FDA Executive Summary

Prepared for the
June 27, 2007 meeting of the
Circulatory System Devices Panel

P050024
CryoCor Cryoablation System, CryoCor, Inc.

Introduction

This is an Executive Summary for the CryoCor Cryoablation System (P050024). The device has been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration.

The Executive Summary begins with a brief discussion of the regulatory history of this device, followed by a summary of FDA's review of the device description, preclinical, and clinical information.

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Regulatory History

A chronology of the key milestones with respect to this PMA application is provided below.

- **July 15, 2005** - PMA (P050024) was originally submitted with preclinical modules submitted over the previous six months. FDA's bench and engineering issues were largely addressed in the preclinical modules and in the PMA submission.
- **October 12, 2005** - A major deficiency letter was issued due to several clinical and statistical issues.
- **October 25, 2005** - The sponsor responded to FDA's major deficiency letter (P050024/A007).
- **January 26, 2006** - FDA notified the sponsor that it did not believe that the data submitted provided a reasonable assurance of effectiveness for the long-term treatment of atrial flutter. Specifically, the pre-specified objective performance criterion (OPC) for chronic effectiveness was a 90% point estimate with a lower 95% confidence bound of 80% while the sponsor's submission reported a chronic effectiveness point estimate (simple proportion) of 71.22% with a lower 95% confidence bound of 62.24%.
- **November 28, 2006** - The sponsor subsequently determined that some event monitor recordings were originally incorrectly classified (i.e. episodes of rhythm other than atrial flutter were identified as atrial flutter), and arranged for an independent core lab readjudication of the recordings. The sponsor submitted an amendment based upon the readjudication (P050024/A010).
- **March 1, 2007** - The sponsor submitted a "Major Amendment" which provided updated statistical information and additional analyses (P050024/A014).

This review and Panel discussion focus on the data submitted in Amendments 10 and 14.

Proposed Indications for Use

The CryoCor Cryoablation System is intended to be used for the treatment of Isthmus-dependent atrial flutter in patients 18 years or older.

Device Description

The CryoCor Cryoablation System includes a console and a sterile, single-use percutaneous catheter. The system is designed to be operated as a unit, and will not function without both components. The CryoCor Cryoablation System is designed to block electrical conduction in myocardial tissue by applying extreme cold at the tip of the catheter during an atrial flutter ablation procedure.

The system uses a two-stage cooling process. The primary refrigerant is delivered to the catheter tip via a replenishable open-loop process and is initially pre-cooled by a separate closed loop refrigerant system. The pre-cooler extracts heat from the primary refrigerant through a heat exchanger located in the articulating arm attached to the console, cooling the primary refrigerant to -30°C. The pressurized, liquefied primary refrigerant expands at the catheter tip, changing to its gas phase and causing a rapid additional reduction in temperature (<-80°C). The refrigerant gas is then returned from the catheter through the console to an outlet line.

Cryoablation Console

The console houses the user interface, control electronics and software, the refrigerant supply system (both pre-cooling and primary) and an articulating arm that supports and suspends the catheter over the patient during the procedure. The user interface presents the user with control options and feedback pertaining to temperature, active freeze time, and total cycle time. Pressure and flow measurements are monitored continuously during operation.

Catheter

The CryoCor Cryoblator Catheters are single-use, disposable 10F catheters with either 5 cm or 7 cm articulation length and 6.5 mm tip length. Placement of the catheter tip is accomplished under fluoroscopy, by manipulation of the catheter handle (applying torque to the shaft and/or deflecting the articulation segment). The catheter has a handle to facilitate steering, and the distal portion of the catheter is capable of being deflected (uni-directionally) to 180°. The metal tip of the catheter is the point of application for heat transfer from the tissue. A temperature sensor located within the catheter tip provides continuous temperature monitoring during active ablation. An additional 1.3 mm wide band electrode is incorporated for sending or receiving intra-cellular cardiac electrical signals. Both the catheter tip and band electrode are radiopaque to provide visualization when utilizing standard fluoroscopy.

The handle at the proximal end of the catheter shaft includes a lever to control the articulation segment deflection and a manual locking feature to hold the deflection angle. The three connectors at the proximal end of the catheter shown in the figure below are used for electrical signal transmission (mapping and temperature), refrigerant delivery and recovery, and tip pressure monitoring.

