

**NAVISTAR[®] THERMOCOOL[®] Catheter
for the Radiofrequency Ablation
of Symptomatic Paroxysmal
Atrial Fibrillation**

PMA # P030031/S11

Panel Meeting - November 20, 2008

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Agenda

Study History & Design

Marcia S. Yaross, Ph.D.

Bayesian Statistics & Interim Analysis

Donald A. Berry, Ph.D.

Demographics & Effectiveness Results (Final Analysis)

David J. Wilber, M.D., F.A.H.A., F.A.C.C.

Safety Results

Albert L. Waldo, M.D., F.A.C.C., F.A.H.A., F.H.R.S.

Conclusions and Wrap-up

Marcia S. Yaross, Ph.D.

Atrial Fibrillation

Important Public Health Issue

- Atrial Fibrillation (AF) most prevalent arrhythmia
 - Estimated over 2.3-5.6 million US adults with AF
- Symptomatic, paroxysmal AF
 - Debilitating disease
 - Increased morbidity and mortality risk
 - Reduced Quality of Life
- Drugs frequently ineffective
- Surgical techniques effective, but highly invasive with associated risks

Growth of Catheter Ablation for Atrial Fibrillation

- Radiofrequency ablation - an important therapeutic tool in treatment of arrhythmias
 - Standard of care for many “simple” arrhythmias (e.g. Wolff-Parkinson-White syndrome, Type 1 atrial flutter, AVNRT)
- Increasingly used for more complex arrhythmias (e.g. VT, AF)
- Catheter ablation for AF recognized in 2006 as second-line therapy in ACC/AHA/ESC practice guidelines

Growth of Catheter Ablation for Atrial Fibrillation

- HRS / EHRA / ECAS Expert Consensus Statement (2007) affirmed indications
 - Symptomatic AF refractory or intolerant to at least one Class I or III antiarrhythmic medication
 - In rare clinical situations, it may be appropriate to perform AF ablation as first line therapy
 - Selected symptomatic patients with heart failure and/or reduced ejection fraction
- **No ablation catheter approved for treatment of AF in US**

NAVISTAR THERMOCOOL Irrigated Catheters

- Marketed in 39 countries since introduced in 1998
- Over 250,000 THERMOCOOL catheters distributed Worldwide to date
 - In the US, over 70,000 THERMOCOOL catheters sold since January 2005

NAVISTAR THERMOCOOL Irrigated Catheters

NAVISTAR THERMOCOOL Diagnostic/Ablation catheter:

- steerable, multi-electrode, deflectable
- 3.5 mm tip and 3 ring electrodes
- 6 saline ports in the tip for irrigation and cooling (open irrigation)
- a location sensor, and a temperature sensor incorporated into the tip



THERMOCOOL Catheter Instructions for Use

- Current PMA Approved Indications for Use
 - Catheter-based cardiac electrophysiological mapping and for the treatment of:
 - a) **Type I atrial flutter** in patients age 18 or older (NAVISTAR and CELSIUS)
 - b) Recurrent drug/device refractory sustained monomorphic **ventricular tachycardia (VT)** due to prior myocardial infarction (MI) in adults (NAVISTAR only)
 - The NAVISTAR THERMOCOOL Catheter provides location information when used with the CARTO[®] EP Navigation System
- Proposed additions to current indications for use
 - c) **Drug refractory symptomatic paroxysmal atrial fibrillation** (NAVISTAR and CELSIUS)

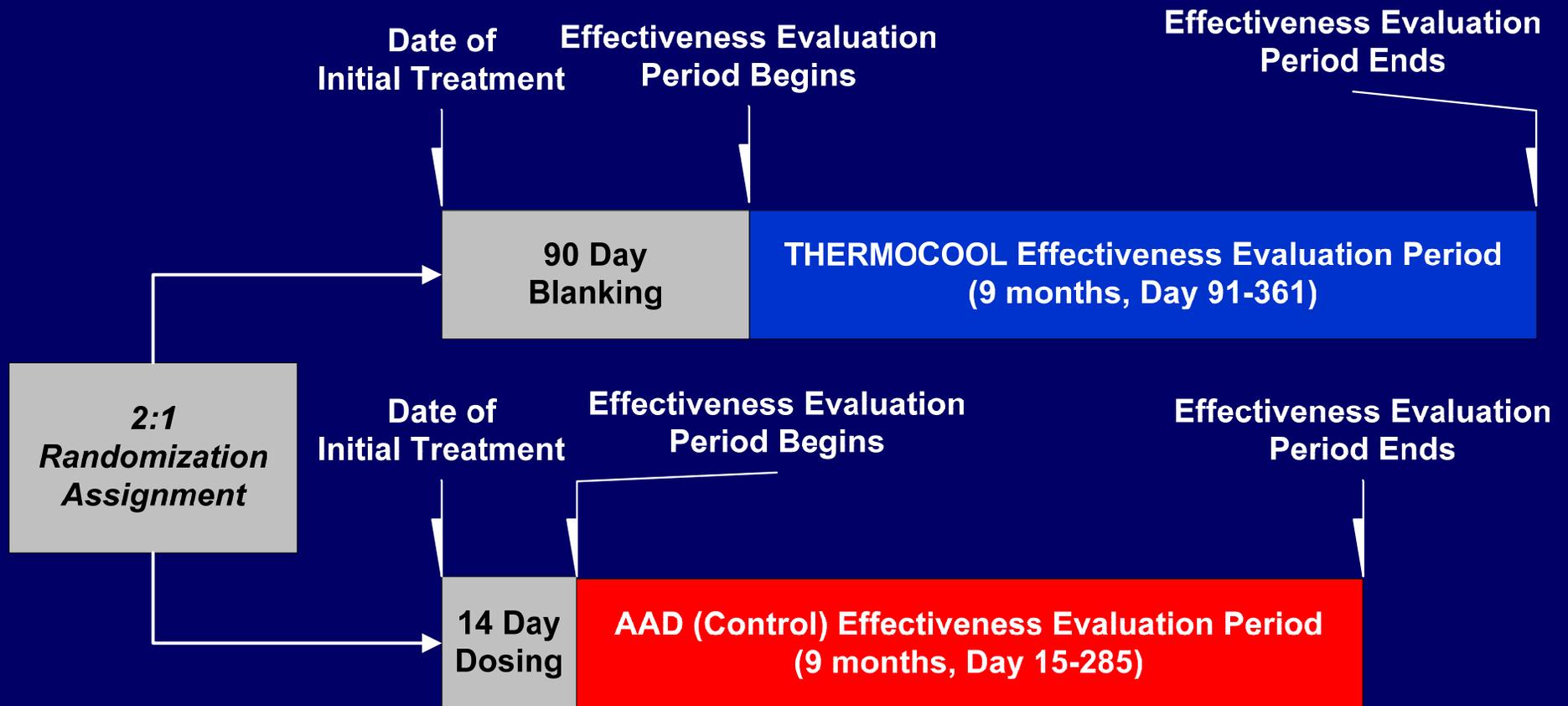
THERMOCOOL AF Clinical Trial Design

- Randomized (2:1), unblinded, controlled trial consistent with FDA 2004 Guidance Document
- Symptomatic, paroxysmal AF patients, refractory to at least one anti-arrhythmic drug (AAD)
- Targeted up to 30 sites enrolling a maximum of 230 subjects
- Pre-planned interim analysis per Bayesian protocol starting at 150 subjects

