A Pivotal Clinical Study to Evaluate the Safety and Effectiveness of the CryoCor™ Cardiac Cryoablation System for the Treatment of Cavo-Tricuspid Valve Isthmus-Dependent Atrial Flutter

Protocol Number: GL-AFL-02

PMA Number: P050024

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1. Device Description

The CryoCor™ Cardiac Cryoablation System includes a console and a single-use percutaneous cryoablation catheter. The Cryoablation Catheter is a 10 French 6.5 mm tip steerable ablation catheter that handles like a standard RF catheter.

The CryoCor Cryoablation System provides the cardiac electrophysiologist with a means for ablating cardiac tissue through freezing. Internally, the catheter has a coaxial configuration with a small central capillary tube that delivers pressurized nitrous oxide to the catheter's metal tip, where it is released into a larger space. This sudden drop in pressure and consequent refrigerant expansion allows the metal tip to becomes very cold (~ -90˚C) and the tissue with which it is in contact freezes rapidly creating an ice ball. The size of the ice ball varies with heat load and grows with time. A 6-8 mm diameter around the tip is typical. Tissue cell death is certain where the temperature is about -10˚C or colder. Although myocardial cells within the ice ball die as a result of freezing, there is no disruption in the inherent structure of the frozen tissue. This entire process requires as little as 30 seconds, but may be extended to several minutes to maximize lesion size.

Nitrous oxide was chosen as the refrigerant for reasons of safety: it is relatively non-toxic internally and has a high blood solubility coefficient. Additionally, the catheter is maintained at vacuum pressures to ensure that blood is drawn into the catheter rather than gas released should there be a breach.

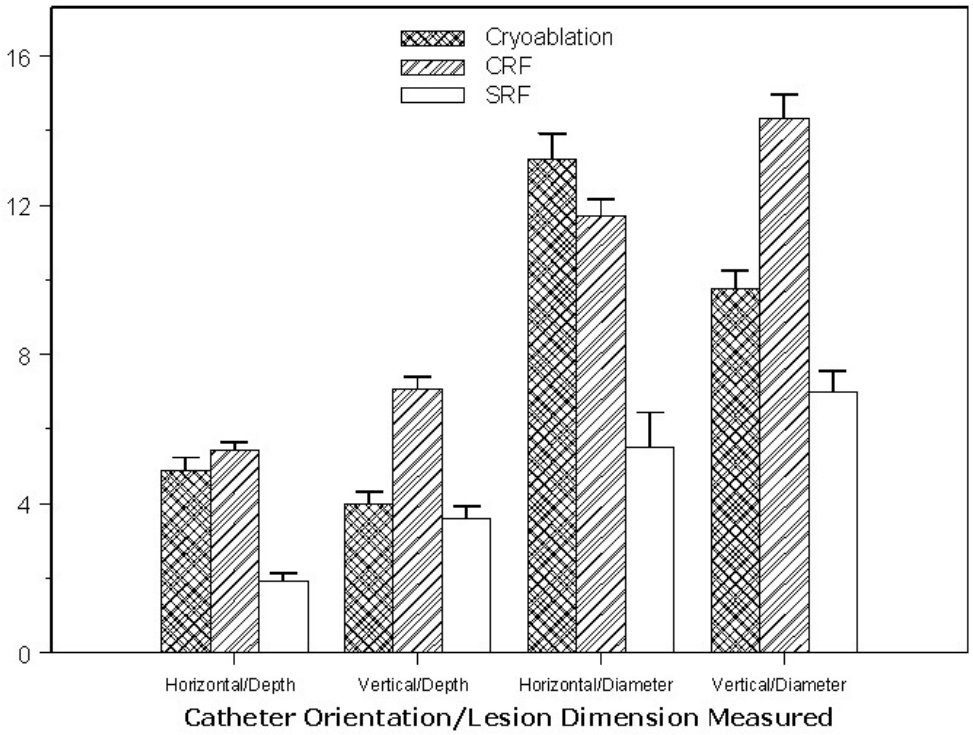
The CryoCor Cryoablation System is unique in its ability to achieve such cold temperatures at the catheter tip, close to the physical limits for nitrous oxide. The extremely cold temperatures reaching as low as -90˚C are the result of a second completely independent refrigeration system (a patented Pre-Cooler), that cools the nitrous oxide refrigerant just prior to entering the catheter.

2. Pre-Clinical Data

2.1 Comparison of Lesion Dimensions for Cryoenergy vs. Radiofrequency energy

A thigh muscle preparation study compared lesion width and depth for cryoenergy and radiofrequency ablation, both standard (SRF) and saline-irrigated cooled radiofrequency (CRF), using both vertical and horizontal catheter tip orientations. Figure 1 shows the comparisons of diameter and width, respectively. Only vertically oriented catheter CRF lesions were larger than those created by cryoenergy. <u>Overall, cryo lesions were slightly larger than RF lesions.</u>

Figure 1: Lesion Sizes with Cryo, RF and SRF based on catheter orientation



2.2 Conclusion from Animal Study

In conclusion, Cryoenergy is able to produce lesions of greater or similar size to that of those created by radiofrequency. Therefore, it will have the same ability as RF to create lesions across the tricuspid isthmus for the treatment of atrial fibrillation.