Figure 1: CryoCor Cryoablation System (figure provided by the sponsor)

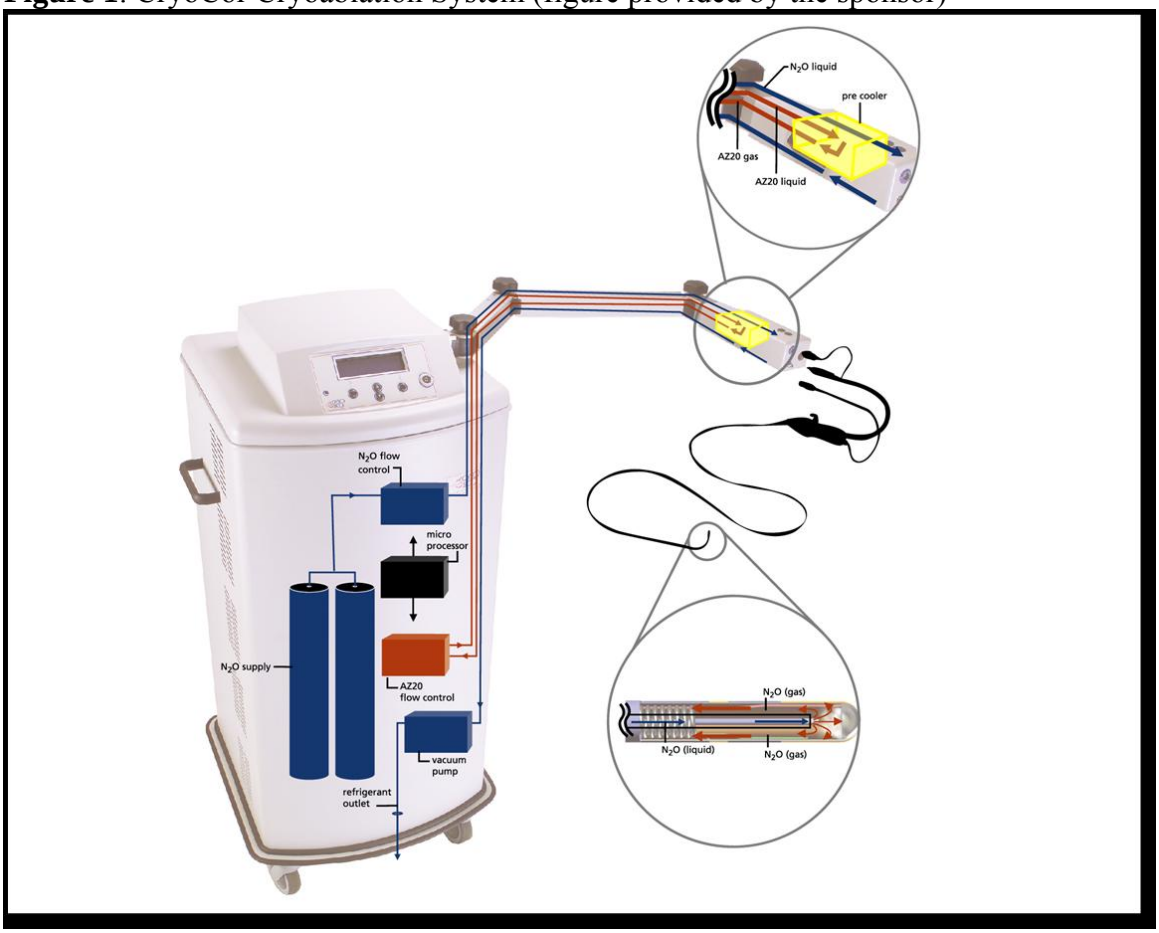


Table 1: Summary of the catheter specifications:

Component or Feature	**Cryoblator$_x$-05, Cryoblator$_x$-07**
Catheter Diameter	10 Fr
Catheter Tip Diameter	3.1 mm
Catheter Tip Length	6.5 mm
Tip Material	Stainless Steel
Shaft Length	95 cm (Cryoblator$_x$-05) 97 cm (Cryoblator$_x$-07)
ECG Electrode Band	90% Platinum, 10% Iridium
ECG Electrode Band Placement	2-4 mm from catheter tip
Capillary Tube	0.008” Diameter, 9.8” Long
ECG Connector	Lemo Type

Engineering Review Summary

FDA conducted an extensive engineering review of the sponsor's preclinical testing. The following areas of review were included in FDA's engineering evaluation:

- Catheter and console mechanical evaluation
- Electrical performance
- Electromagnetic compatibility
- Software
- Biocompatibility
- Sterilization
- Device and packaging shelf life

At this time, FDA has no outstanding engineering concerns.

Clinical Data

Feasibility Study

The sponsor conducted a feasibility study prior to initiation of the pivotal trial. The primary purpose of the feasibility study was to define the procedure for ablation in the cavo-tricuspid isthmus and to provide an initial evaluation of the CryoCor Cardiac Cryoablation System. The study population was limited to subjects with right atrial isthmus-dependent atrial flutter who were refractory to medical management.

Of the 58 subjects enrolled in the US feasibility study, 48 met all screening criteria and received treatment with the CryoCor system.

Acute effectiveness, as defined by bi-directional block (BDB) and achievement of AFL conversion to normal sinus rhythm, was demonstrated in 45 of the 48 (93.8%) subjects.

Chronic effectiveness, defined as freedom from recurrence of atrial flutter, was evaluated through six months follow-up in all subjects who had acute effectiveness at the index procedure. Of the 45 subjects that demonstrated acute effectiveness, 38 (84%) met the chronic effectiveness endpoint at six months.