Primary Study Goals

- To demonstrate:
 - 1) **Superior chronic effectiveness** of THERMOCOOL catheter ablation vs. AAD treatment in prevention of symptomatic AF recurrence w/o new AAD during 9-month effectiveness window
 - 2) **Clinically acceptable safety profile** vs. pre-specified adverse event rate

Effectiveness Evaluation Periods by Randomization Group



- Symptomatic AF recurrence assessed via trans-telephonic monitoring throughout Effectiveness Evaluation Period
- Quality of Life assessment at baseline, 3, 6, and 9 months of Effectiveness Evaluation Period

Primary Safety Endpoints

- Incidence of early onset (within 7 days of ablation procedure) primary adverse events

Death

Atrio- esophageal fistula

Atrial perforation

Cardiac Tamponade

Myocardial infarction (MI)

Stroke

Cerebrovascular accident (CVA)

Thromboembolism

Transient Ischemic Attack (TIA)

Diaphragmatic paralysis

Pneumothorax

Heart block

Pulmonary vein (PV) stenosis

Pulmonary edema

Pericarditis

Hospitalization (initial and prolonged)

Pericardial effusion

Vascular access complications

- Performance goal was 16.0% based on literature review
- Incidence of Pulmonary Vein Stenosis
 - CT/MRA at baseline, 3 and 12 months in THERMOCOOL group
 - Assessed by independent core laboratory.
 - Significant stenosis defined as $\geq 70\%$

Study Population

Inclusion Criteria

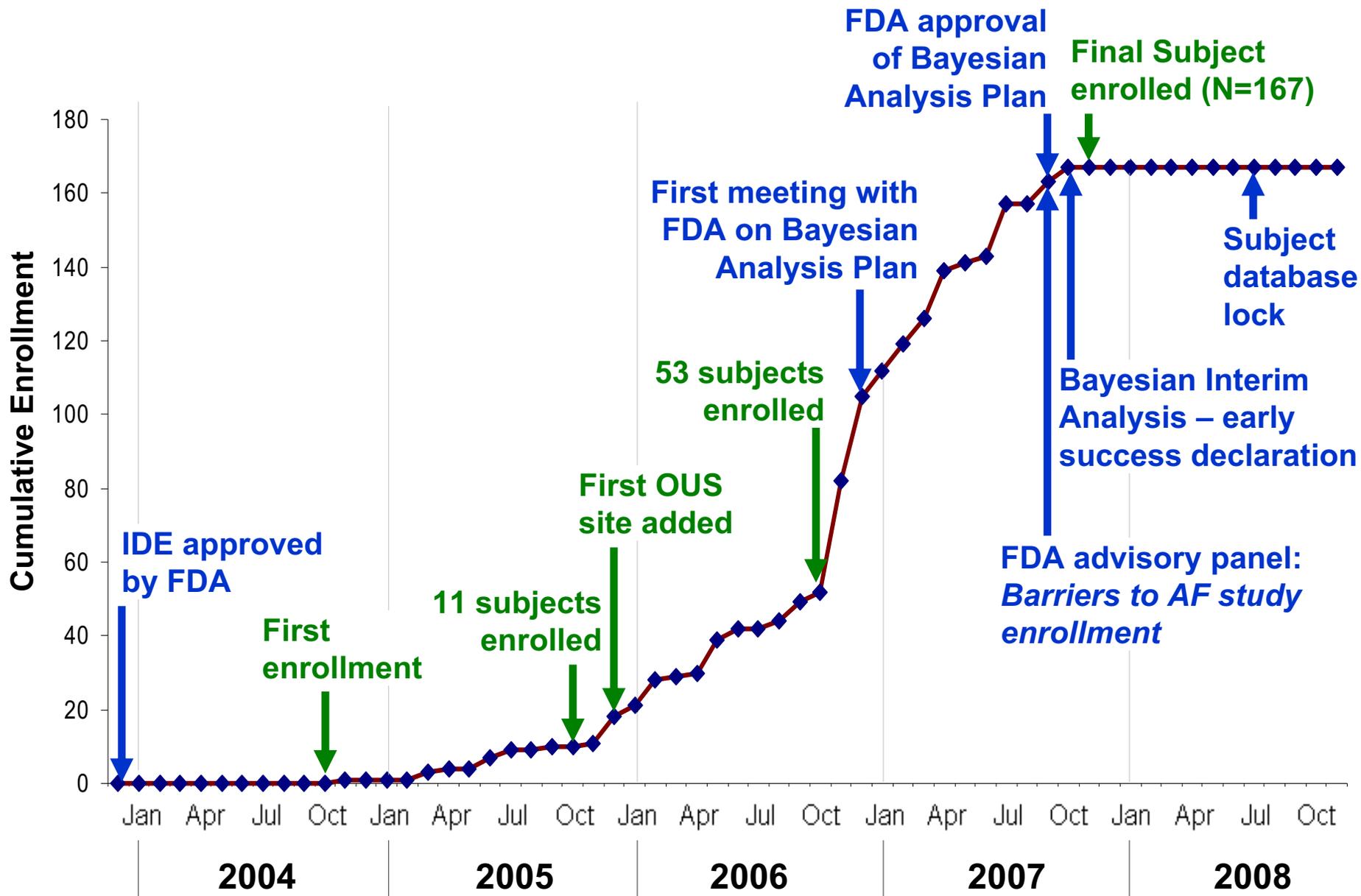
- Patients with symptomatic PAF - have had 3 AF episodes (one documented) in the 6 months prior to randomization
- Failure of at least 1 AAD (Class I or III, BB, CCB)
- Age 18 years or older
- Signed and dated Patient Informed Consent form
- Able and willing to comply with all pre-, post-, and follow-up testing and requirements

