

# CryoCor Cardiac Cryoablation System

FDA review of P050024

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Division of Cardiovascular Devices

Office of Device Evaluation

Food and Drug Administration

June 27, 2007

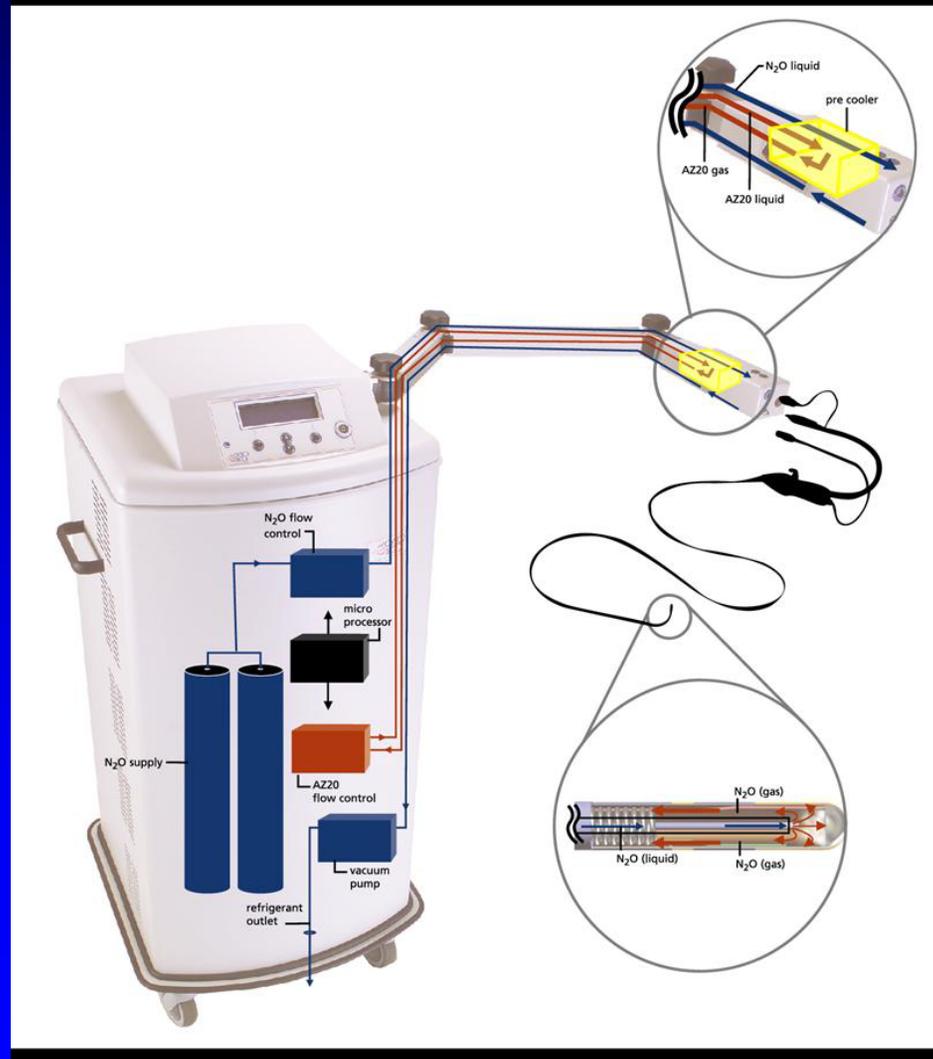


# FDA Review Team

- Randall Brockman, M.D.
- Lesley Ewing M.D.
- Owen Faris, Ph.D.
- Shanti Gomatam, Ph.D.
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- Lisa Leveille
- Pamela Reynolds
- Dale Tavis, M.D., M.P.H.



# Device Description



# 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.

# Preclinical Review

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

# Clinical Studies

- Feasibility
  - 58 subjects, 48 receiving cryoablation
  - Evaluated for safety and acute and chronic effectiveness
- Pivotal
  - 189 subjects, 160 receiving cryoablation
  - 24 US sites

# Performance Goal History

Study Endpoint	Performance Goal	
	Target Value	95% Confidence Bound
Safety (7-day SAEs)	< 2.5%	< 7% UCB
Acute effectiveness	> 95%	> 80% LCB
Chronic effectiveness	> 90%	> 80% LCB

# Review background

- **July 15, 2005** – Sponsor submitted original PMA.
- **October 12, 2005** – FDA issued letter which identified outstanding clinical and statistical issues.
- **October 25, 2005** - Sponsor provided response (Amendment 7).
- **January 26, 2006** - FDA issued letter which identified outstanding issues with chronic effectiveness.
- **November 28, 2006** - Sponsor provided response based on re-adjudication of chronic effectiveness results (Amendment 10).
- **March 1, 2007** - Sponsor provided updated statistical information and additional analyses (Amendment 14).

# Core Lab Adjudication

- Original analysis
  - Relied solely upon event monitor company interpretation
  - Did not include investigator over-read or expert core lab
  - May have misinterpreted some complex electrocardiograms, specifically those with atrial fibrillation, as a recurrence of atrial flutter
- Readjudication
  - Dr. Scheinman expert core lab
  - Reviewed all tracings that were not from patients with clearly documented recurrence of atrial flutter as demonstrated by electrophysiologic study or other treatments for atrial flutter
- FDA considers the readjudication to be scientifically valid.



