36.0%)

D. SAFETY AND EFFECTIVENESS RESULTS

1. Safety Results

The primary safety objective is to demonstrate chronic safety (through 6 months) of the Freezor Xtra Catheter when used for the treatment of AVNRT using an endocardial approach. The mITT analysis cohort is used for this analysis.

Subjects who had at least one safety event during or after their cryoablation procedure or through 6 months of follow-up are considered a primary safety failure.

- A safety event is defined as the occurrence of any adverse event that is adjudicated by the AEAC as being serious and study ablation procedure-related and/or Freezor *Xtra* Catheter related that:
 - Results in death
 - Results in a life-threatening illness or injury
 - Results in permanent impairment of a body function or permanent damage to a body structure
 - Necessitates significant intervention, such as major surgery or even intravenous medical therapy (e.g. vasopressors), to prevent permanent impairment of a body function or permanent damage to a body structure, or
 - Requires in-patient hospitalization or a prolongation of an existing hospital stay

Of the 397 mITT subjects, 4 had a primary safety event through 6 months of follow-up. All 4 of these adverse events were classified as serious and procedure-related. None of the 4 events were considered related to the Freezor *Xtra* Catheter. Three (3) of the events occurred on the day of procedure and 1 occurred 25 days post-procedure.

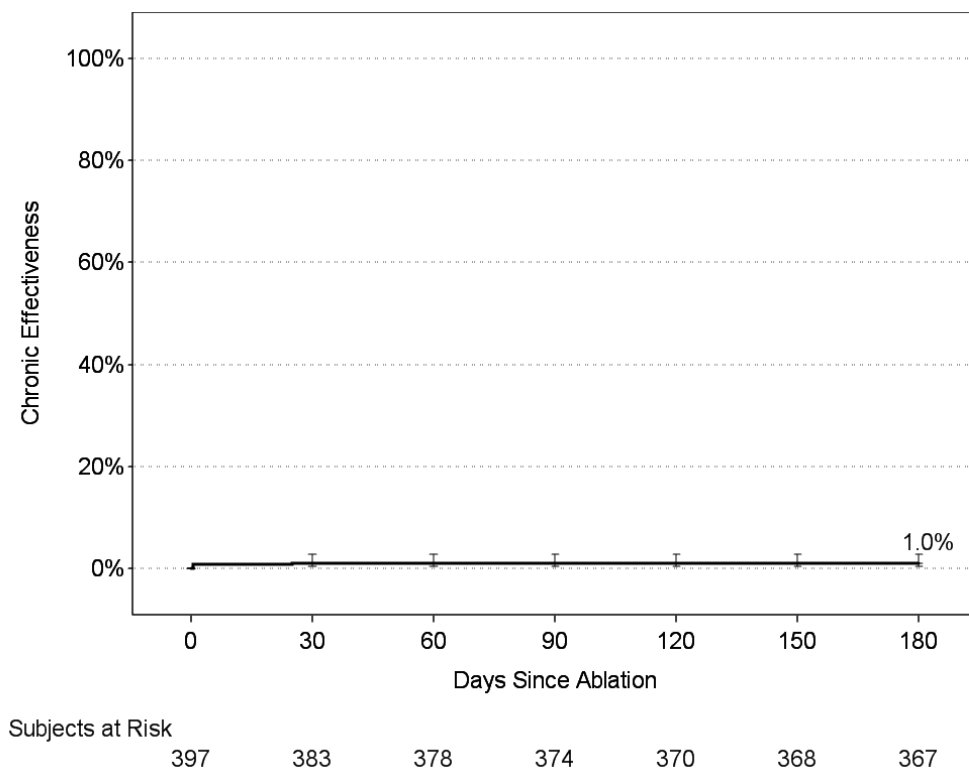
The Kaplan-Meier estimate of chronic safety events through 6 months is 1.0%, with a 2-sided 95% upper confidence bound equal to 2.7%. The primary safety objective was met because the upper bound of the 95% confidence interval is below the pre-defined performance goal of 7.0%. Results of the primary safety objective are displayed in **Table 5** and **Figure 3**.

Table 5: Primary Safety Objective

Chronic Safety	Kaplan-Meier Estimate at Six Months (%)	95% Two-Sided Confidence Interval ¹	P-value for H _a : P _S < 0.07
Treated subjects with at least one chronic safety event through six months	1.0%	(0.4%, 2.7%)	<0.0001

¹ Kaplan-Meier log-log confidence interval

Figure 3: Kaplan-Meier Plot - Primary Safety Objective



Adverse Events Occurring in the ICY-AVNRT Clinical Study

All adverse events (AEs) were reported and classified throughout the study. AEs were classified using the Medical Dictionary for Regulatory Activities (MedDRA) which uses a 5-step hierarchical system, starting with the Lowest Level Term (level 1) or diagnosis followed by the Preferred Terms (level 2) and progressively losing specificity up to a System Organ Class (level 5). Preferred Terms (PT) are captured as the Keyterms in the Adverse Event tables below.