Study Population

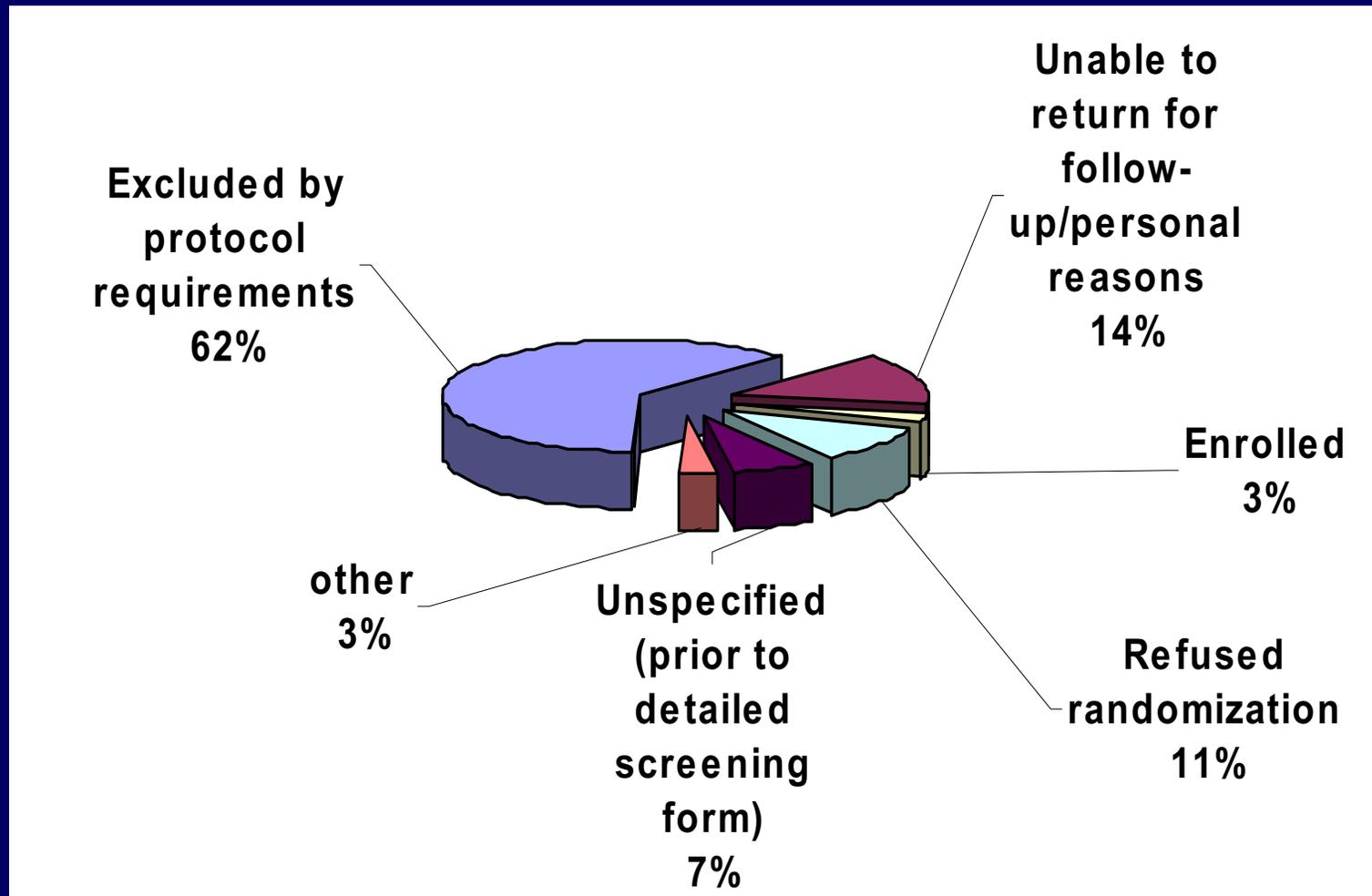
Key Exclusion Criteria

- Previous ablation for atrial fibrillation
- Amiodarone therapy at any time during previous 6 months
- AF episodes lasting longer than 30 days and terminated via cardioversion
- CABG procedure within last 180 days
- Documented left atrial thrombus on imaging
- History of a documented thromboembolic event within the past one year
- Presence of implanted ICD
- Unstable angina
- Myocardial infarction within the previous 60 days
- LVEF <40%
- Uncontrolled heart failure or NYHA Class III or IV heart failure
- Left atrial size \geq 50mm

NAVISTAR THERMOCOOL AF Study Timeline



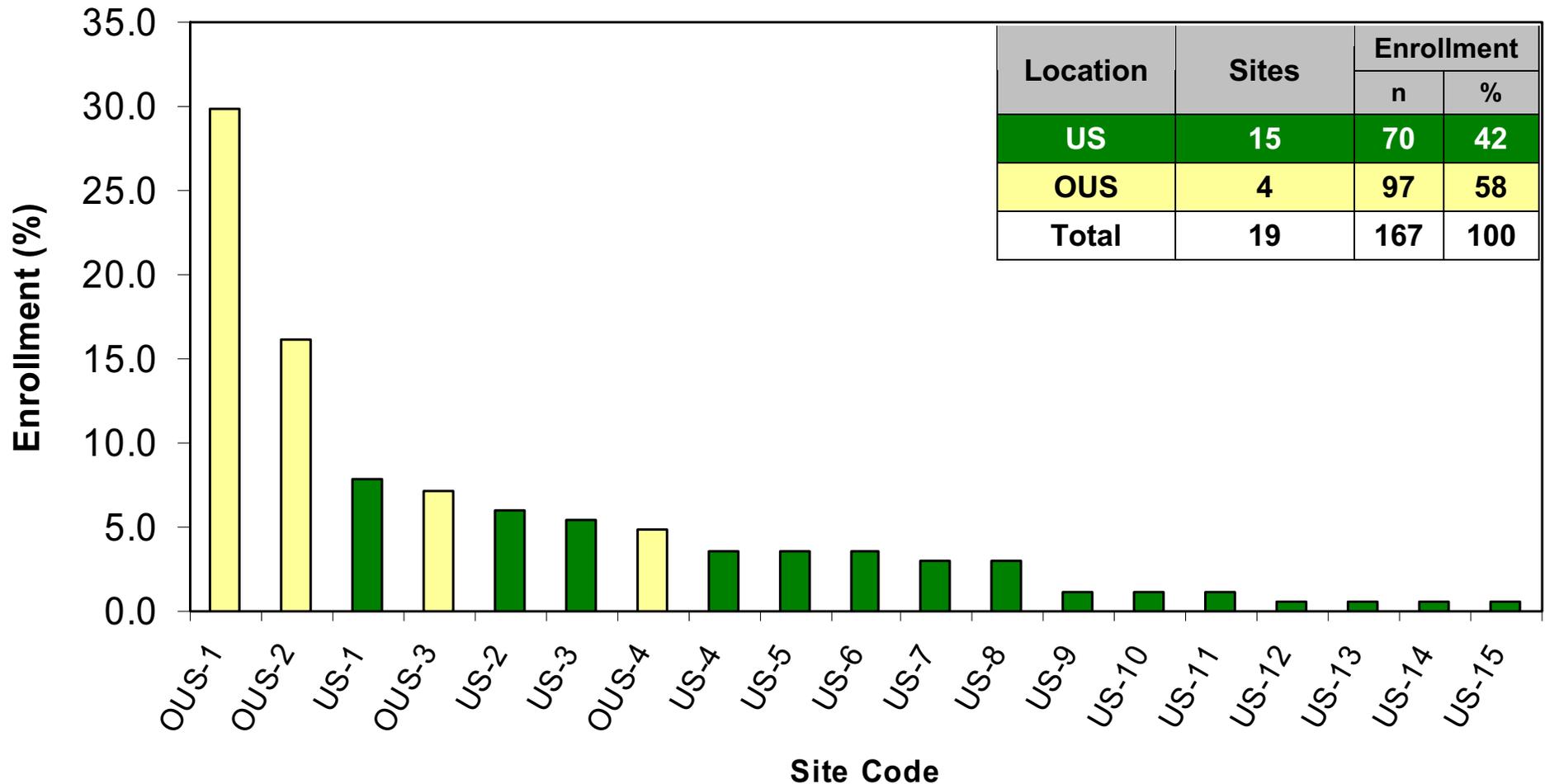
Approximately 5500 Patients Screened to Enroll 167 Subjects



Circulatory System Devices Panel meeting, September 20, 2007

- ~ 1/3 of subjects were study eligible

Enrollment by Site



Poolability

Justification for Poolability:

- Uniform study protocol with well-defined inclusion and exclusion criteria
- Identical data collection methods
- Standardized monitoring to verify protocol compliance across study sites

Donald A. Berry, Ph.D.