# FDA Presentations

- Randall Brockman, MD – Clinical
- Shanti Gomadam, PhD – Statistical
- Dale Tavriss, MD, MPH - Epidemiology

# FDA Clinical Review of the CryoCor Cryoablation System

Randall Brockman, MD

June 27, 2007



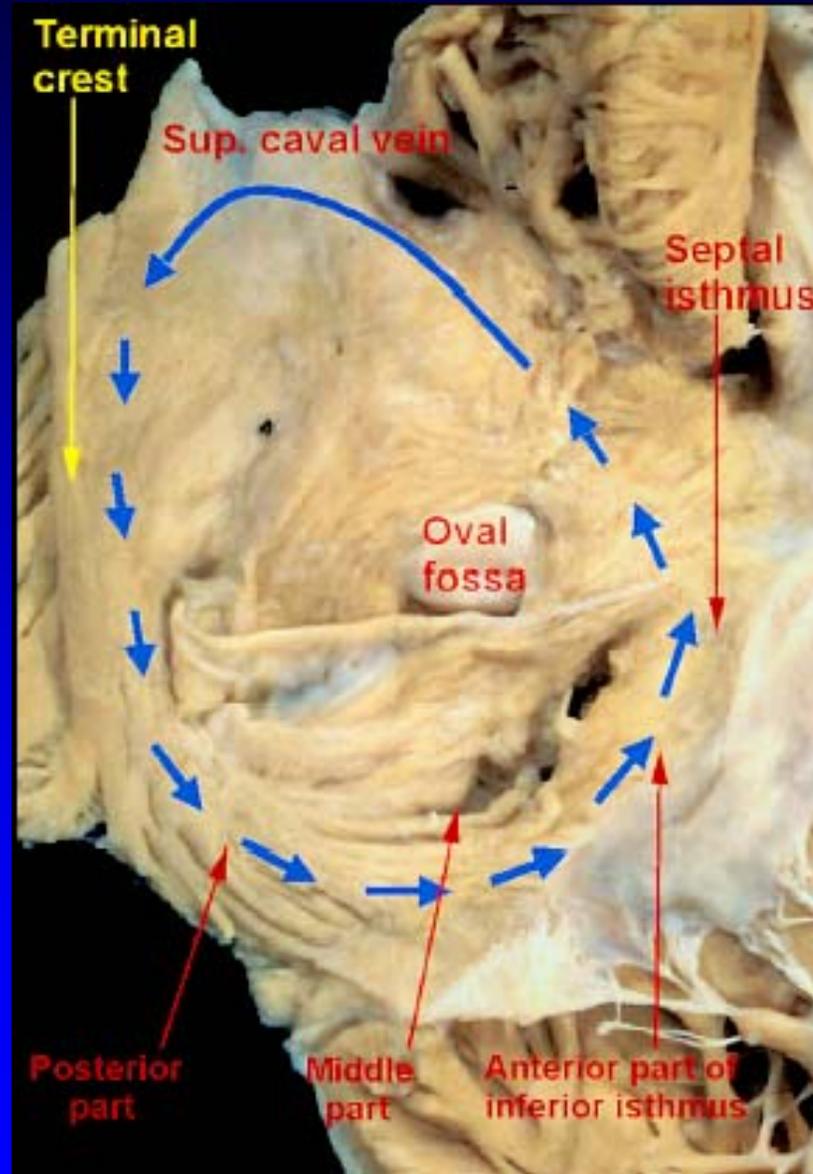
# Topics

- Basics of Atrial Flutter and Ablation
- Feasibility study
- Pivotal study
  - Design
  - Safety results
  - Effectiveness results