3. Clinical Data

3.1 Background

Radiofrequency ablation of the cavo-tricuspid isthmus is an accepted method of treating typical atrial flutter. Lesions are created until bi-directional block has been created. The CryoCor™ Cardiac Cryoablation System uses cryoablation to create similar lesions for the treatment of atrial flutter as demonstrated by bi-directional block across the cavo-tricuspid isthmus and long term clinical follow-up.

3.2 Study Design

This was a prospective single-arm study conducted with 160 subjects at 24 U.S. sites to evaluate safety and effectiveness of the CryoCor System. Subjects were evaluated at discharge, one, three, and six months post-procedure as well as weekly via trans-telephonic event recordings collection. Subjects who met the established inclusion and exclusion criteria were enrolled.

3.3 Cryoablation Treatment Procedure

Subjects were sedated and venous access was obtained according to the standard of care at each clinical site.

Just prior to cryoablation, baseline electrophysiology measurements were performed to document isthmus-dependent atrial flutter. If documentation of isthmus-dependent atrial flutter could not be established, the subject was considered to be a secondary screen failure and was not allowed to proceed with the cryoablation.

Freezes/ablations of up to five minutes in duration were performed along the cavo-tricuspid isthmus. Lesions were made until there was clear evidence of bidirectional block across the isthmus. A minimum of thirty minutes after the last ablation was performed was required prior to re-testing for bi-directional block (BDB) using standard pacing methods. If conduction had returned, additional ablations were allowed, and the clock for determination of BDB was restarted. The use of isoproteronol for additional assessment of the block was optional.

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

3.4 Study Objectives

3.4.1 Study Primary Endpoints

The primary endpoints were the following acute safety and effectiveness measures:

- Measurement of all serious adverse events (SAEs) that occurred within seven days after the procedure
- Creation of bi-directional block with cryoablation as the surrogate measure of procedural effectiveness

3.4.2 Study Secondary Objectives

The secondary objectives were the following chronic safety and effectiveness measures:

- Measurement of serious adverse events that occurred more than seven days after the cryoablation procedure
- Long-term absence of recurrences of atrial flutter
- Re-treatment effectiveness

3.5 Selection of Study Population

3.5.1 Inclusion Criteria

Subjects were eligible for inclusion in the study if they met all of the following Inclusion Criteria:

- 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

3.5.2 Exclusion Criteria

Subjects were excluded from the study if any of the following conditions were present:

- 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

3.5.3 Prior and Concomitant Therapies Allowed

Subjects with concomitant atrial fibrillation (AF) requiring drug therapy, other than with Class IC or Class III antiarrhythmic drugs, for conversion to atrial flutter were excluded from the study.

The study allowed inclusion of subjects with a history of AF who had converted to symptomatic atrial flutter when placed on anti-arrhythmic drugs (specifically Class IC and Class III drugs). After cryoablation was performed, the continuation, discontinuation or modification of all pre-procedure Class IC and Class III drugs for the purpose of AF control was at the discretion of the investigator.

3.6 Adverse Events

3.6.1 Adverse Event Definitions

An adverse event was defined in the protocol as any undesirable experience occurring to a subject during the course of the study, whether or not it was related to the device or procedure.

A serious adverse event (SAE) was defined (21 CRF Part 803.3(bb)(1)) as any clinical event resulting in:
- death,
- a life-threatening complication,

- a persistent or significant disability/incapacity that requires inpatient hospitalization or prolongs hospitalization or requires intervention to prevent a permanent impairment of a body function or damage to a body structure.

3.7 Objective Performance Criteria (OPC) for Radiofrequency (RF) Catheters

Objective Performance Criteria (OPC) for radiofrequency ablation of atrial flutter were used as a comparison for success. The endpoints for this study were taken from the FDA guidance document "Cardiac Ablation Catheters Generic Arrhythmia Indications for Use; Guidance for Industry, July 1, 2002." The OPCs were taken from previously approved RF devices and published literature that used a different way of evaluating the data.

The OPCs used in the study protocol are included in Table 1.

Table 1: Protocol GL-AFL-02 OPCs for RF

Study Endpoint	Target Value	95% Confidence Bound
Acute Success	> 95%	≥ 80%
Chronic Success	>90%	≥ 80%
7 Day SAEs	< 2.5%	≤7%

3.8 Significant Protocol Revisions

During the course of the pivotal study, minor changes were made to the protocol in accordance with IDE regulations. In addition, there were two significant protocol changes.

- The protocol was amended to reflect a change in the bi-directional (BDB) re-assessment time from 60 to 30 minutes.
- There was a change in catheter model from the 1100 series to the 1200 series. Animal studies revealed that the lesion sizes were slightly larger for the 1200 catheters.

Neither change had a statistically significant impact on the results.