Regarding safety, among the 48 treated subjects, 6 subjects presented with 10 serious adverse events (12.5%). Of these 10 events, 1 event (10.0%) was characterized as procedure-related while 3 events (30.0%) were characterized as disease-related. The remaining 6 events were not attributed to the procedure, device, or cardiac disease. None of the serious adverse events were attributed to the device.

Pivotal Study – Design and Conduct

The pivotal study was a prospective, non-randomized, multi-centered, single-arm study at 24 US sites. The purpose of this study was to determine the acute and chronic safety and effectiveness of the CryoCor Cardiac Cryoablation System when used for the treatment of cavo-tricuspid valve isthmus-dependent atrial flutter as compared to established objective performance criteria (OPC) for current standard ablation modalities. A total of 189 patients were enrolled and 160 had the CryoCor catheter inserted. The first subject was treated on December 1, 2003, and the last subject was treated on November 11, 2004. The last subject completed follow-up on April 26, 2005.

Study Endpoints
The following were the pre-specified endpoints for the trial:

Acute safety:	The occurrence of serious adverse events within seven days of the procedure.
Acute effectiveness:	The presence of bi-directional block (BDB) in the cavo-tricuspid valve isthmus.
*Chronic effectiveness**:	Six-month freedom from recurrence of atrial flutter for those patients who achieve acute success.
Additional Endpoints:	Re-treatment effectiveness
	Serious adverse events that occurred more than seven days after the cryoablation procedure

* FDA believes that there is a lack of evidence in the clinical literature demonstrating that acute effectiveness from cryoablation for the treatment of atrial flutter is predictive of chronic effectiveness. While chronic effectiveness was described as a secondary endpoint in the clinical protocol, FDA conveyed to the sponsor prior to the initiation of the pivotal trial that FDA would consider the chronic effectiveness evaluation critical in the assessment of overall device effectiveness for approval.

The OPCs developed for RF ablation were used as a guide to develop the acute safety, acute effectiveness, and chronic effectiveness endpoints.

Table 2: OPCs used for assessing study endpoints.

Study Endpoint	OPC	
	Target Value	95% Confidence Bound
Acute safety (7-day SAEs)	< 2.5%	< 7% (upper bound)
Acute effectiveness	> 95%	> 80% (lower bound)
Chronic effectiveness	> 90%	> 80% (lower bound)

Enrollment Criteria

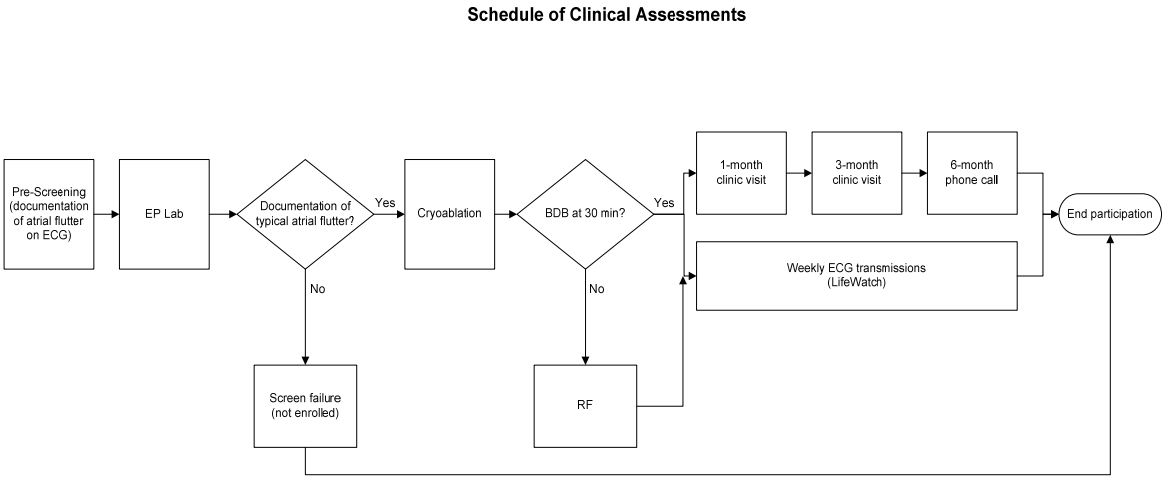
Inclusion

- Age between 18 and 75
- Symptomatic atrial flutter with at least one episode within the last six months, documented on ECG
- Documentation of isthmus-dependent right-atrial flutter as evident from pacing and/or mapping (performed in the EP lab just prior to ablation)
- Willingness, ability and commitment to participate in follow-up evaluations.