There were no unanticipated adverse events in the study.

There were 542 AEs reported for the 397 eligible treated (mITT) subjects. All 542 AEs (100%) were adjudicated for seriousness and relatedness by the AEAC. An overview of the AEs is shown in **Table 6**.

Table 6: Adverse Event Overview

Number of Adverse Events (Number, % of mITT Subjects) for 397 mITT Subjects				
	Related*	Not Related	Unknown**	Total Reported
Serious	4 (4, 1.0%)	30 (26, 6.5%)	0 (0, 0.0%)	34 (30, 7.6%)
Non- Serious	43 (40, 10.1%)	443 (170, 42.8%)	22 (22, 5.5%)	508 (197, 49.6%)
Total	47 (43, 10.8%)	473 (176, 44.3%)	22 (22, 5.5%)	542 (205, 51.6%)

*Related to procedure and/or device

**Unknown relatedness to procedure and/or device

Table 7 displays a summary of all adverse events adjudicated by the AEAC to be related to a procedure and/or device.

Table 7: Summary of Adverse Events Related to a Procedure and/or Device

Number of Events (Number, % of mITT Subjects)		
Adverse Event Classification	Related	Unknown
SERIOUS ADVERSE EVENTS		
Procedure Relatedness		
Cryo Procedure	0 (0, 0.0%)	0 (0, 0.0%)
EP Procedure	2 (2, 0.5%)	0 (0, 0.0%)
RF Procedure	0 (0, 0.0%)	0 (0, 0.0%)
Other Procedure	0 (0, 0.0%)	0 (0, 0.0%)
Unspecified	2 (2, 0.5%)	0 (0, 0.0%)
Device Relatedness		
Freezor <i>Xtra</i> Catheter	0 (0, 0.0%)	0 (0, 0.0%)
Other cryocatheter	0 (0, 0.0%)	0 (0, 0.0%)
RF catheter	0 (0, 0.0%)	0 (0, 0.0%)
Diagnostic catheter	2 (2, 0.5%)	0 (0, 0.0%)
Sheath	1 (1, 0.3%)	0 (0, 0.0%)
Introducer	0 (0, 0.0%)	0 (0, 0.0%)
Other system component	0 (0, 0.0%)	0 (0, 0.0%)
Total Serious Procedure and/or Device Related*	4 (4, 1.0%)	0 (0, 0.0%)
NON-SERIOUS ADVERSE EVENTS		
Procedure Relatedness		
Cryo Procedure	19 (19, 4.8%)	3 (3, 0.8%)
EP Procedure	6 (6, 1.5%)	0 (0, 0.0%)
RF Procedure	1 (1, 0.3%)	0 (0, 0.0%)
Other Procedure	0 (0, 0.0%)	0 (0, 0.0%)
Unspecified	17 (17, 4.3%)	4 (4, 1.0%)
Device Relatedness		
Freezor <i>Xtra</i> Catheter	10 (10, 2.5%)	7 (7, 1.8%)

Number of Events (Number, % of mITT Subjects)		
Adverse Event Classification	Related	Unknown
Other cryocatheter	1 (1, 0.3%)	0 (0, 0.0%)
RF catheter	1 (1, 0.3%)	0 (0, 0.0%)
Diagnostic catheter	1 (1, 0.3%)	6 (6, 1.5%)
Sheath	0 (0, 0.0%)	11 (11, 2.8%)
Introducer	1 (1, 0.3%)	9 (9, 2.3%)
Other system component	2 (2, 0.5%)	0 (0, 0.0%)
Total Non-serious Procedure and/or Device Related*	43 (40, 10.1%)	22 (22, 5.5%)

*Procedure and/or Device-Related events are not mutually exclusive; an event may be related to both

AV Block Assessment

No subjects received a permanent pacemaker due to AV block as a result of the study procedure or Freezor *Xtra* Catheter.

There were 3 (3/397, 0.76%) adverse events of 1st degree AV block in 3 subjects, first observed at the pre-discharge visit. These events were adjudicated by the Adverse Events Adjudication Committee (AEAC) as not serious, and related to both the Freezor *Xtra* Catheter and the cryoablation procedure. Those 3 subjects had 1st degree AV block observed during at least one subsequent follow-up visit over the 6 month follow-up period.

2. Effectiveness Results

The primary effectiveness objective is to demonstrate chronic effectiveness (through 6 months) of the Freezor *Xtra* Catheter for the treatment of AVNRT using an endocardial approach. The mITT analysis cohort is used for this analysis.