3.9 Statistical Methods Planned in the Protocol and Determination of Sample Size

3.9.1 Study Population

A subject was considered for analysis when the CryoCor Inc. cryoablation catheter was inserted into the subject's body

3.9.2 Primary Endpoints

3.9.2.1 Safety

3.9.2.1.1 Hypothesis:

The null hypothesis for this objective was the incidence of serious adverse events with Cryoablation therapy (CCS) is more than 7%. The alternative hypothesis was that the incidence of serious adverse events with Cryoablation therapy is 7% or less. These hypotheses may be stated as:

$$H_O: P_{CCS} > 0.07 \quad \text{vs.} \quad H_A: P_{CCS} \leq 0.07$$

where "P" is the proportion of subjects experiencing at least one serious adverse event through seven days after the cryoablation procedure. By rejecting the null hypothesis we demonstrate that cryoablation meets the OPC for safety (upper bound of 7%).

3.9.2.2 Effectiveness

3.9.2.2.1 Hypothesis:

The null hypothesis for this objective was that the effectiveness (bi-directional block as a surrogate endpoint for freedom from atrial flutter) with Cryoablation therapy is worse than 80%. The alternative hypothesis was that the effectiveness of CCS therapy is 80% or better. These hypotheses may be stated as:

$$H_O: P_{CCS} < 0.80 \quad \text{vs.} \quad H_A: P_{CCS} \geq 0.80$$

where "P" is the proportion of subjects with successful therapy post-procedure. Successful therapy during the ablation procedure is defined as the successful creation of bi-directional block. By rejecting the null hypothesis we would demonstrate that cryoablation meets the OPC for effectiveness (lower bound of 80%).

3.9.2.3 Determination of Sample Size

The sample size required to test the primary safety hypothesis was determined using the following formula:

$$N = \left[\frac{Z_\alpha \sqrt{p_0 q_0} + Z_\beta \sqrt{p_1 q_1}}{p_1 - p_0} \right]^2$$

where:

α=0.05 (Type I error, one-sided)
β=0.20 (80% power)
p_0=0.07 (OPC upper bound for safety)
p_1=.025 (expected incidence of SAEs, based on prior studies)
q_0=1-p_0
q_1=1-p_1

With these assumptions, the required sample size was 160 subjects, the number recruited into the study and treated.

3.9.2.4 Secondary Endpoint

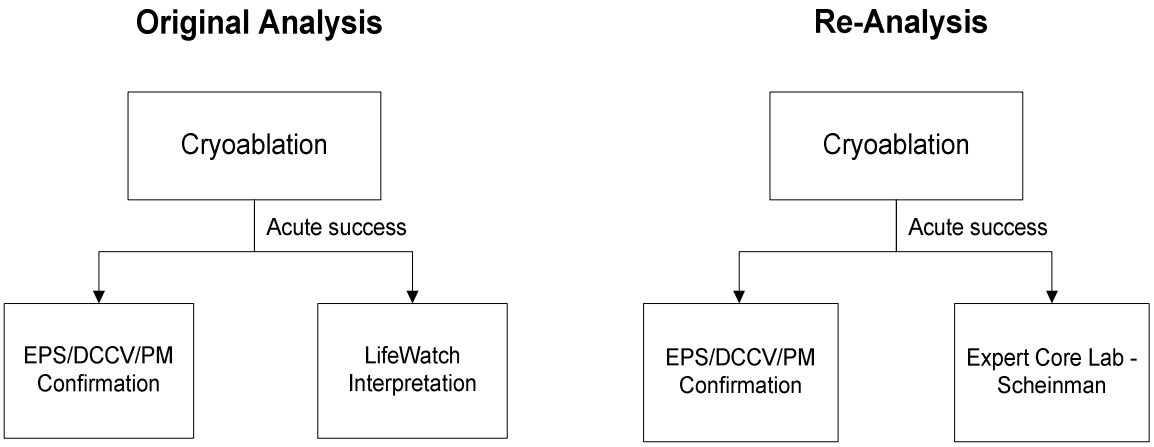
After consultation with the FDA in the development of the study protocol, it was determined that an estimate of long-term effectiveness (freedom from recurrence of atrial flutter) would best be derived using survival methods (Kaplan-Meier). Long-term effectiveness was defined as freedom from recurrence of isthmus-dependent atrial flutter, as evidenced by event recordings or other ECG, and was to be evaluated at six months.

3.9.3 Data Flow

The original PMA submission 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 (EPS/DDCV/PM), were interpreted by an expert who was blinded to the study, Dr. Mel Scheinman. He interpreted the event recordings individually and without the benefit of ancillary data, including clinical or ECG data.

A comparison of the two processes is show in Figure 2.

Figure 2: Data Flow Comparison



3.9.4 Expert Core Lab (Scheinman) Review

The expert core lab reviewed 3909 event recordings from 122 subjects. Of these subjects, 31 had an indeterminate determination for one or more event recordings. For 23 of these subjects, the expert core lab identified "artifact" as the explanation for classification as indeterminate, this was 68 out of 82 indeterminate event recordings.

Subjects were considered failures if there was evidence of recurrence of atrial flutter. Each event recording was read separately and without the benefit of 12 lead ECGs or other ancillary data.