Exclusion

- Structural heart disease of clinical significance including:
  - Cardiac surgery within six months of screening
  - Unstable symptoms of congestive heart failure (CHF) including NYHA Class III or IV CHF at screening and/or ejection fraction <30% as measured by ECHO or catheterization
  - Right-sided heart valve prosthetics
  - Myocardial infarction (MI) within three months of screening
  - Unstable angina or ongoing myocardial ischemia
  - Corrected or uncorrected atrial septal defect (ASD)
  - Congenital heart disease where either the underlying abnormality or its correction prohibits or increases the risk of cryoablation
- Any prior ablation for atrial flutter
- Any prior ablation (other than atrial flutter) within three months of screening
- Concomitant atrial fibrillation requiring AAD treatment other than Class IC or Class III for conversion to atrial flutter
- Any concomitant ventricular arrhythmia requiring pharmacological treatment that would interfere with the interpretation of the results from this study
- Severe electrolyte abnormalities at the time of treatment
- Pregnancy
- Any contraindication to cardiac catheterization
- Poor general health that, in the opinion of the investigator, will not allow the subject to be a good study candidate (i.e. other disease processes, mental capacity, etc.).
- Enrollment in any other ongoing protocol

Figure 2: Study Flow (figure provided by the sponsor)



Investigational procedure

Subjects were sedated and venous access was obtained according to the standard of care at each clinical site. Documentation of these procedures was made on the appropriate source documentation and case report forms.

Just prior to cryoablation, baseline electrophysiology measurements were performed to document isthmus-dependent atrial flutter. These included: inducing atrial flutter and entrainment pacing, measuring activation sequences, and/or 3D electro-anatomical mapping. If documentation of isthmus-dependent atrial flutter could not be established, the subject was considered to be a secondary screening failure and was not allowed to proceed with the cryoablation.

After isthmus conduction was documented, the cryoablation catheter was placed in the region of the cavo-tricuspid isthmus. Freezes/ablations of no more than five minutes in duration were performed within the targeted structure(s). Each freeze cycle or ablation was performed at the coldest temperature that the console could provide. In some subjects treatment with more than one ablation at a given site was necessary to produce a continuous lesion without gaps. While it was advantageous to ablate during atrial flutter, if normal sinus rhythm was present, it was recommended that pacing from the coronary sinus be performed during applications of cryoenergy to assess unidirectional block.

Upon appearance of conduction delay from the medial to lateral direction, the investigator was required to document bi-directional block by established mapping methods. A minimum wait time of thirty minutes after the last ablation was required prior to testing for BDB. If conduction had returned, additional ablations were allowed, and the clock for determination of BDB was restarted. The use of isoproterenol for additional assessment of the block was optional. If BDB was not achieved, the patient was declared an acute effectiveness failure and could undergo treatment with another ablation device (i.e. RF ablation).

After completion of all ablation and monitoring procedures, all catheters and sheaths were removed and hemostasis was obtained.

Follow-up monitoring and compliance
For the purpose of evaluating chronic effectiveness, subjects who had acute procedural success using only the sponsor's device were monitored for evidence of recurrence of AFL for six months following the procedure. These subjects were provided with an event recorder and instructed to make a recording during any perceived symptoms of their arrhythmia and to record a random, once per week recording until the study ended at the Month 6 telephone follow-up visit. At the end of the study, the event recorder was returned to LifeWatch, Inc.

A minimum standard for compliance with ECG recording and transmission was used during data analysis. It was estimated that weekly recordings for 6 months would result in approximately 26 random ECGs for review. A subject was deemed compliant if at least 3 ECGs were recorded per month for at least 5 of the 6 months of observation. It was required that the 6-month chronic effectiveness evaluation be conducted within a window of +/- 30 days of the 6-month point.

Core lab event recording adjudication
As stated previously, the sponsor performed a readjudication of the event recorder tracings and a subsequent reanalysis of the chronic effectiveness endpoint. The following is taken from the sponsor's Clinical Study Report (Amendment 10, page 34) to explain the process:

> *"The original PMA submission (P050024) relied solely on the LifeWatch Core Lab interpretation of the transmitted event recording and did not take into account any investigator over-read of the tracings. Upon review of this process, it was determined that there may have been misinterpretations of complex electrocardiograms, specifically those with atrial fibrillation being misinterpreted as a recurrence of atrial flutter. In order to rectify this process, all those tracings that were not from patients with clearly documented recurrence of atrial flutter as demonstrated by electrophysiologic study or other treatments for atrial flutter, were interpreted by an expert in interpretation of electrocardiograms, Dr. Mel Scheinman."*

This readjudication is the primary basis for the amended submission currently under review and is presented in the chronic effectiveness results discussed later in this review. FDA's review included examination of all tracings from patients for whom the chronic effectiveness classification was changed by the readjudication. While the readjudication was not explicitly pre-specified in the clinical investigational plan, the readjudication mechanism is conceptually consistent with the investigational plan. FDA considers the core lab revised chronic effectiveness patient classifications to be scientifically valid.

Pivotal Study – Enrollment, Demographics, and Accountability

Twenty-eight (28) subjects failed secondary screening prior to the ablation procedure for the following reasons: Investigator was not able to induce isthmus-dependent atrial flutter (25 subjects); subject developed atrial fibrillation and could not be electrically or chemically cardioverted (1 subject); subject's ejection fraction was lower than 30% (1 subject); and catheter was not inserted due to device failure (1 subject). In addition, one (1) subject withdrew consent before the procedure. Of the 189 subjects enrolled, 160 had the catheter inserted.