Statistical Consultant, Berry Consultants
Chairman, Department of Biostatistics
& Frank T. McGraw Memorial Chair of Cancer Research
The University of Texas M.D. Anderson Cancer Center
(Houston, TX)

Primer on Bayesian Methods in Device Clinical Trials

1997 FDAMA and “least burdensome”

- “The Secretary shall consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.”
- First Bayesian approval in 1997
- Draft Bayesian guidance in 2006

Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials Draft Guidance for Industry and FDA Staff

<http://www.fda.gov/cdrh/osb/guidance/1601.html>

- 1 Introduction
- 2 The Least Burdensome Approach
- 3 Foreword
- 4 Bayesian Statistics
- 5 Planning a Bayesian Clinical Trial
- 6 Analyzing a Bayesian Clinical Trial
- 7 Post-Market Surveillance
- 8 References
- 9 Appendix

Current Use of Bayesian Adaptive Designs

- MDACC (> 300 trials)
- Many device companies
(> 20 PMAs, many 510(k)s)
- All top drug companies; many biotechs

Some Bayesian Device Applications

- Orthopedics (esp. spinal implants)
- Diagnostics & screening
- Stents
- Shunts
- Defibrillators
- Bronchial thermoplasty
- Ablation catheters
- PFO closure
- Contraceptives
- Neurostimulation

Bayes Rule

Rule of inverse probabilities:

$$P(H|\text{data}) \propto P(\text{data}|H)*P(H)$$

Familiar application: positive predictive value of diagnostic test:

$$P(\text{dis}|+) \propto P(+|\text{dis})*P(\text{dis})$$

Bayes Rule

Rule of inverse probabilities:

$$P(H|\text{data}) \propto P(\text{data}|H) * P(H)$$



Bayesian Approach

- Formalism for learning under uncertainty
- Probabilities of any unknown: hypotheses, future data
- Hypothesis test: Posterior probability of no treatment effect
- Interval estimation: Posterior probability that parameter is in interval
- Inherently synthetic

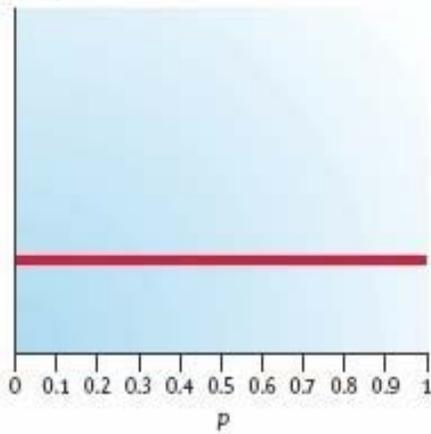
Advantages of Bayes

- Naturally adaptive - on-line learning (e.g., predictive probability)
- Uses early by-patient information (via modeling)
- Uses historical data (e.g., hierarchical modeling)

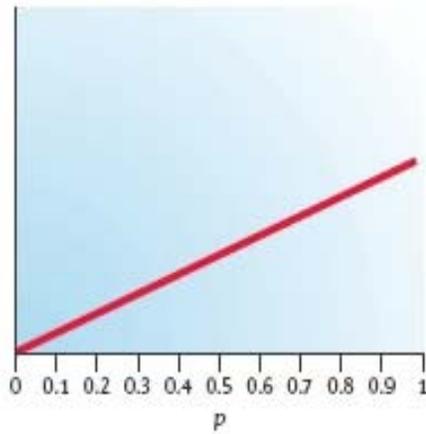
Bayesian Updating

- Paired observations, T vs C
- $P(S) = P(\text{T wins pair})$
- $H_0: P(S) = 1/2$
- Data: SSFSS FSSSF
 SFSSS SS

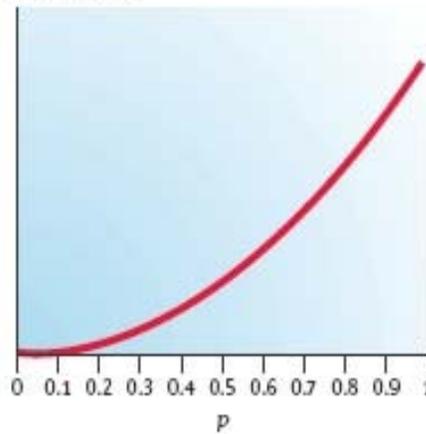
Prior



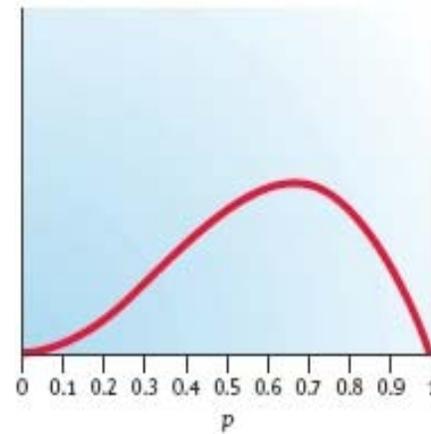
After S



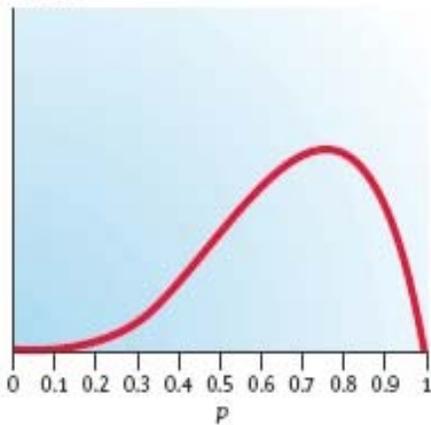
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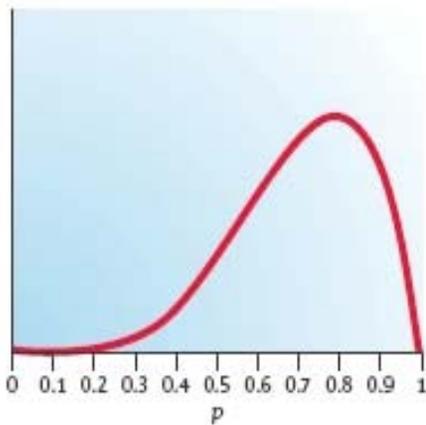
Then F