The expert core lab reversed decisions from the results reported from the original LifeWatch analysis in 22 cases. Six went from success to failure and 16 went from failure to success. Table 2 lists the patients.

Table 2: Comparison of Results from Lifewatch and Scheinman Core Labs

Subject	LifeWatch interpretation	Scheinman interpretation
	Failure	Success
	Failure	Success
	Failure	Success
	Failure	Success
	Failure	Success
	Failure	Success
	Failure	Success
	Failure	Success

Subject	LifeWatch interpretation	Scheinman interpretation
	Success	Failure
	Success	Failure
	Failure	Success
	Failure	Success
	Failure	Success
	Success	Failure
	Failure	Success
	Success	Failure
	Failure	Success
	Success	Failure
	Failure	Success
	Failure	Success
	Failure	Success
	Success	Failure

4. Study Subjects

4.1 Subject Enrollment

A total of 24 US sites enrolled 189 subjects for participation in this study. 160 subjects actually participated in the study and had a CryoCor catheter used.

4.2 Demographic and Other Baseline Characteristics

The study population was composed of 160 subjects diagnosed with cavo-tricuspid isthmus dependant atrial flutter. The summary of subject demographics is seen in Table 3.

Table 3: Subject Demographics

	Subject No. (%)
Male/Female	[illegible]
Age (mean ± SD)	[illegible]
AF History	[illegible]
Cardiomyopathy	[illegible]
Congestive Heart Failure	[illegible]
Diabetes	[illegible]
Hyperlipidemia	[illegible]
Ischemic Heart Disease	[illegible]
Obesity	[illegible]
Previous MI	[illegible]
Systemic Hypertension	[illegible]
Tobacco Abuse	[illegible]
Ejection Fraction <= 40	[illegible]

4.3 Sites and Investigators

Subjects were enrolled at 24 study sites listed in Table 4 below.

Table 4: Investigators and Sites

Principal Investigator	Site Name/Location	Enrollment
James Daubert	University of Rochester, Rochester, NY	21
Vijendra Swarup	Arizona Arrhythmia Consultants, P.L.C., Phoenix, AZ	17
Raul Weiss	Riverside Methodist Hospital, Columbus, OH	12
Gregory Botteron	Metro Heart Research Foundation, St. Louis, MO	11
William Miles	Southwest Florida Heart Group, Fort Myers, FL	11
Ulrika Birgersdotter-Green	University of California, San Diego, San Diego, CA	10
Arjun Sharma	Regional Cardiology Associates, Sacramento, CA	9
Thabet Al-Sheikh	Cardiology Consultants, Pensacola, FL	8
Robert Hoyt	Iowa Heart Center, Des Moines, IA	8
Roy John	Lahey Clinic, Burlington, MA	7
Mark Niebauer	The University of Nebraska Medical Center, Omaha, NE	7
Kalyanam Shivkumar	University of California, Los Angeles, Los Angeles, CA	7
Abraham Kocheril	Carle Clinic Association, P.C., Urbana, IL	7
Jazbir Sra	Heart Care Associates L.L.C., Milwaukee, WI	6
John Miller	Indiana University, Indianapolis, IN	6
Charles Athill	San Diego Cardiac Center, San Diego, CA	6
Peter Zimetbaum	Beth Israel Deaconess Medical Ctr., Boston, MA	6
Andrew Corsello	Maine Medical Center, Portland, ME	6
Tariq Salam	Cardiac Study Center, Tacoma, WA	6
Donald Rubenstein	Arrhythmia Consultants, P.A., Greenville, SC	5
Michael Kwasman	Deaconess Medical Center, Spokane, WA	5
Jack Kron	Oregon Health and Science University, Portland, OR	4
Eric Johnson	The Stern Cardiovascular Center, Memphis, TN	3
David Callans	University of Pennsylvania, Philadelphia, PA	1

5. Summary of Results

5.1 Safety Evaluation

5.1.1 Primary Endpoint- Acute Safety -- Serious Adverse Events

Ten (10) subjects (6.25%) reported 11 serious adverse events within 7 days of the index procedure. One subject had atrial fibrillation secondary to hyperthyroidism, so this was counted as one event. All acute events were resolved by the end of the study. Of these events, 4 (2.50%) were attributed to either the study device or procedure. The device-related and procedure-related SAEs occu[illegible]ys included one case each of [illegible]cedural hematoma [illegible]atrioventricular blo[illegible]ete [illegible]cardiac tamponade [illegible]) and acute respiratory failure [illegible] Table 5 contains the frequency of events during the 7 day period are described below.

Table 5: 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%)
Pos Procedural Haematoma	0	1	0	1	1	(0.63%)

5.1.2 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Three (3) subjects died during the course of the study. The deaths were not related [illegible]tion procedure. The c auses of death included: suicide [illegible] and pulmonary emboli during a prolonged hospitali[illegible]

5.1.3 Safety Conclusions

The use of cryoablation to treat atrial flutter in this study was shown to be acutely safe. The incidence of all SAEs within the first 7 days was 6.25% with a 95%, two-sided, upper confidence limit of 11.19% and the incidence of device-related and procedure-related events was 2.50% with a 95%, two-sided, upper confidence limit of 6.28%.