Table 3: Subject Demographics

	Subject # (%)
Male/Female	
Age (mean ± SD)	
AF History	
Angina	
Cardiomyopathy	
Congestive Heart Failure	
Diabetes	
Hyperlipidemia	
Hyperthyroid	
Hypothyroid	
Ischemic Heart Disease	
Obesity	
Previous MI	
Pulmonary Disease	
Systemic Hypertension	
Tobacco Abuse	
Ejection Fraction <= 40	
Prior Treatment with AADs	
Prior Ablation	

There were 104 protocol deviations in 73 patients in this study. Of these, 29 were major deviations (in 26 patients) and 75 were minor deviations. Major deviations included deviations involving study inclusion/exclusion criteria, patient consent, or collection and analysis of key safety or efficacy variables. The sponsor concluded that none of the major deviations affected the safety and effectiveness analyses.

Pivotal Study - Poolability

The sponsor has presented results of the Fisher exact test (Freeman-Halton modification for the *r* by *c* table case) acute effectiveness, acute safety and chronic effectiveness, by each of site, gender, catheter model (1100 or 1200), and protocol version ("Revision A-D" or "Revision E and above"). During the course of the study a protocol revision that changed the bidirectional block wait time from 60 to 30 minutes was implemented. Revisions A-D required a 60-minute wait time, while Revision E onwards required a 30-minute wait time. For acute safety and acute effectiveness these results are based on 160 patients. For chronic effectiveness these results are based on 132 patients with 6 month follow-up.

Table 4: Fisher exact p-values for poolability tests

Endpoint	**Site**	**Gender**	**Model**	**Protocol**
Acute Safety	0.2612	0.2500	0.3409	0.5046
Acute Effectiveness	0.2652	1.0000	0.8111	$3x10^{-6}$
Chronic Effectiveness	0.4424	0.8037	0.2776	0.8059

Overall, the Fisher exact p-values and table percentages do not show any significant evidence against pooling. One exception is the protocol revision for the acute effectiveness endpoint. Revisions E and above showed higher acute effectiveness than revisions A-D. This difference appears to hold across model types. Table 5 below summarizes the acute effectiveness proportions.

Table 5: Patients with acute effectiveness by protocol revision and model number.

Model Number	**Protocol Revision**	
	A-D	E and above
Both models	68.63% (35/51)	96.33% (105/109)
1100	74.47% (35/47)	100.00% (42/42)
1200	0.00% (0/4)	94.03% (63/67)

Pivotal Study – Safety Results

The null hypothesis for the primary safety endpoint was that the incidence of serious adverse events within seven days of the cryoablation procedure with the CryoCor Cryoablation System is 7% or greater. The alternative hypothesis was that the incidence of serious adverse events with Cryoablation therapy is less than 7%. These hypotheses may be stated as:

$$H_O: P_{AS} \geq 0.07 \quad \text{vs.} \quad H_A: P_{AS} < 0.07$$

where P_{AS} is the proportion of subjects in the target population experiencing at least one serious adverse event through seven days after the cryoablation procedure.

This analysis was performed as an intent-to-treat analysis. The subject population for safety was the subjects in whom the cryoablation catheter was introduced into the body (n=160).

Ten (10) subjects (6.25%) reported 11 serious adverse events within 7 days of the index procedure. The 7-day SAE rate 95% upper confidence bound was 11.19% and is summarized in the table below.

Table 6: Safety Results

Study Endpoint	----------	Percent	95% UCB	OPC Goal
7-day SAEs	---------	6.25%	11.19%	2.5 % (7% UCB)

The safety endpoint was not met.

Below is the list of SAEs that occurred within 7 days of the procedure.

Table 7: SAEs occurring within 7 days of the procedure

	Events				Patients	
MedDRA Preferred Term	Mild	Mod	Severe	Total	Total	Pct
Atrial Flutter	0	2	0	2	2	(1.25%)
Sick Sinus Syndrome	0	1	1	2	2	(1.25%)
Acute Respiratory Failure	0	0	1	1	1	(0.63%)
Atrial Fibrillation	0	0	1	1	1	(0.63%)
Atrioventricular Block-Complete	0	1	0	1	1	(0.63%)
Cardiac Tamponade	0	0	1	1	1	(0.63%)
Dizziness	0	1	0	1	1	(0.63%)
Hyperthyroidism	0	0	1	1	1	(0.63%)
Post Procedural Hematoma	0	1	0	1	1	(0.63%)

Below is a list of the SAEs that occurred after the first 7 days.