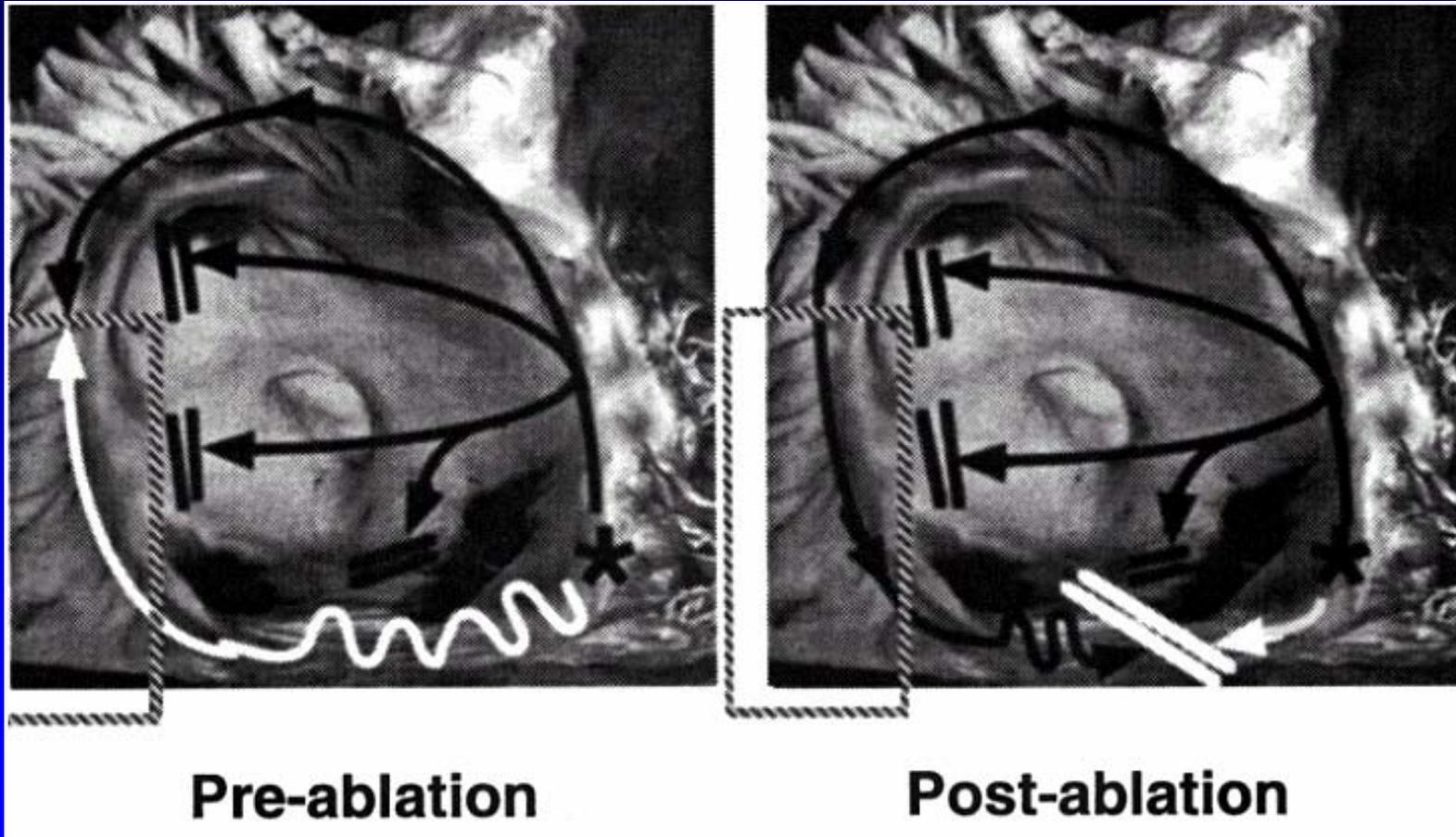
# Atrial Flutter Recording



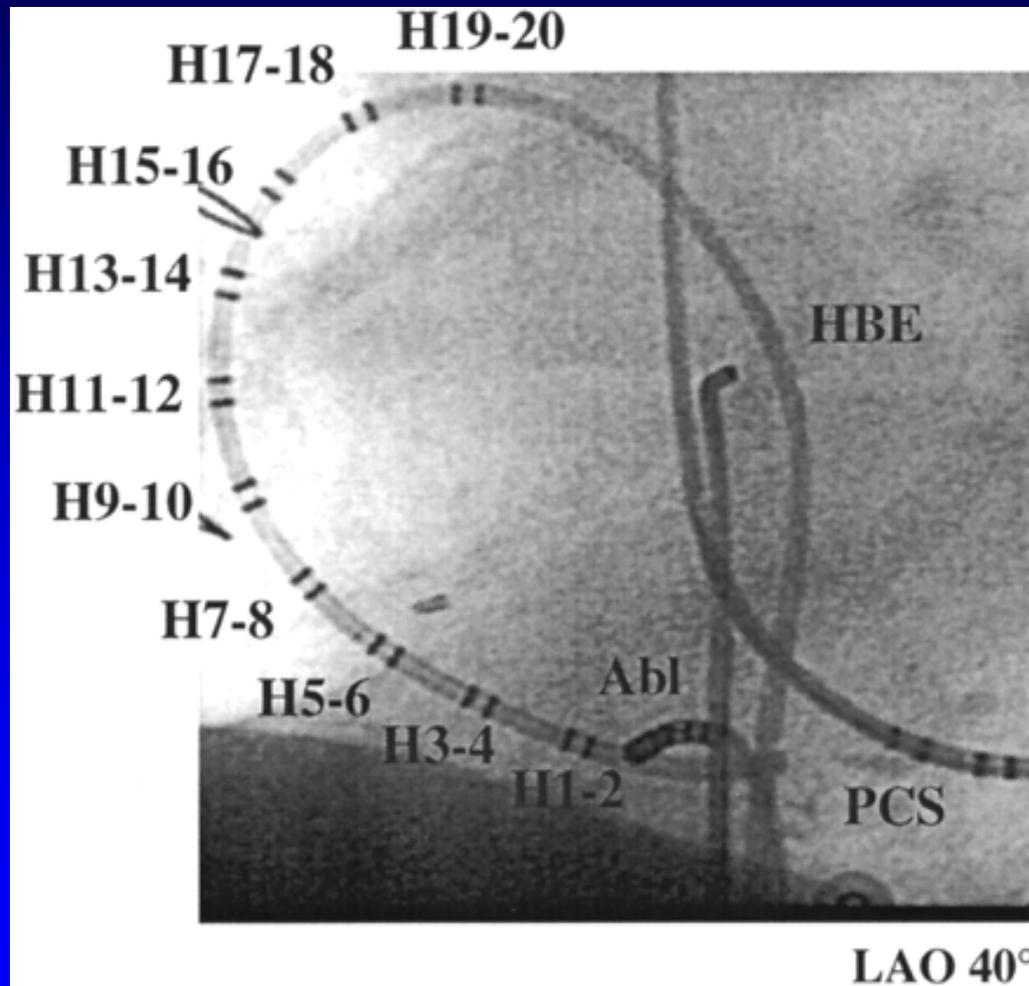
# Atrial Flutter Circuit



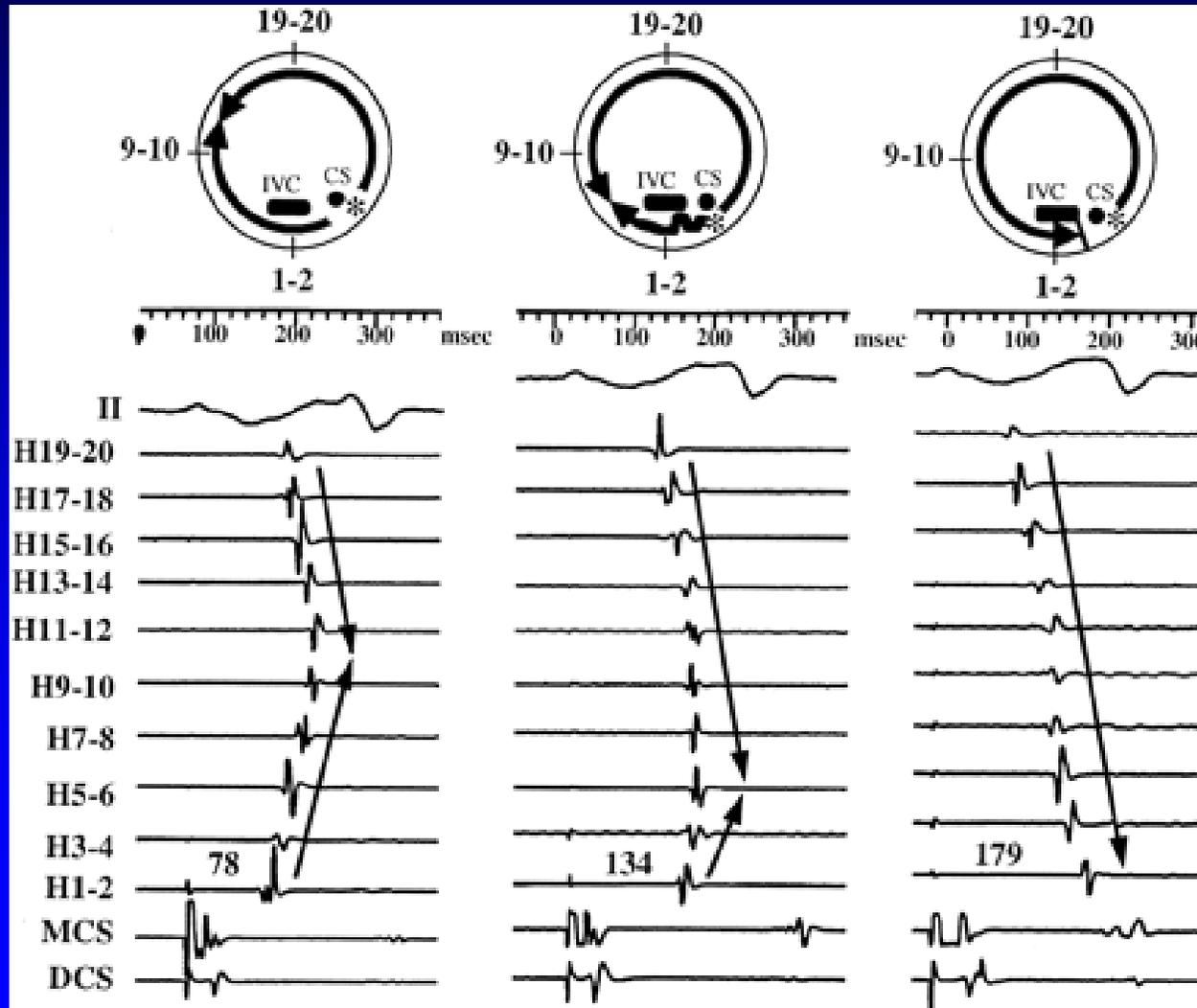
# Conduction Block



# Multi-pole Catheter in Right Atrium



# Clockwise Conduction Block



# Clinical Studies of the CryoCor Cardiac Cryoablation System for Atrial Flutter

# U.S. Feasibility Clinical Trial

- 58 patients with atrial flutter enrolled
- 48 patients underwent cryo-ablation
- Acute effectiveness (BDB) – 94%
- Chronic effectiveness (6 months) – 84%
- Serious adverse event rate – 12.5%

# Pivotal Clinical Trial Design

- Prospective, multi-center, single-arm trial