During the extensive review process, the FDA has expressed no concerns verbally or in writing over the safety of the device.

The Safety results are summarized in Table 6

Table 6: Safety Results

Study Endpoint	Count	Percent	95% One-Sided CL	95% Two-Sided CL
Acute Safety				
7 Day SAEs	10/160	6.25%	UCL: 10.37%	(3.04%; 11.19%)
7 Day SAEs (D&P)*	**4/160**	**2.50%**	**UCL: 5.63%**	**(0.69%; 6.28%)**
Chronic Safety				
SAEs post-7 days	27/160	16.88%	UCL: 22.51%	(11.43% ; 23.59%)

* SAEs related to study device or procedure only

5.2 Effectiveness Evaluation

5.2.1 Data Sets Analyzed

The evaluation of acute effectiveness was carried out in all 160 subjects in whom the CryoCor cryoablation catheter was inserted into the body. The subset of the population that was shown to have acute effectiveness was also evaluated for the secondary objective of chronic effectiveness.

5.2.2 Primary Effectiveness Results

One hundred forty (140) of 160 (87.50%) subjects achieved acute effectiveness as defined by bi-directional block across the cavo-tricuspid isthmus.

Table 7: Acute Effectiveness

Count	Percent	95% One-Sided CL	95% Two-Sided CL
140/160	**87.50%**	**82.36%**	**(81.36%; 92.19%)**

These results provide evidence the CryoCor™ Cardiac Cryoablation System is effective in the treatment of isthmus-dependent atrial flutter.

5.2.3 Secondary Effectiveness Results

5.2.3.1 Statistical Analysis of Chronic Effectiveness

The clinical protocol established a secondary objective of investigating the chronic effectiveness of the cryoablation procedure. Subjects eligible to be evaluated for long-term effectiveness were identified as those subjects achieving acute effectiveness (140 of 160 subjects).

The fo - -- - - patients were censored from the survival analysis at specific points.

1) - - -- - - subject was censored at the time of the last event recording of August 18, 2004 (day 19). He was censored because of a successful - - - - - on August 28, 2004.
2) - - -- - - - ubject was censored on day 147 but had a clinic visit with an ECG showing no atrial flutter on day 157.

3 subject censored on November 15, 2004 (day 113) because of death. Last event recording was on October 13, 2004 but was hospitalized with continuous monitoring from 10/18/2004 to 11/15/2004 with no nce of atrial flutter.

4) subject non-complaint for first month of event recordings, but was ompliant for 171 days. Subject was censored at day 2.

5 subject did not comply with the requirement of 3 event recordings/month after the 3 month visit so was censored on day (123) but there were additional event recordings out to 169 days with no ce of recurrence.

6) subject was hospitalized for bacteremia and was non-compliant with transmitting event recordings during that time so was censored on day 55. However, there were no recurrences on daily ECGs that were obtained during that hospitalization. The subject became compliant with ecordings after that hospitalization until day 182.

7 subject was censored on August 7, 2004 (Day 88) for non-compliance but had additional event recordings on October 1 and October 26, 2004 that were sinus rhythm. There was a successful suicide on ber 26. 2004.

8) subject never complied with event recordings so was censored on day 2 but clinical follow-up with ECGs in the clinic showed no recurrence out to 6 months.

All other patients not recurring were censored at their last known visit or compliance with event recording. Patients failing were failed at their first reported AFL event.

Subjects were classified as either having atrial flutter or not during the 6-month follow-up period based on Dr. Scheinman's interpretation.

5.2.3.4 Chronic Effectiveness- Re-Analysis results

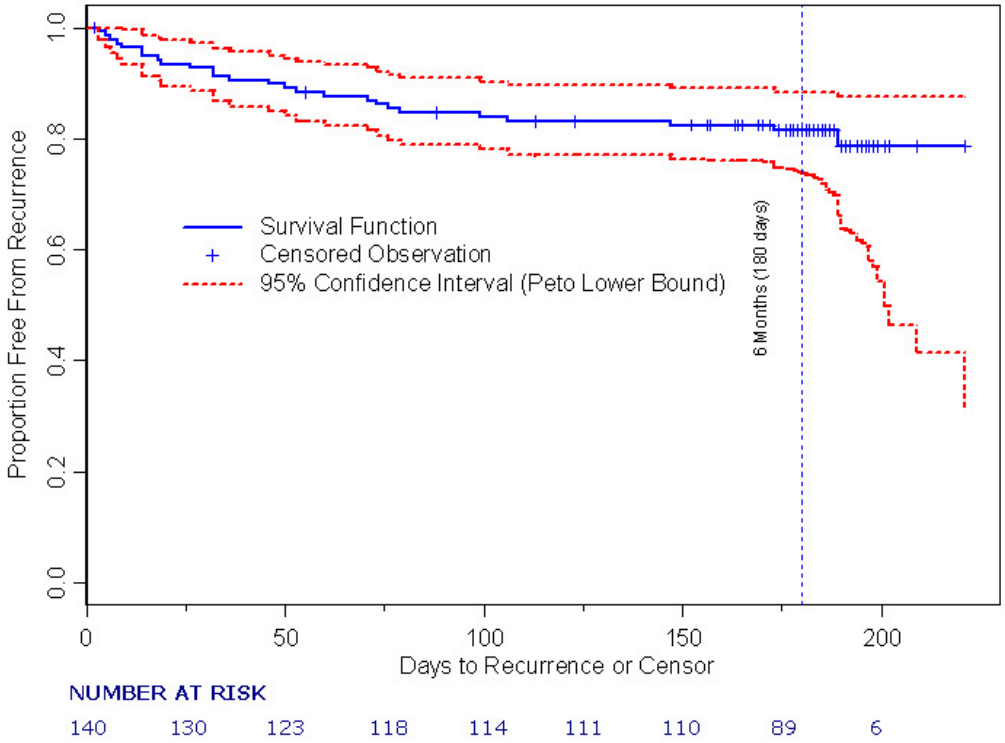
Indeterminate readings by Dr. Scheinman were censored. This resulted in a chronic success of 81.60% (74.70%; 88.40%) as shown in Table 8.