Table 8: SAEs occurring more than 7 days following procedure

	Events				Patients	
MedDRA Preferred Term	**Mild**	**Mod**	**Severe**	**Total**	**Total**	**Pct**
Atrial Fibrillation	1	6	1	8	8	(5%)
Atrial Flutter	1	2	0	3	2	(1.25%)
Completed Suicide	0	0	2	2	2	(1.25%)
Ankle Fracture	1	0	0	1	1	(0.63%)
Bradycardia	0	1	0	1	1	(0.63%)
Bronchospasm	0	1	0	1	1	(0.63%)
Carotid Artery Stenosis	0	0	1	1	1	(0.63%)
Chest Discomfort	0	1	0	1	1	(0.63%)
Colon Cancer	0	0	1	1	1	(0.63%)
Complex Partial Seizures	0	1	0	1	1	(0.63%)
Dehydration	0	1	0	1	1	(0.63%)
Hyperglycaemia	0	1	0	1	1	(0.63%)
Hypokalaemia	1	0	0	1	1	(0.63%)
Intracardiac Thrombus	0	1	0	1	1	(0.63%)
Osteomyelits	0	0	1	1	1	(0.63%)
Pulmonary Embolism	0	1	0	1	1	(0.63%)
Sepsis	0	0	1	1	1	(0.63%)
Sick Sinus Syndrome	1	0	0	1	1	(0.63%)
Suicide Attempt	0	1	0	1	1	(0.63%)
Surgery	1	0	0	1	1	(0.63%)
Tachycardia	0	1	0	1	1	(0.63%)
Transient Ischaemic Attack	0	1	0	1	1	(0.63%)

Subject Deaths

The following 3 deaths occurred during the follow-up phase.

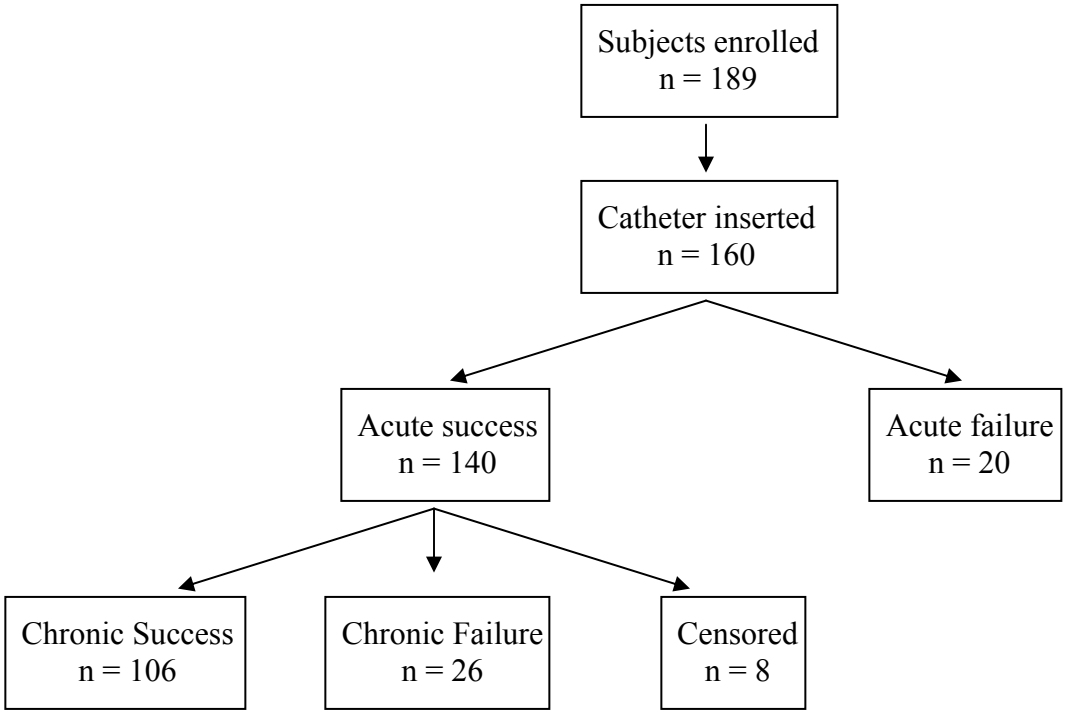
Table 9: Subject deaths

Subject #	**Death Description**
-------	Suicide 18 days post-ablation
-------	Pulmonary emboli approximately 10 weeks post-ablation; expired approximately 14 weeks post-ablation
-------	Illicit drug overdose approximately 6 months post-ablation

The DSMB reviewed all deaths and felt that none were related to the investigational device or procedure.

The Panel will be asked to comment on the safety of the device.

Figure 3: Effectiveness results summary



Pivotal Study – Acute Effectiveness Results

Acute effectiveness was defined as the ability to achieve bi-directional block. The null hypothesis for this objective was that the acute effectiveness with Cryoablation therapy is 80% or lower. The alternative hypothesis was that the acute effectiveness of the therapy is greater than 80%. These hypotheses may be stated as:

$$H_O: P_{AEf} \leq 0.80 \quad \text{vs.} \quad H_A: P_{AEf} > 0.80$$

where P_{AEf} is the proportion of subjects in the target population with successful therapy post-procedure. Successful therapy during the ablation procedure is defined as the successful creation of bi-directional block.