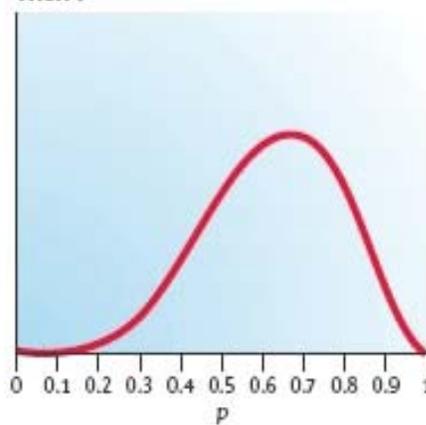
Then S



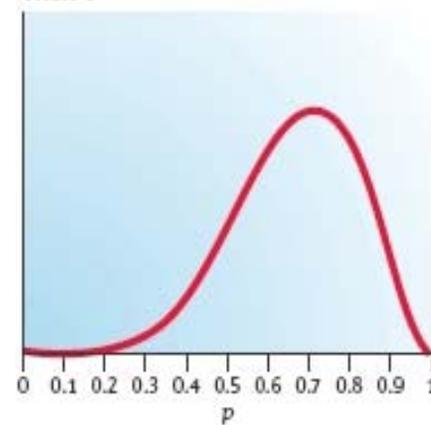
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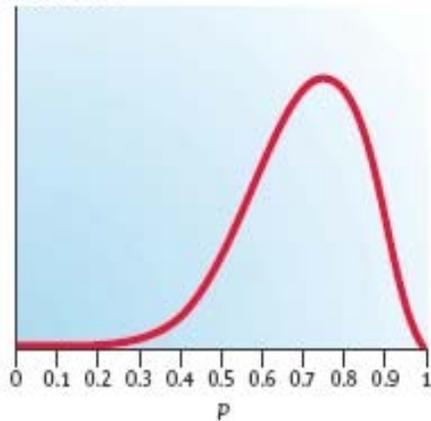
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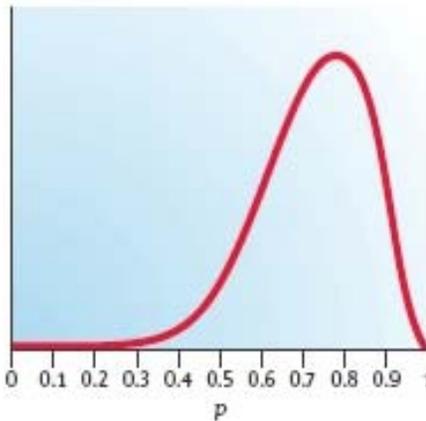
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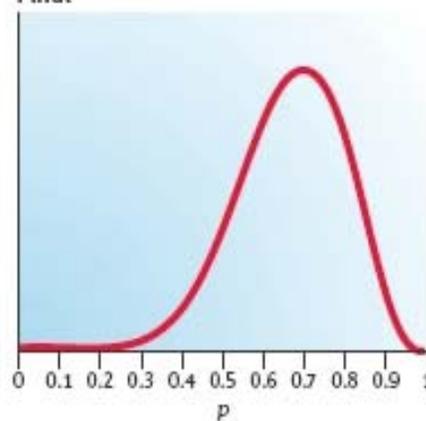
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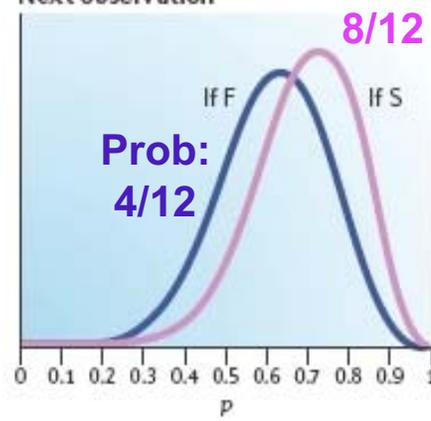
Another S