Table 8: Chronic Effectiveness

Analysis	Proportion Free From AFL Recurrence	95% CI Lower Bound	95% CI Upper Bound
Survival Estimate	81.60%	74.70 % (Peto)	88.40%

The Kaplan-Meier plot in Figure 3.

Figure 3: Kaplan-Meier Plot



5.2.3.5 Additional Clinical Analysis

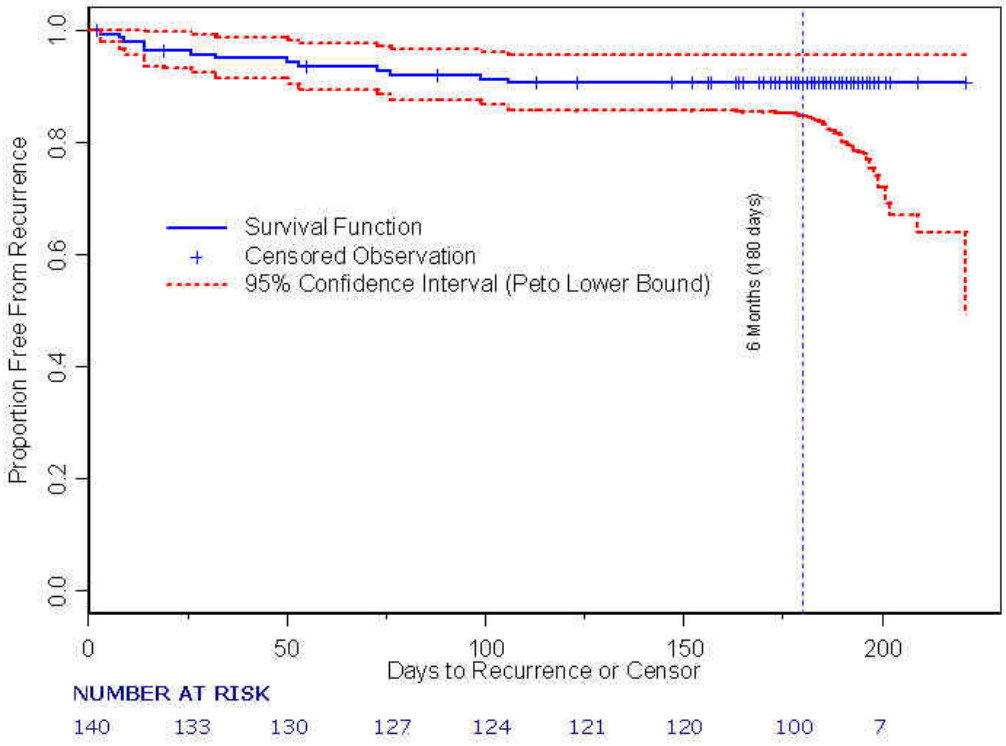
The previously approved catheters for the treatment of atrial flutter, as well as the literature that the OPCs were based upon and the literature on atrial flutter in general, used a clinical definition of success as opposed to an independent event recording core lab. While very few of these studies used event recordings, no study used an independent reading lab.

If the data from this study are placed through a similar evaluation, the results are shown in Table 9 and Figure 4. This allows for the ability to compare comparable study results to the published literature as well as to previously approved devices for the treatment of atrial flutter.

Table 9: Clinical Determination: Survival (Days to Recurrence of Atrial Flutter)

Analysis	Proportion Free From AFL Recurrence	95% CI Lower Bound	95% CI Upper Bound
Clinical Determination: Survival Estimate	90.50%	85.70% (Peto)	95.60%

Figure 4: Clinical Determination: Days to Recurrence of Atrial Flutter



5.2.3.6 Analysis of Re-Treatment Success

Ten subjects underwent repeat ablation for atrial flutter and were considered failures. Five subjects were re-treated with cryoablation and five subjects were retreated with radiofrequency ablation. See Table 10.