140/160 ablated subjects were reported to achieve bidirectional block. The lower confidence bound was 81.36% which exceeds the pre-specified performance goal of 80%.

Table 10: Acute Effectiveness

# Subjects	Percent	95% LCB	OPC Goal
140/160	87.50%	81.36%	95% (80% LCB)

The acute effectiveness endpoint was met.

Pivotal Study – Chronic Effectiveness Results

The sponsor presented the following analyses to assess freedom from recurrence of atrial flutter at 6 months:

Core Lab Determination	Based directly upon the blinded adjudication by the Scheinman core lab.
Clinical Determination	Used the treating clinician's judgment regarding success/failure to readjudicate some patients as successes who were considered to be failures by the Scheinman core lab based upon event recordings.

Censoring

Only subjects who were acute effectiveness successes were considered in the chronic effectiveness analysis. Of the 140 patients with acute effectiveness success, eight patients were censored from the survival analysis due to non-compliance or death. Atrial flutter was not identified for any of the 7 censored subjects in whom electrograms were available. For one patient, no electrograms were available.

Core Lab Determination

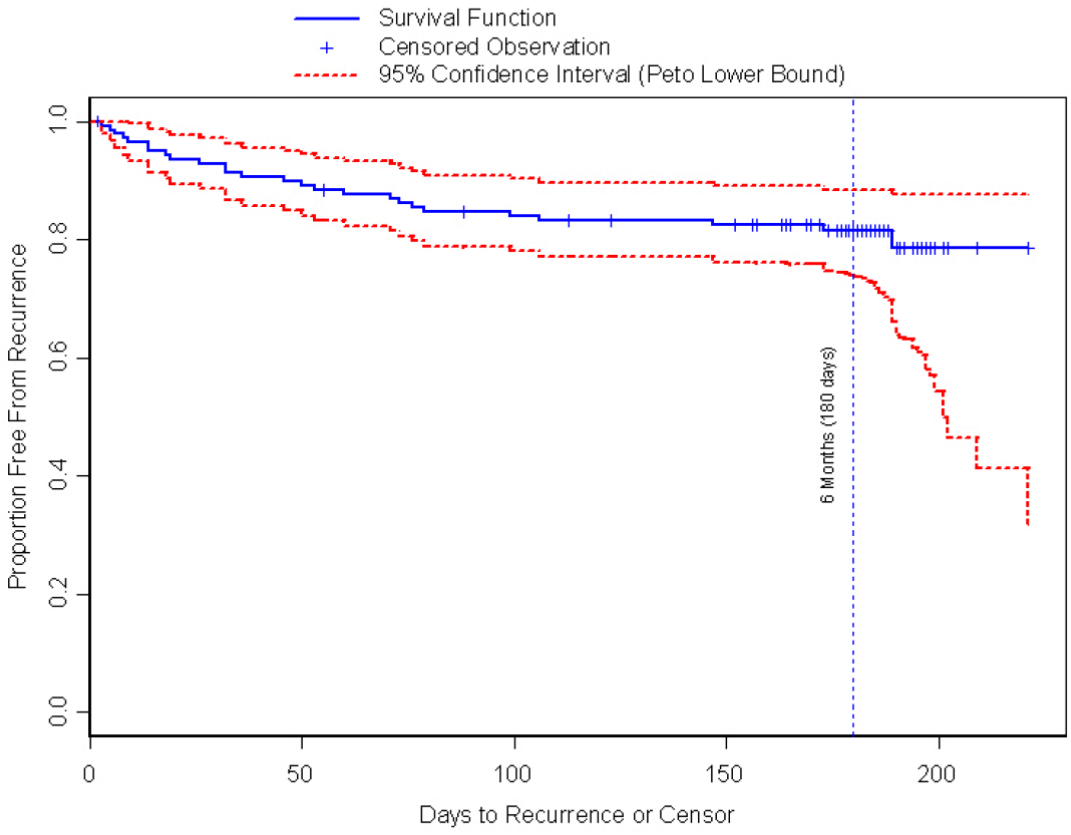
Using the blinded adjudication by the Scheinman core lab, the 6-month survival estimate for freedom from atrial flutter recurrence was 81.60%, with a lower 95% confidence bound of 74.70%.

Table 11: Chronic Effectiveness, Core Lab Determination

Analysis	Proportion Free From AFL Recurrence	95% LCB	OPC Goal
Survival Estimate	81.60%	74.70% (Peto)	90% (80% LCB)

The chronic effectiveness endpoint was not met.

Figure 4: Core Lab Determination days to recurrence of atrial flutter (figure provided by the sponsor)



The Panel will be asked to comment on the chronic effectiveness results based on the Core Lab Determination.