The primary effectiveness endpoint is a chronic clinical success/failure measure for each subject through 6 months after the study cryoablation procedure (first procedure using the Freezor *Xtra* Catheter). Subjects must have met both of the following acute and chronic conditions to be considered a chronic effectiveness (treatment) success:

- Acute Success: The inability to induce more than one echo beat by the same pacing maneuvers that induced AVNRT before cryoablation (with drug provocation if required for induction before cryoablation) at the conclusion of the study cryoablation procedure assessment
- Chronic Success: Lack of documented recurrence of clinical AVNRT during the 6-month follow-up period after the study cryoablation procedure

Of the 397 mITT subjects in the study, 29 subjects were clinical failures; 19 were due to acute procedural failure, and 10 were due to recurrence of AVNRT documented between the end of procedure and 6 months.

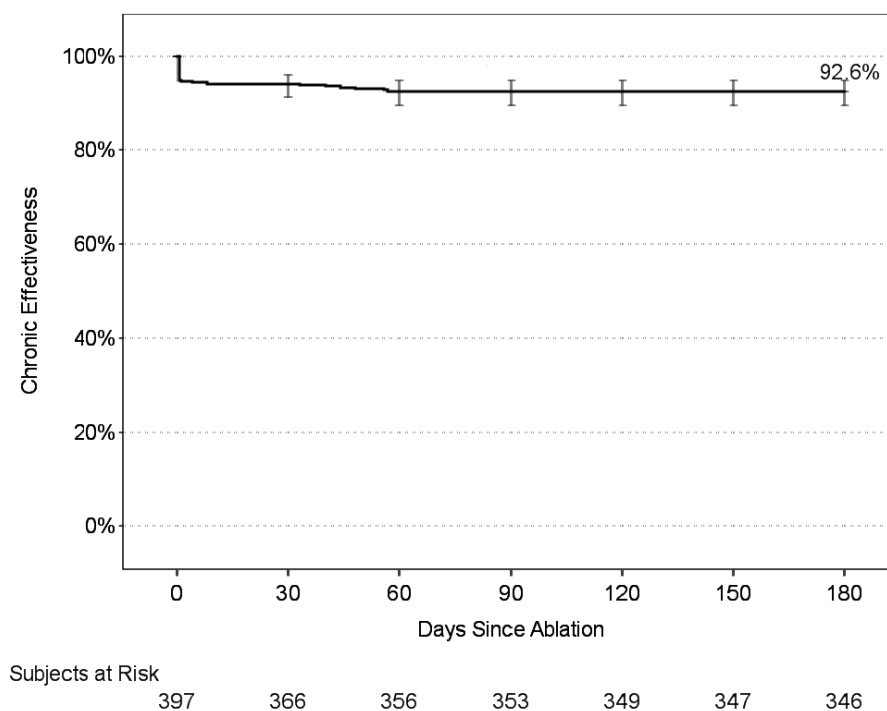
The Kaplan-Meier estimate of chronic clinical success at 6 months is 92.6%, with a two-sided 95% lower confidence bound equal to 89.5%. The primary effectiveness objective was met because the lower bound of the 95% confidence interval is above the pre-defined performance goal of 83.0%. The results of the primary effectiveness objective are displayed in **Table 8** and **Figure 4**.

Table 8: Primary Effectiveness Objective

Chronic Effectiveness	Kaplan-Meier Estimate at Six Months (%)	95% Two-Sided Confidence Interval ¹	P-value for $H_a: P_E > 0.83$
Treated subjects without acute procedural failure or AVNRT recurrence through six months	92.6%	(89.5%, 94.8%)	<0.0001

¹ Kaplan-Meier log-log confidence interval

Figure 4: Kaplan-Meier Plot – Primary Effectiveness Objective



The primary effectiveness endpoint is reported independent of medication usage. Of the 397 mITT subjects, 26 subjects initiated or had an increased dose of oral beta blockers, Diltiazem, or Verapamil after the index cryoablation procedure, through 6 months of follow-up, for the purpose of arrhythmia suppression.

E. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 91 investigators of which none were full-time or part-time employees of the sponsor and 9 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: 9
- 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)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA-S was not referred to the Circulatory System Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA-S substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

F. SAFETY CONCLUSIONS

Of the 397 mITT subjects in the ICY-AVNRT study, 4 had a primary safety event through 6 months of follow-up. All 4 of these adverse events were classified as serious and procedure-related. None of the 4 events were considered related to the Freezor *Xtra* Catheter.

The Kaplan-Meier estimate of chronic safety events through 6 months is 1.0%, with a 2-sided 95% upper confidence bound equal to 2.7%. The primary safety objective was met because the upper bound of the 95% confidence interval is below the pre-defined performance goal of 7.0%.