Table 10: Treatment Failures Receiving Re-Treatment

	AFL Direction	Documented AFL	Mode of Treatment
	Counterclockwise	Yes	RF
	Counterclockwise	Yes	RF
	Counterclockwise	Yes	CRYO
	Counterclockwise	Yes	CRYO
	Counterclockwise	Yes	RF
	Undetermined	Yes	RF
	Counterclockwise	Yes	CRYO
	Clockwise	Yes	CRYO
	Clockwise	Yes	CRYO
	Both	Yes	RF

One additional subject -- - -- - - underwent electrophysiologic study for presumed atrial flutter, but was found to have bidirectional block. This patient was considered a chronic success.

5.2.3.7 Potential Training Effect Analysis

A review of all treated subjects at each site was conducted, attempting to identify any potential training effect as evidenced by outcomes in acute or chronic effectiveness. Due to the disparity of sample sizes within sites, no statistical analysis of pattern was conducted. The qualitative analysis conducted identified no discernible pattern to early enrollments within sites showing a higher rate of acute or chronic failure.

5.2.3.8 Effect of Catheter Change on Acute and Chronic Outcomes

Analyses were performed to establish whether or not results from the 1100 and 1200 series catheters differed in either acute or chronic (long-term) effectiveness. A Fisher's Exact Test was performed in each case, testing the interaction of catheter model with endpoint outcome.

The primary effectiveness endpoint, the proportion of subjects achieving acute effectiveness, as indicated by attaining bi-directional block was analyzed. A Fisher's Exact Test was performed, yielding a table probability of approximately .1754 (p=.8111). This indicates sufficient evidence of no difference in acute outcome due to catheter model.

Fisher's Exact Test revealed a table probability of .0920 for long-term effectiveness (p=.2776). This indicates sufficient evidence of no difference in chronic outcome due to catheter model.

Catheter Model	N	Acute Effectiveness	Acute Safety	Chronic Effectiveness (Analysis 1)
1100	89	77 (86.52%)	4 (4.49%)	62 (80.52%)
1200	71	63 (88.73%)	6 (8.45%)	44 (69.84%)
Table Probability		0.1754	0.1538	0.0920
Fisher Exact p		0.8111	0.3409	0.2776

5.2.3.9 Effect of Block Wait Time on Acute and Chronic Outcomes

During the course of the study, a protocol revision was implemented, changing bi-directional block wait time from 60 to 30 minutes. An evaluation was performed to determine whether this change had a significant impact on the primary and/or secondary effectiveness endpoints.

The primary and secondary effectiveness endpoints were evaluated to identify any dependence with protocol revisions related to bi-directional block waiting period. A Fisher's Exact Test was performed to determine dependence of the protocol revision and primary endpoint outcome.

When the primary effectiveness endpoint was analyzed, there was evidence of a statistically-significant interaction between acute effectiveness and protocol revision. In the case of those subjects with a 60-minute waiting period, only 68.63% of the 51 achieved acute effectiveness, whereas 96.33% of the 109 subjects treated using a 30 minute wait time achieved acute effectiveness. Fisher's Exact Test yielded an extremely small p-value (3.00 E-06).

Fisher's Exact Test revealed a table probability of .1827 for long-term effectiveness (Analysis 1, p=.8059). There does not appear to be any dependence of chronic outcome due to block wait time. However, since the evaluation of long-term effectiveness is dependent upon acute success, one may infer long-term effectiveness outcome is dependent on block wait time.

When a Cochran-Armitage Test for Trend was performed for long-term effectiveness the resulting test statistic, Z, was -.2510, p=.0818. Among the 35 subjects evaluable for long-term effectiveness treated under the 60 minute BDB wait time, 6 (17.14%) had evidence for a recurrence of atrial flutter. Among the 105 subjects evaluable for long-term effectiveness treated under the 30 minute BDB wait time, 20 (19.05%) had evidence for a recurrence of atrial flutter. There is, therefore, not sufficient statistical evidence to conclude there is a trend in long-term effectiveness due to protocol version (60 vs. 30 minute BDB wait time). However, when once again the dependence of evaluation for long-term effectiveness is dependent on acute effectiveness, it may be inferred that there is likewise a relationship between protocol version (block wait time) and outcome.

Protocol Version	N	Acute Effectiveness	Acute Safety	Chronic Effectiveness (Analysis 1)
60-Minute Wait Time	51	35 (68.63%)	2 (3.92%)	29 (82.86%)
30-Minute Wait Time	109	105 (96.33%)	8 (7.34%)	77 (73.33%)
Table Probability		2.77E-06	0.2130	0.1827
Fisher Exact p		3.00E-06	0.5046	0.8059

5.3 Effectiveness Conclusions

In this study, use of the CryoCor™ Cardiac Cryoablation System was shown to be acutely effective for the treatment of symptomatic atrial flutter. Acute effectiveness was 87.50% (81.36%; 92.19%).

At 6 months, use of the CryoCor™ Cardiac Cryoablation System was shown to be associated with long-term freedom of recurrence from atrial flutter based on a core lab interpretation of event recordings of 81.60% (74.70%; 88.40%). When a clinical interpretation as seen in the published literature was used, the results are comparable to other approved devices at 90.50% (85.70%; 95.60%).