- Patients meeting all enrollment criteria received Cavo-Tricuspid Isthmus ablation using the CryoCor Cardiac Cryoablation System
- Endpoints tested against performance goals

# Key Inclusion Criteria

- Symptomatic atrial flutter with at least one episode within 6 months prior to enrollment, 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)

# Key Exclusion Criteria

- Structural heart disease
- Any prior ablation for atrial flutter
- Concomitant atrial fibrillation requiring AAD treatment other than Class IC or Class III for conversion to atrial flutter

# Major Endpoints

- *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.

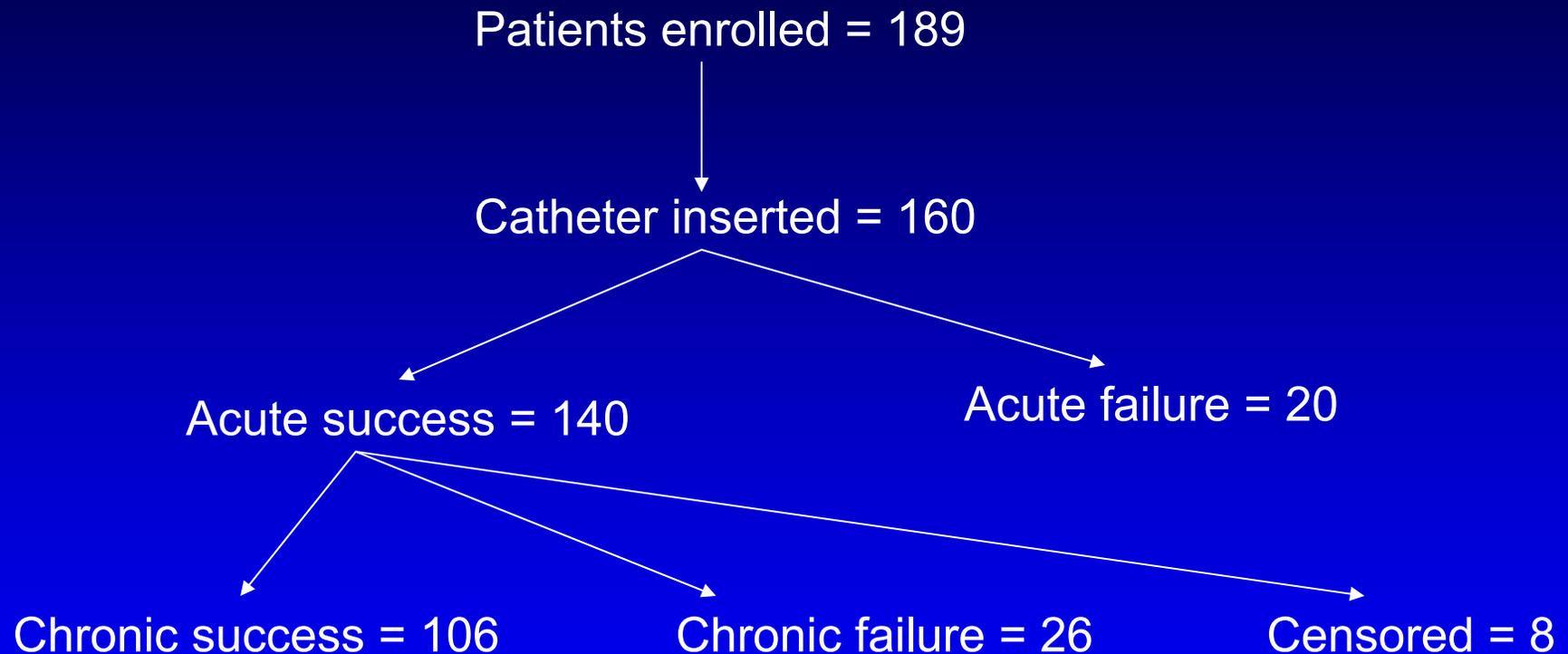
# Major Endpoints (cont.)