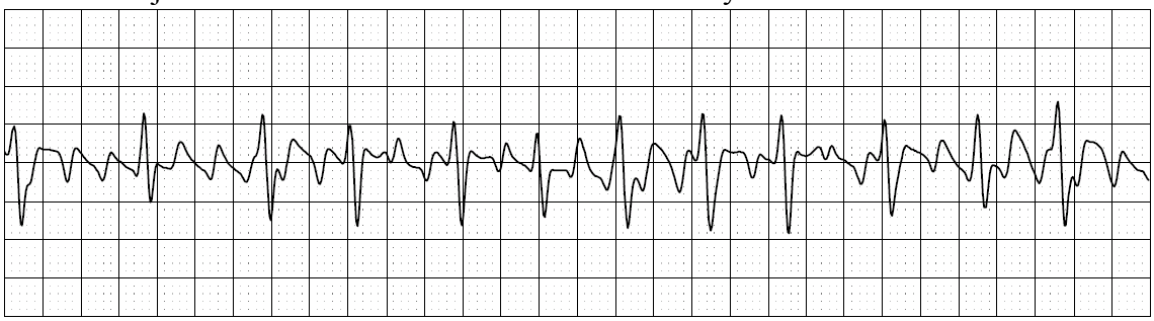
Clinical Determination
The Clinical Determination Analysis is a *post hoc* analysis which readjudicates some patients as chronic effectiveness successes who were adjudicated as chronic effectiveness failures by the Scheinman core lab. The readjudication is based on the investigator's assessment of whether or not an individual subject was a chronic success.

The Clinical Determination Analysis readjudicates 13 patients, deemed by the Scheinman core lab as chronic effectiveness failures to be chronic effectiveness successes, resulting in a 6-month survival estimate for freedom from atrial flutter recurrence of 90.50%, with a lower 95% confidence bound of 85.70%.

Table 12: Clinical Determination Results

	Proportion Free From AFL Recurrence	**95% LCB**
Survival Estimate	90.50%	85.70% (Peto)

Figure 5: Event recorder tracing demonstrating a recurrence of atrial flutter in a patient who was adjudicated in the Clinical Determination Analysis to be a chronic success.



Subject 30-15 recorded November 11, 2004 at 12:24 PM.

In assessing the merits of the Clinical Determination Analysis, FDA considered the following points:

- This analysis readjudicates some patients who were objectively documented to have recurrent atrial flutter as being chronically free of atrial flutter based upon a clinical assessment.
- This analysis is unblinded and may be susceptible to bias.
- This analysis does not consider the possibility that there may have been patients without documented atrial flutter (considered chronic successes by the Scheinman core lab) who would have been considered by their clinician to be chronic effectiveness failures based upon an emergency room visit or some other assessment indicating recurrence. This analysis readjudicates the failures that might be changed to success but does not consider the successes that might be changed to failure.

The Panel will be asked to comment on the chronic effectiveness results based on the Clinical Determination analysis.

Additional Data

OUS Experience

The sponsor has presented additional data from 111 sequential subjects with atrial flutter who were treated with the CryoCor Cryoablation System between June, 2001 and January, 2006 at a single OUS center. Acute effectiveness was defined as the presence of bi-directional block. Chronic effectiveness was defined as the absence of atrial flutter as documented by electrocardiograms collected during regular clinical follow-up.

Table 13: OUS Effectiveness Results *

	# Subjects	**95% LCB**
Acute effectiveness	104/111= 93.69%	87.44%
Chronic Effectiveness at 6 months (survival estimate)	93.70%	89.08%

* The results in Table 13 were provided by the sponsor; FDA's chronic effectiveness calculations do not agree exactly.

In assessing the utility of the OUS data, FDA considered the following points:

- The clinical experience reported is based on a single site and apparently a single investigator.
- While the experience consisted of sequential patients, this was a retrospective evaluation.
- There was no clinical protocol and there were no case report forms.
- The sponsor could not make the ECG recordings available to FDA in order for FDA to perform an adjudication of the results.
- Patients were not systematically provided event monitors for rhythm monitoring.
- Only acute device related complications were evaluated.

The Panel will be asked to comment on the value of the OUS experience data.

Pain Perception

The sponsor provided a report on the pain perception associated with cryoablation vs. RF ablation (Timmermans, *et al*. "Randomized Study Comparing Radiofrequency Ablation with Cryoablation for the Treatment of Atrial Flutter with the Emphasis on Pain Perception". *Circulation* 2003; 107:1248-1250). This was a study of 14 patients randomized to RF or the CryoCor Cryoablation System for the treatment of atrial flutter. There were no significant differences in the procedure parameters with the exception of pain perception. The authors used a Visual Analogue Scale (VAS) and all the 7 patients treated with RF perceived pain with at least one application, whereas only one of the 7 cryoablation patients perceived pain. Importantly, the cited paper makes no reference to the pain assessment being performed in a blinded fashion.

The Panel will be asked to comment on the value of the pain perception data.

Conclusions

The data presented in the PMA characterize the acute and long term safety and effectiveness of the CryoCor Cryoablation System. While the pre-specified acute effectiveness endpoint was met, the safety and chronic effectiveness endpoints were not met. FDA requests input from the Advisory Panel in interpreting these data and rendering an approvability recommendation.