The results summarized in Table 11 below show that the use of the CryoCor™ Cardiac Cryoablation System is associated with acute and chronic treatment success rates that are clinically relevant and consistent with other available treatment modalities.

Table 11: Effectiveness Results

Study Endpoint	Percent	95% Two-Sided CL
Acute Effectiveness	87.50%	(81.36%; 92.19%)
Chronic Effectiveness*	81.60%	(74.70%; 88.40%)
Chronic Effectiveness **	90.50%	(85.70%; 95.60%)

*As per strict electrogram interpretation

** As per clinical analysis

6. Additional Supportive information

6.1 Confirmatory Study for the Use of CryoCor™ Cardiac Cryoablation System for the treatment of Cavo-Tricuspid Isthmus-Dependant Atrial Flutter

In order to confirm the effectiveness results from the US pivotal study, retrospective evaluation of the Academic Hospital Maastricht's experience with the CryoCor system was analyzed. This hospital has prospectively collected data on all their patients that have been treated with the CryoCor system.

111 sequential subjects with atrial flutter that were treated with the CryoCor™ Cardiac Cryoablation System between June, 2001 and January, 2006 were evaluated. The demographics for these subjects were similar to those in the US study, as shown below in Table 12.

Table 12: Maastricht Subjects Demographics

Gender	Count	Age	AF History Yes
Female	25 (22.52%)	59.88 +/-13.27	15 (60%)
Male	86 (77.48%)	55.57 +/-13.17	72 (83.72%)
ALL	111 (100%)	56.54 +/-13.26	87 (78.38%)

Table 13 contains the acute and chronic results from the Maastricht study. The acute effectiveness was 93.69% (87.44%; 97.43%). In order to accurately compare this result to the pivotal study results, 6 month effectiveness was 93.81% (87.02%; 97.7%). These results confirm the US pivotal study.

Table 13: Acute, 6-month and Long-term Effectiveness Results

	Count	95% CI	Ave FU time (days)
Acute effectiveness	104/111= 93.69%	(87.44%; 97.43%)	N/A
Chronic Effectiveness at 6 months	**91/97 = 93.81%**	**(87.02%; 97.7%)**	N/A

6.1.1 Conclusion from Confirmatory Study

This single center retrospective analysis demonstrates that Cryoablation is an effective alternative to RF for the treatment of typical atrial flutter when used by an experienced operator. Both the acute and chronic effectiveness rates are excellent and consistent with RF data.

6.2 Pain Perception

Timmermans et al from Maastrict published "Randomized Study Comparing Radiofrequency Ablation with Cryoablation for the Treatment of Atrial Flutter with the Emphasis on Pain Perception" in *Circulation* 2003; 107:1248-1250.

This was a study of 14 patients randomized to RF or Cryoablation for the treatment of atrial flutter. The patients were blinded to the energy source. 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 patients treated with RF perceived pain with at least one application, whereas only one of the cryo patients perceived pain with VAS results of 38.3 ± 25.3 and 0.32 ± 0.86 respectively ($p<0.05$).

These results were verified in a study done with a competitor's cryoablation product in which patients with atrial flutter were randomized to cryoablation or RF ablation. This paper, "Cryoablation versus Radiofrequency Ablation in the treatment of Atrial Flutter trial (CRAAFT)" by Collins et al in the Journal of Interventional Cardiac Electrophysiology. 2006, Oct 6 .

This concept of less painful procedures becomes important in patients that are at high risk for sedation such as those with pulmonary disease or sleep apnea. Cryoablation provides a safer alternative to RF in the patient that is at higher risk for sedation. In addition, there are those patients that do not want to undergo a repeat ablation because of the pain associated with RF. Cryoablation would provide a safe and effective alternative for these patients.

7. Conclusions

Use of the CryoCor™ Cardiac Cryoablation System was shown in this study to be safe and effective for the treatment of symptomatic atrial flutter. The CryoCor system clearly has an excellent safety profile, especially compared to those devices already on the market.

The CryoCor™ Cardiac Cryoablation System has demonstrated an excellent level of chronic effectiveness. When using comparable analysis techniques, they are equivalent to results seen in the published literature as well as to previously approved devices. To corroborate this, we have provided supportive data from a large single center study demonstrating that in the hands of an experienced operator the chronic effectiveness at 6 months was 93.81% (87.02%; 97.7%). In the US pivotal trial, no center had experience with more than 20 subjects.

Also in support of the ability of cryoenergy to create adequate lesions, we provided animal data clearly demonstrating that cryoablation creates lesions are as large or larger than those created by radiofrequency. The implication is that if the procedure is done correctly, similar results with cryoablation or RF should be obtained. Again, this is supported by the information provided by the single center confirmatory study.

The clinical study has demonstrated the CryoCor™ Cardiac Cryoablation System is safe and effective for use in the treatment of isthmus-dependent atrial flutter. It provides a safe and effective alternative to traditional RF ablation for patients where there is a concern for sedation or have an aversion to the pain associated with RF.