- FDA was uncomfortable using APS as the primary effectiveness endpoint for this trial since we believe 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.
- So 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 we would consider the chronic effectiveness evaluation critical in the assessment of overall device effectiveness for purposes of approval.

# Performance Goals

Study Endpoint	Target Value	95% Confidence Bound
Acute Success	> 95%	$\geq 80\%$
Chronic Success	>90%	$\geq 80\%$
7 Day SAEs	< 2.5%	$\leq 7\%$

# Subject Accountability per Protocol



# Baseline Demographics

	Subject # (%)
Male/Female	122/38 (77% male)
Age (mean $\pm$ SD)	63.03 $\pm$ 9.25 years
AF History	94 (59)
Angina	19 (12)
Cardiomyopathy	16 (10)
Congestive Heart Failure	27 (17)
Diabetes	27 (17)
Hyperlipidemia	84 (53)
Hyperthyroid	1 (1)
Hypothyroid	20 (13)
Ischemic Heart Disease	30 (19)
Obesity	44 (28)
Previous MI	26 (17)
Pulmonary Disease	22 (14)
Systemic Hypertension	98 (62)
Tobacco Abuse	18 (12)
Ejection Fraction $\leq$ 40	25 (16)
Prior Treatment with AADs	130 (82)
Prior Ablation	2 (2)

# Chronic Effectiveness Monitoring

- Assessed for patients with Acute Success
- Event Monitoring
  - Transmit random tracings weekly
  - Transmit for symptoms
- Additional methods
  - EPS ± repeat ablation
  - Cardioversion
  - Pacemaker logs

# Protocol Deviations

- Total = 104
  - 75 minor
  - 29 major
    - Enrollment criteria = 9
    - Informed consent = 2
    - Acute effectiveness verified at wrong time = 2
    - Non-compliance with Event Recordings = 7
    - Missed follow-up visits = 9
- FDA's review indicated the reported deviations did not substantially alter the study results

# Results



# Safety Endpoint

- Goal: The occurrence of serious adverse events within seven days of the procedure will be  $\leq 7\%$  (95% UCB).
- Result: Nine (9) patients (5.6%) reported 10 serious adverse events within 7 days of the index procedure. The 7-day SAE rate 95% one-sided upper confidence bound was 9.6%
- The safety endpoint was not met.

# Serious Adverse Events (within 7 days)

(n=160)

Description	Events				Patients	
	Mild	Mod	Severe	Total	Total	Pct
Atrial Flutter	0	1	0	1	1	(0.63%)
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%)

# Serious Adverse Events (after 7 days)

Event	# of SAEs	# of patients	Percent
Atrial Fibrillation	8	8	(5%)
Atrial Flutter	4	3	(1.88%)
Completed Suicide	2	2	(1.25%)
Ankle Fracture	1	1	(0.63%)
Bradycardia	1	1	(0.63%)
Bronchospasm	1	1	(0.63%)
Carotid Artery Stenosis	1	1	(0.63%)
Chest Discomfort	1	1	(0.63%)
Colon Cancer	1	1	(0.63%)
Complex Partial Seizures	1	1	(0.63%)
Dehydration	1	1	(0.63%)
Hyperglycemia	1	1	(0.63%)
Hypokalemia	1	1	(0.63%)
Intracardiac Thrombus	1	1	(0.63%)
Osteomyelitis	1	1	(0.63%)
Pulmonary Embolism	1	1	(0.63%)
Sepsis	1	1	(0.63%)
Sick Sinus Syndrome	1	1	(0.63%)
Suicide Attempt	1	1	(0.63%)
Surgery	1	1	(0.63%)
Tachycardia	1	1	(0.63%)
Transient Ischemic Attack	1	1	(0.63%)

# Patient Deaths

- suicide 18 days post-ablation
- pulmonary emboli ~ 10 weeks post-ablation; expired ~ 14 weeks post-ablation
- illicit drug overdose ~ 6 months post-ablation
- The DSMB reviewed all deaths and felt that none of the three were related to the investigational device and/or procedure.

# Acute Effectiveness Endpoint

- Goal: The proportion of patients achieving bidirectional block (BDB) across the cavo-tricuspid isthmus will be  $\geq 80\%$  (95% LCB).
- Result: One hundred forty (140) patients out of 160 (87.5%) had BDB. The 95% one-sided lower confidence bound was 82%
- The acute effectiveness endpoint was met.