The safety outcome of the clinical study demonstrates that patients with AVNRT treated with the Freezor *Xtra* Catheter have an event rate of 1.0% at 6 months post-procedure, with no primary safety events related to the Freezor *Xtra* Catheter.

G. EFFECTIVENESS CONCLUSIONS

Of the 397 mITT subjects in the ICY-AVNRT study, 29 subjects were clinical failures; 19 were due to acute procedural failure, and 10 were due to recurrence of AVNRT documented between the end of procedure and 6 months.

The Kaplan-Meier estimate of chronic clinical success at 6 months is 92.6%, with a two-sided 95% lower confidence bound equal to 89.5%. The primary effectiveness objective was met because the lower bound of the 95% confidence interval is above the pre-defined performance goal of 83.0%.

The effectiveness outcomes of the clinical study demonstrate that patients with AVNRT treated with the Freezor *Xtra* Catheter have a chronic effectiveness success rate of 92.6% at 6 months post-procedure.

H. BENEFIT-RISK DETERMINATION

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The benefits of the devices include reduction of symptoms and improvement of quality of life. Based on the ICY-AVNRT study, there is a greater than 90% probability that AVNRT patients will experience relief from arrhythmia-related symptoms for at least 6 months after treatment with the Freezor *Xtra* Catheter. While there is potential evidence that females are marginally more likely to gain benefit than males (effectiveness success rate of 89% and 94.3% for male and female genders respectively), both gender subpopulations derived high degrees of benefit from the treatment.

Serious risks of the devices include cardiac tamponade, incision site hemorrhage, and thromboembolism. Based on the ICY-AVNRT study, there is approximately 1% probability of serious harmful events from the procedure. Minor complications related to the Freezor *Xtra* Catheter and AVNRT ablation procedures may occur in 10% of treated patients. There is no evidence that the risks of the devices differ between gender, age, or race subgroups.

The ICY-AVNRT study is well designed and reasonably conducted. Overall, the safety and effective results are robust and applicable to general adult population who undergo a catheter ablation procedure in clinical practice. In addition, the study results are consistent with that from other clinical trials with the same devices to treat AVNRT. The device performance is not expected to be significantly different between the real world and premarket experience.

While AVNRT is generally not considered to be life-threatening, it can be disruptive and chronically reoccurring with significant symptoms. The disease can be satisfactorily managed in majority of affected patients using medications, though pharmacologic therapy may be associated with other side-effects and lower effectiveness than catheter ablation therapy with the Freezor *Xtra* Catheter or other marketed ablation devices. Radiofrequency catheter ablation is another option and represents the most common non-pharmacologic treatment being performed in patients with AVNRT. The therapy offers the same benefits of symptom reduction. In a large randomized comparative OUS study, there was no statistically significant difference in acute procedural success between cryoablation and radiofrequency ablation. Long-term arrhythmia recurrence was lower with RF ablation (4.4% vs. 9.4%; $P=0.029$) at the 6-month follow-up, though 0.4% risk of high grade AV block requiring permanent pacemaker implant was also reported. Permanent AV block did not occur in any patient undergoing cryoablation in the trial. For comparison, the late arrhythmia recurrence rate of 2.6% in the ICY-AVNRT study is comparable to those generally observed with radiofrequency ablation.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device. Nevertheless, it is reasonable to assume that patients would value ablation using the study catheter similarly to other approved catheters for AVNRT. For some patients, the low risk of serious heart blocks comparing to competing technologies may provide extra assurance. Other risks associated with the study device may be further mitigated by limiting the device use to physicians who have specialized training, and requiring the device use in accordance with the proposed indications for use may mitigate the risks.

In conclusion, the data support that the probable benefits outweigh the probable risks for catheter ablation treatment of AVNRT with the Freezor *Xtra* Catheter .

I. OVERALL CONCLUSIONS

The data from the ICY-AVNRT study demonstrate safety and effectiveness of the Freezor *Xtra* Cardiac CryoAblation Catheter for the treatment of patients with AVNRT.

All primary safety and primary effectiveness objectives met the pre-specified performance criteria. The ICY-AVNRT clinical study demonstrated that patients with AVNRT treated

with the Freezor *Xtra* Catheter have a chronic effectiveness success rate of 92.6% at 6 months post-procedure and the safety risk is low, as demonstrated by an event rate of 1.0% at 6 months post-procedure, with no primary safety events related to the Freezor *Xtra* Catheter.

The collective data in this application provide reasonable assurance that the Freezor *Xtra* Catheter is safe and effective when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on 08/31/2016. The final conditions of approval cited in the approval order are described below.

The applicant's manufacturing facilities were 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

None cited.