Final



Next observation



Prob:
8/12

Prob:
4/12

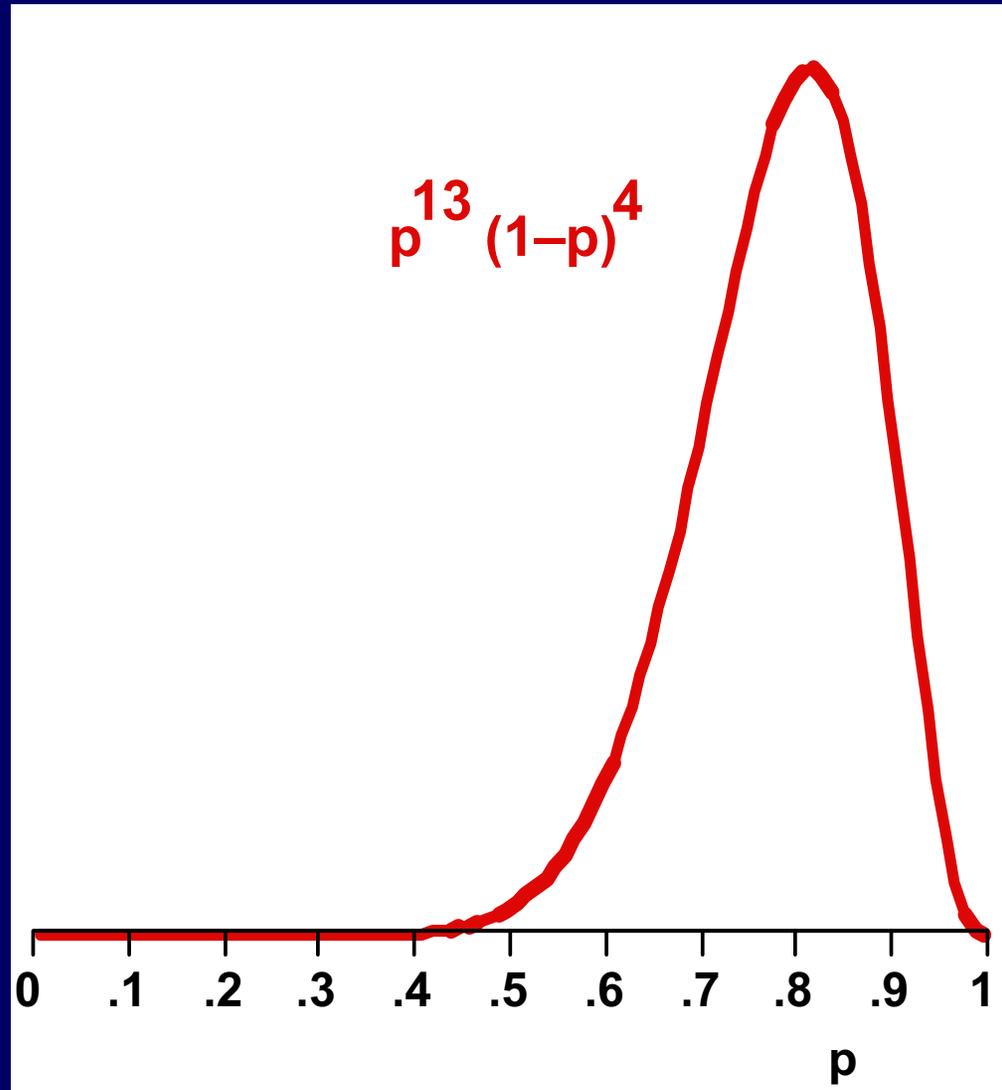
Predictive Probabilities

- Essential for monitoring trials
- Critical component of experimental design

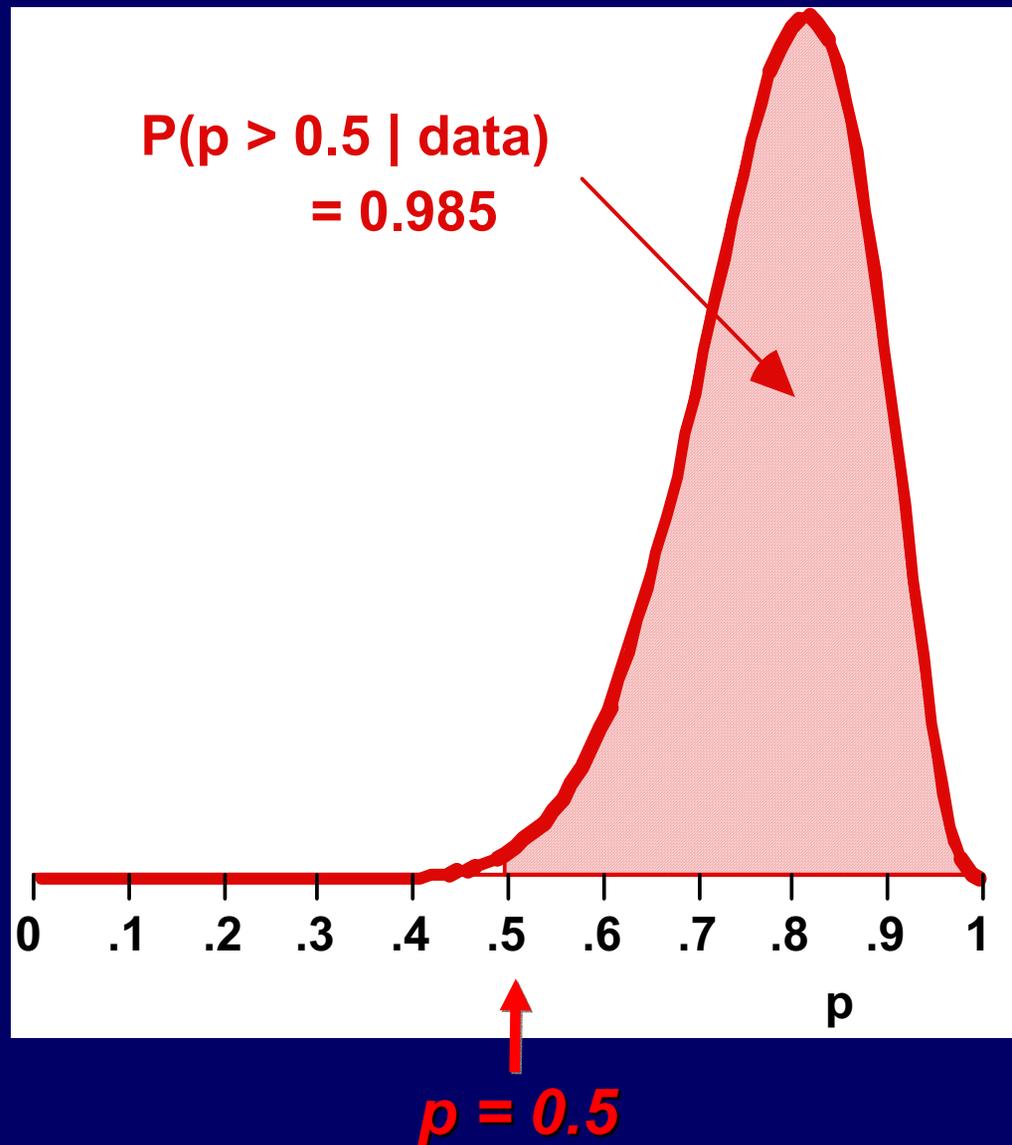
**“We must ask where we are and
whither we are tending.”**

— Abraham Lincoln

Current (posterior) for $p = P(S)$

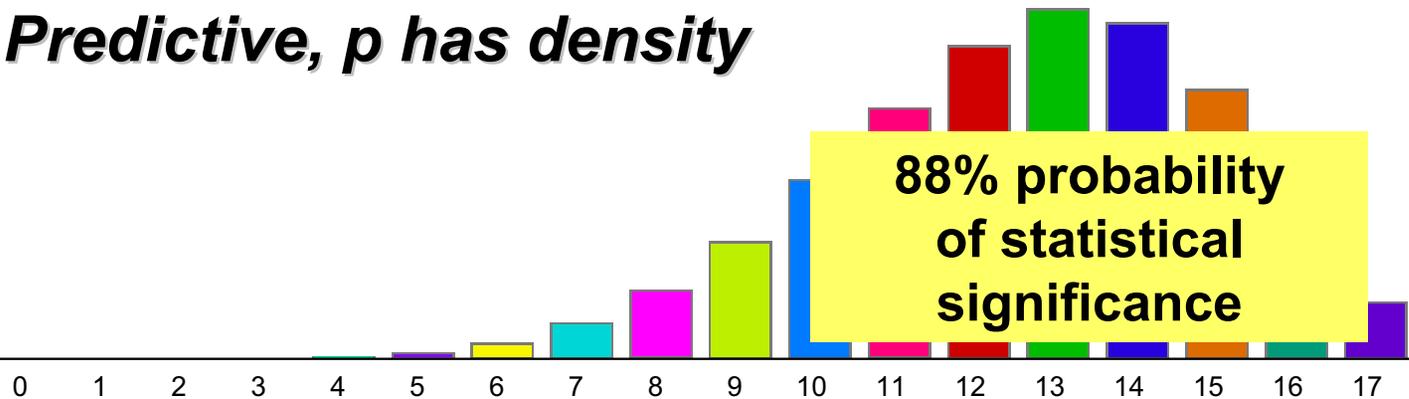


Posterior Probability that $p > 0.5$ is Area Under Curve

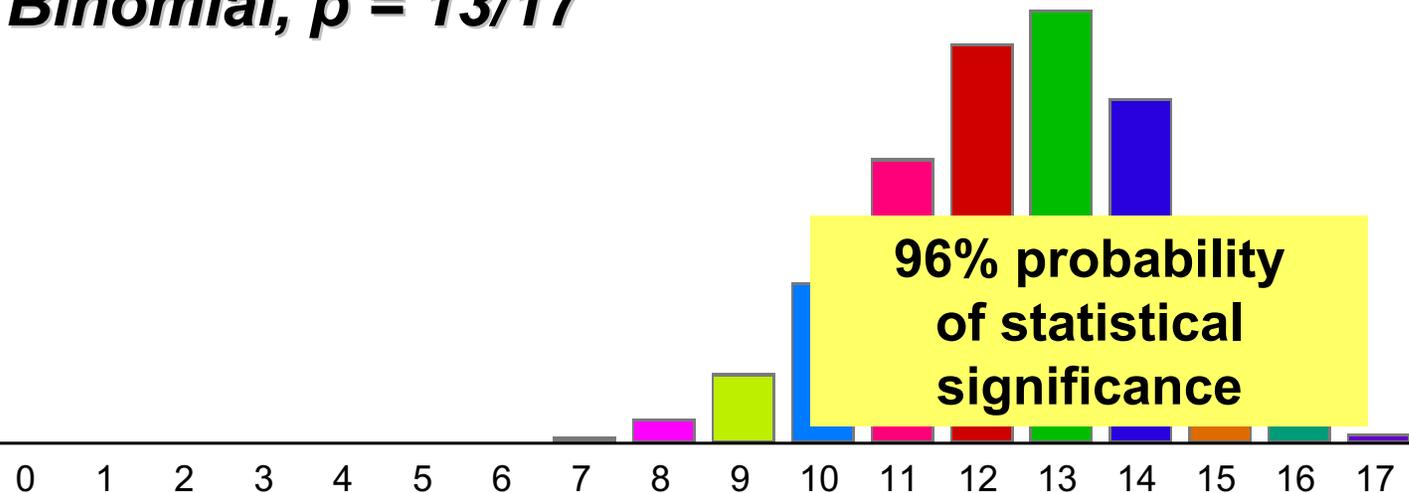


Probabilities for # Successes in Next 17 Observations

Predictive, p has density



Binomial, $p = 13/17$



Important Issues

- Need for prospective design (including agreement w/FDA)
- Changing from frequentist to Bayes

Why Bayes?