# Chronic Effectiveness Endpoint

- Goal: Freedom from recurrence of atrial flutter at six months (for those patients who achieve acute success) will be  $\geq 80\%$  (95% LCB).
- According to the protocol:

Chronic efficacy is defined as those patients who had acute efficacy after the procedure and did not document AFL on event recordings through six months (refer to Section 12.2.2).

# Chronic Effectiveness Endpoint

Analysis	Proportion Free from AFL Recurrence	95% LCB	Performance Goal
Survival Estimate	81.60%	74.70%	90% (80% LCB)

- The chronic effectiveness endpoint was not met.

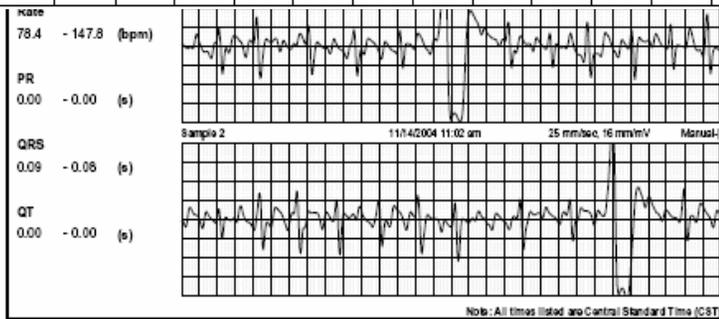
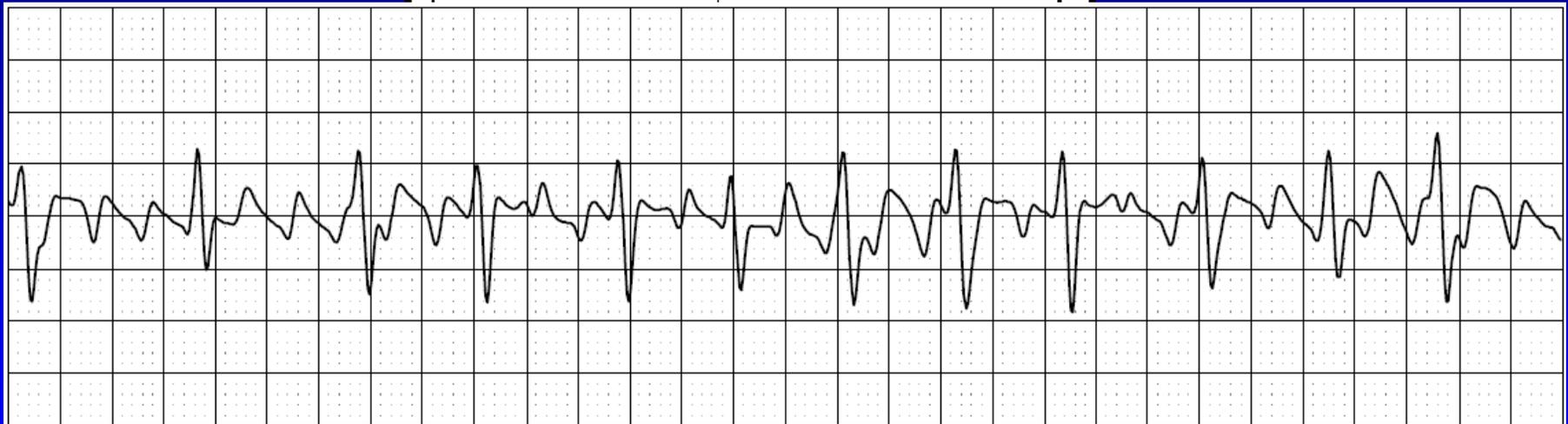
# *Post Hoc* Chronic Effectiveness

- Based on investigator assessment (rather than relying on Event Monitor recordings)
- Final determination made by CryoCor in an unblinded manner
- Resulted in the re-classification of thirteen (13) chronic failures as adjudicated by the Core Lab based on Event Recordings as chronic successes

# Recurrent Atrial Flutter in a Patient Classified in the *Post Hoc* analysis as a Chronic Success

LifeWatch, Inc.  
1351A Abbot Court  
Buffalo Grove, IL 60089  
Phone: (800) 515-4208 Fax: (847) 720-2277

TRANSTELEPHONIC ARRHYTHMIA MONITORING REPORT	
DOCTOR INFORMATION	PATIENT INFORMATION
MD: 30	Name: 030JFW015



Note: All times listed are Central Standard Time (CST).

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# Outside of US Clinical Experience

- The clinical experience reported is based on a single site
- 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
- Patients were not systematically provided event monitors for rhythm monitoring
- Only device related complications that occurred on the day of the procedure were evaluated

# Pain Perception

- The sponsor provided a report on the pain perception associated with cryoablation vs. RF ablation<sup>1</sup>
- 14 patients randomized to RF energy or CryoCor Cryoablation System for atrial flutter ablation (7 in each arm)
- Subjective endpoint (visual analogue scale)
- The cited paper makes no reference to the pain assessment being performed in a blinded fashion



<sup>1</sup> Circulation 2003; 107:1248-1250

# Summary

- The primary safety endpoint was not met; however, FDA believes that the safety events that occurred are consistent with what we would expect for an atrial flutter ablation population
- The acute effectiveness endpoint was met, but the chronic effectiveness endpoint was not met
- FDA is asking for the Panel's clinical interpretation of these aggregate results

# **FDA Statistical Summary**

## **CryoCor CryoAblation System PMA**

**Shanti Gommatam, Ph.D.**

**Division of Biostatistics**  
**Office of Surveillance and Biometrics**



# Study Design

- Prospective, single arm, multi-center study at 24 US sites.
- 189 patients were enrolled; 28 subjects failed secondary screening, 1 withdrew consent before the procedure.
- 160 had a CryoCor Catheter inserted.

# Major Endpoints

- 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 (AFL) for those patients who achieved acute success.