- Smaller trials (usually!)
- More accurate conclusions
- Better treatment of patients in trials

THERMOCOOL AF Trial

Statistical Design & Interim Analysis

Statistical Analyses

- Amended study design with a Bayesian adaptive sample size was prospective
 - Type I error rate was controlled for planned interim analyses
- Bayesian adaptive sample size (from 150 to 230) approved by the agency in September 2007
- Interim analysis performed
 - per the IDE protocol
- Interim analysis determined the effectiveness endpoint was met, enrollment in the trial should stop, and early success was declared

Results of the Interim Analysis (September 2007 dataset)

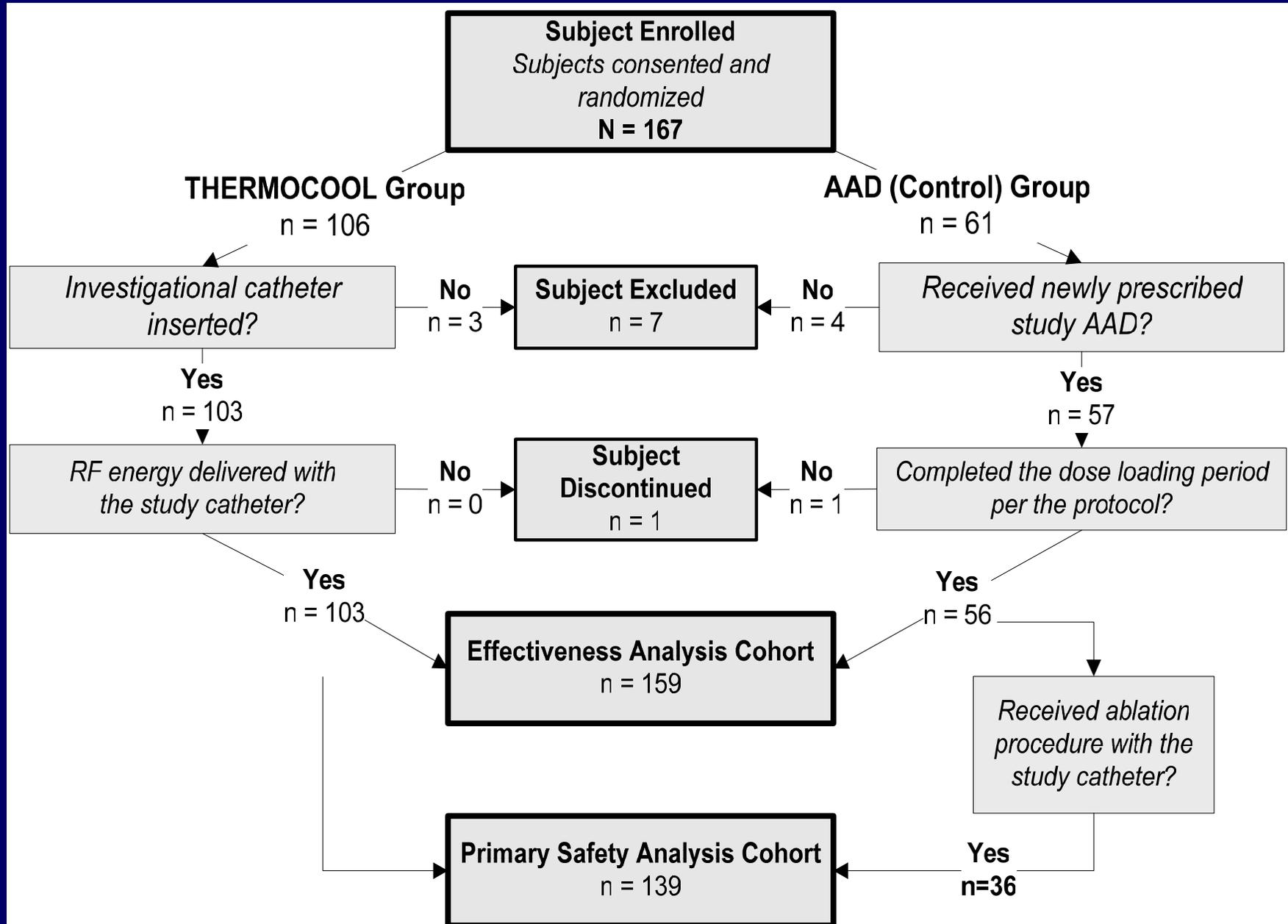
- 160 subjects enrolled (AAD=59, THERMOCOOL=101)
 - 148 eligible for the interim effectiveness analysis
- Protocol: If predictive probability of eventual success (probability THERMOCOOL superior at least 0.98) with 148 patients followed to 9+ months is:
 - ≥ 0.90 then **stop accrual at that sample size**
 - ≥ 0.99 then in addition **declare early success**
- Result of interim analysis: Predictive probability
 - > 0.999 ; therefore **early success declared**

David J. Wilber, M.D., FAHA, FACC

Primary Investigator

George M. Eisenberg Professor of Cardiovascular Sciences;
Director, Division of Cardiology;
Loyola University Medical Center (Maywood, IL)

Overall Subject Accountability



Subject Demographics are Comparable Across Randomization Groups

	Treatment Group		Total n / 167 (%)	p-value
	THERMOCOOL n / 106 (%)	AAD (Control) n / 61 (%)		
Gender				0.3997 ^a
Female	33 (31.1)	23 (37.7)	56 (33.5)	
Male	73 (68.9)	38 (62.3)	111 (66.5)	
Age (years)				0.3009 ^b
Mean	55.5	56.1	55.7	
Standard Deviation	9.3	12.8	10.7	