# Performance Goals

Study Endpoint	Performance Goal 95% CB
Safety (7-day SAEs)	$\leq 7\%$
Acute effectiveness	$\geq 80\%$
Chronic effectiveness	$\geq 80\%$

# Safety

- Endpoint: Patient-level SAEs within 7 days of the procedure.
- The alternative hypothesis was that the proportion of patients with seven day SAEs was less than 7%.
- All patients with CryoCor catheter inserted were used to test this hypothesis.

Study Endpoint	Point Estimate	95% 1-sided UCB	Perf Goal
7-day SAEs	9/160=5.63%	9.61%	7% UCB

# Acute Effectiveness

- Endpoint: Creation of BDB post procedure.
- The alternative hypothesis was that the proportion of patients with successful creation of BDB was greater than 80%.
- All patients with CryoCor catheter inserted were used to test this hypothesis.

Study Endpoint	Point estimate	95% 1-sided LCB	Perf Goal
BDB post proc	140/160=87.50%	82.36%	80% LCB

# Chronic Effectiveness

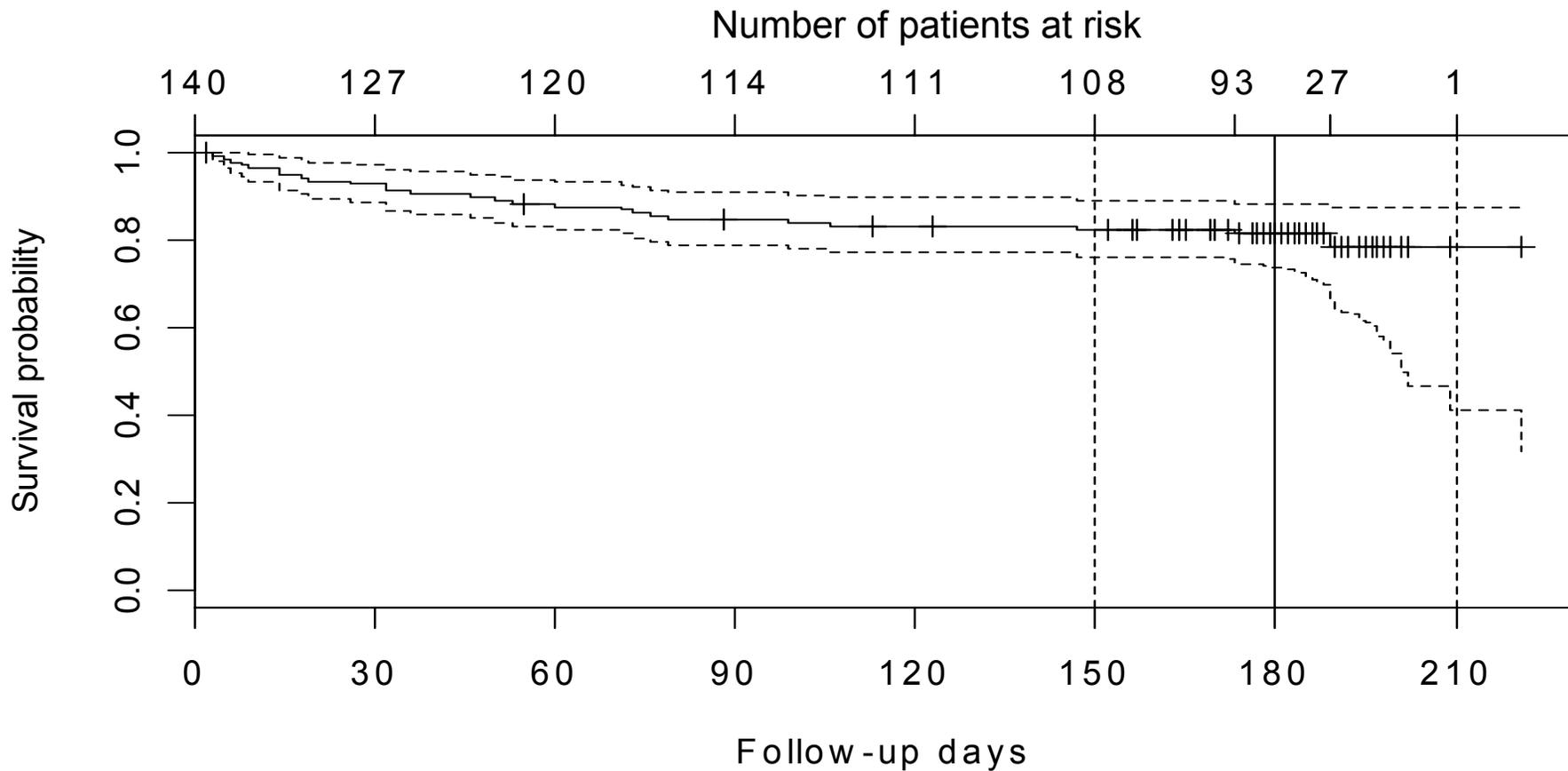
- Chronic effectiveness is conditional on acute effectiveness, so only 140 patients with acute effectiveness are used to ascertain chronic effectiveness.
- Endpoint: Patients with no documented atrial flutter on event recordings through 6 months (w 60 day window, i.e. 150-210 days) were chronically effective.
- Kaplan-Meier estimate of 6 month survival (proportion free from AFL recurrences) used to estimate chronic effectiveness.

# Chronic Effectiveness: Core Lab Determination

- Based on blinded adjudication by Scheinman core lab.
- 8 patients with incomplete follow-up; 26 recurrences.

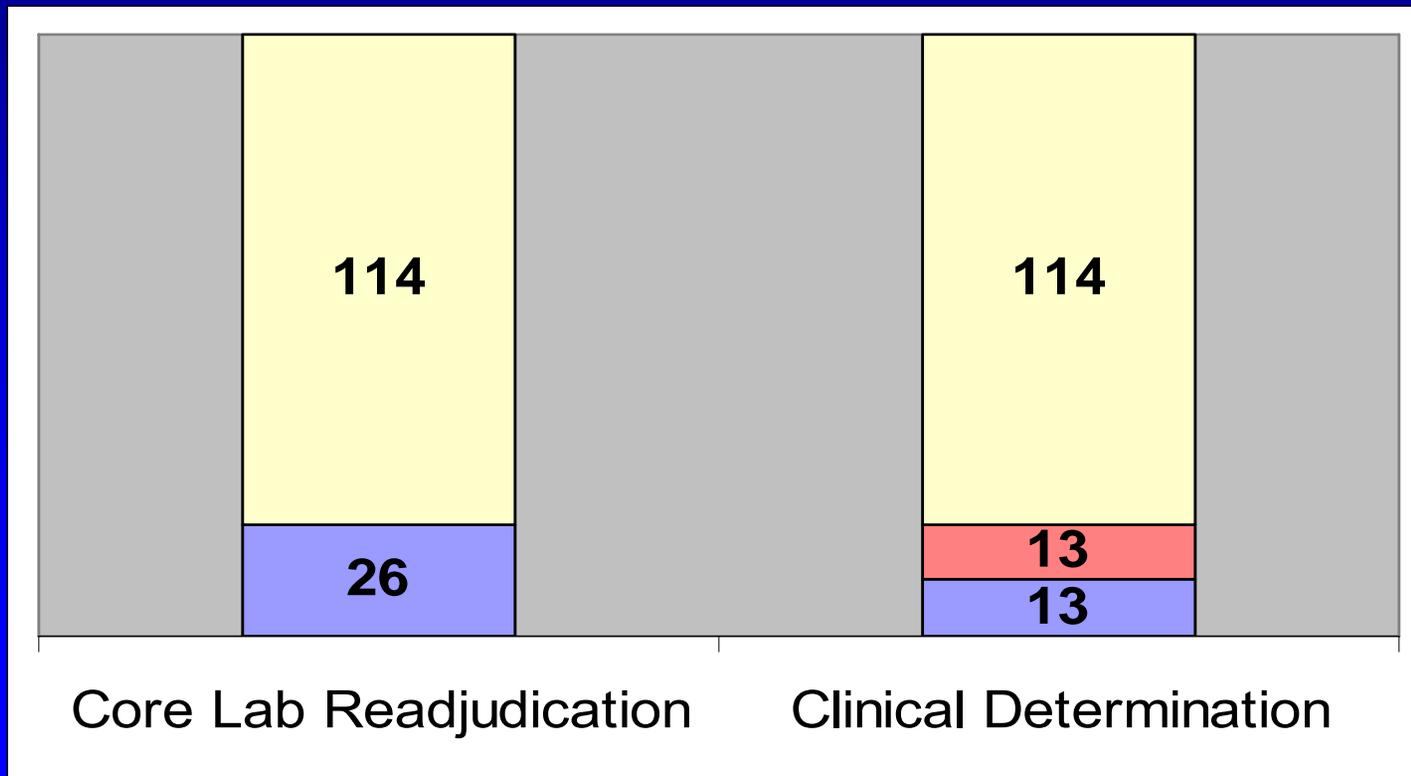
Chronic Effectiveness	Point Estimate	95% 2-sided LCB	Perf Goal
K-M	81.60%	74.40%	80% LCB
Simp Prop (Worst case)	106/140=75.71%	67.75%	

# Chronic Effectiveness: Core Lab Determination



# Chronic Effectiveness: Post hoc Analysis

Clinical interpretation only changed chronic effectiveness for some failures.



# Chronic Effectiveness: Post hoc Analysis

- This analysis was not blinded. Hence this analysis is susceptible to bias.
- This analysis only changes the status of some patients documented to have recurrent AFL as being chronically free of AFL based upon a clinical assessment.

# Pain Perception Experience<sup>1</sup>

- N = 14
- Fisher exact test was used to compare proportions; VAS >0 used to dichotomize patient's pain. It is not clear that cutoff was prespecified, or is clinically appropriate.
- It is not clear if any of the study analyses were pre-specified.
- P-value is uninterpretable.



1: Circulation, 2003

# Endpoint Summary

Endpoint	Study results		Perf Goal for CB
	Estimated proportion	95% CB <sup>1</sup>	
Safety	5.63%	9.61%	≤ 7%
Acute effectiveness	87.5%	82.36%	≥ 80%
Chronic effectiveness (KM)	81.60%	74.40%	≥ 80%
Chronic effectiveness (Worst Case)	75.71%	67.75%	

1: One-sided CBs for safety and acute effectiveness, and two-sided for chronic effectiveness.



# Conclusion

The statistical analyses for this PMA show that:

- The performance goal for the acute effectiveness endpoint was met.
- The performance goals for the safety and chronic effectiveness endpoints were not met.

# Issues to Consider for a Post-Approval Study

Dale R. Tavis, MD, MPH

Epidemiology Branch

Division of Postmarket Surveillance

Office of Surveillance and Biometrics



# Disclaimer

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

# General Principles for Post-Approval Studies

- Objective is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after premarket establishment of reasonable evidence of device safety and effectiveness.
- Post-approval studies **should not** be used to evaluate unresolved issues from the premarket phase that are important to the initial establishment of device safety and effectiveness.

# Need for Post-Approval Studies in General

- Gather postmarket information
  - Longer-term performance
  - Real world community performance
  - Effectiveness of training programs
  - Sub-group performance
  - Rare adverse events
- Account for Panel recommendations



# Post-Approval Study Components

- Fundamental study question or hypothesis
- Safety endpoints and methods of assessment
- Acute and chronic effectiveness endpoints and methods of assessment
- Duration of follow-up