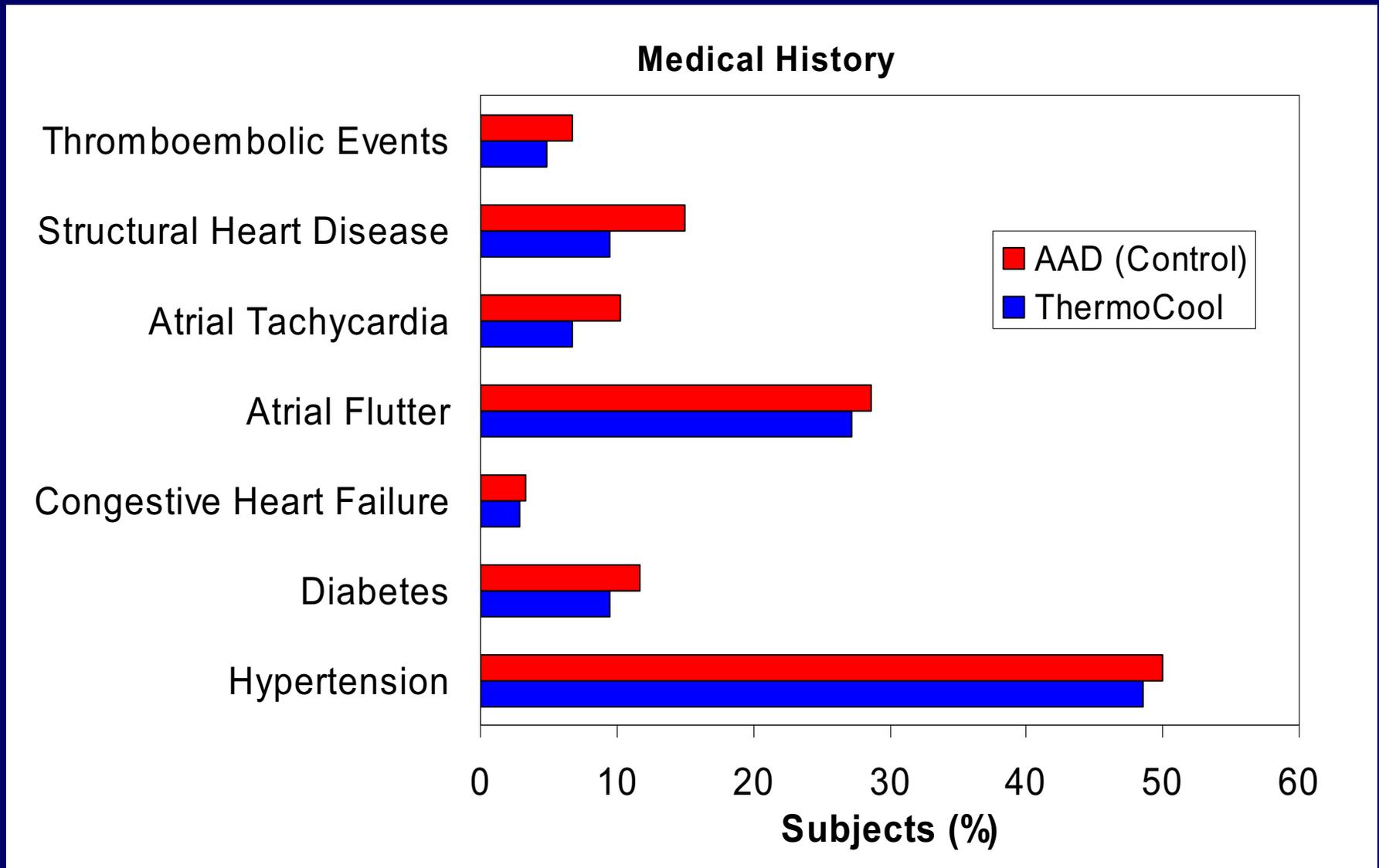
^a Fisher's exact test; ^b Wilcoxon rank sum test.

Total Number of Reported AF Episodes in the 6 Months Prior to Baseline

	Treatment Group		Total	p-value
	THERMOCOOL	AAD (Control)		
Mean	62.3 ± 89.7	64.9 ± 98.0	63.2 ± 92.4	0.7572
Median	28.0	24.0	26.0	
Interquartile Range	12 – 95.5	12.0 - 90.0	12.0 – 90.0	

Subject Demographics

Comparable Cardiac Co-morbidities (N=167)



Subject Demographics

Comparable Prior AAD Failures

AAD Drugs Failed	Treatment Group		Total Mean \pm SD (n)
	THERMOCOOL Mean \pm SD (n)	AAD (Control) Mean \pm SD (n)	
Number of AADs Failed at Baseline	2.2 \pm 1.1 (106)	2.1 \pm 1.4 (61)	2.2 \pm 1.2 (167)
Class I/III AADs Failed at Baseline*	1.6 \pm 0.8 (85)	1.4 \pm 0.6 (52)	1.5 \pm 0.7 (137)
Class II/IV AADs failed at Baseline*	1.3 \pm 0.5 (20)	1.3 \pm 0.5 (7)	1.3 \pm 0.5 (27)

*Subset enrolled based on failing the indicated drug class

AAD (Control) Group

Recommended AAD Regimen

- Subjects prescribed a new, not previously administered, class I/III AAD
 - Minimum Recommended Dosing per ACC / AHA / ESC 2001 Practice Guidelines for Management of Subjects with Atrial Fibrillation

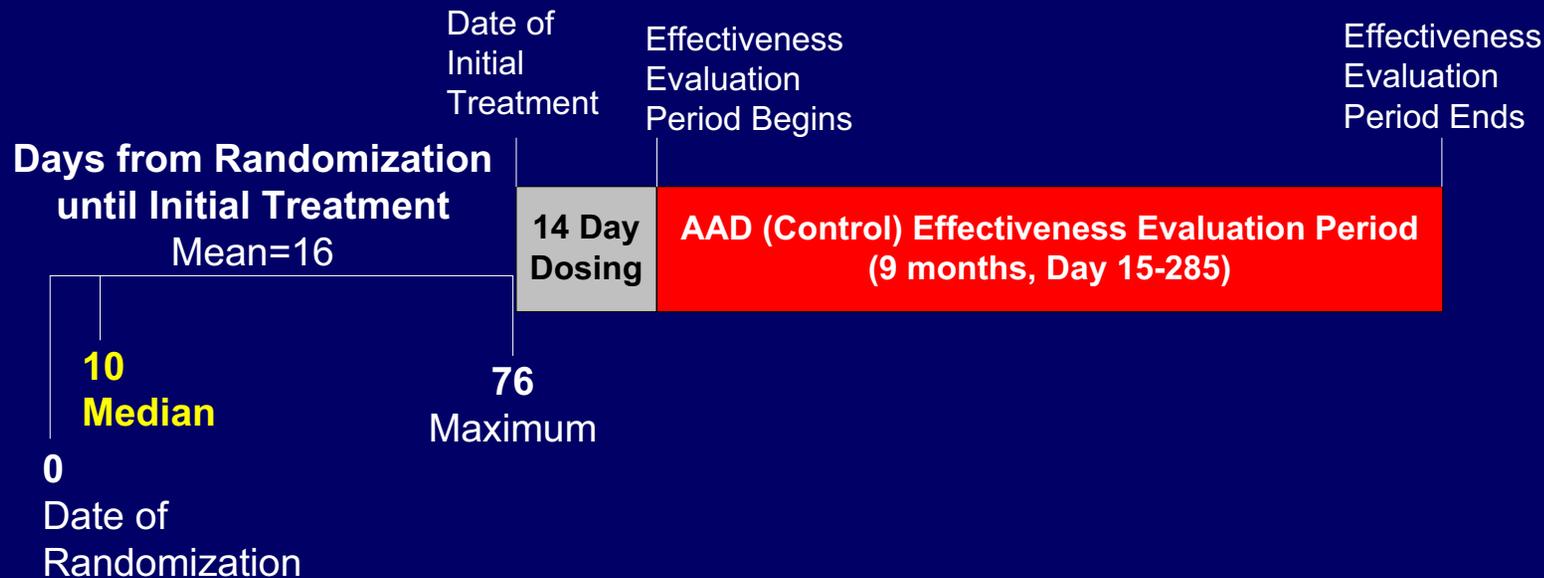
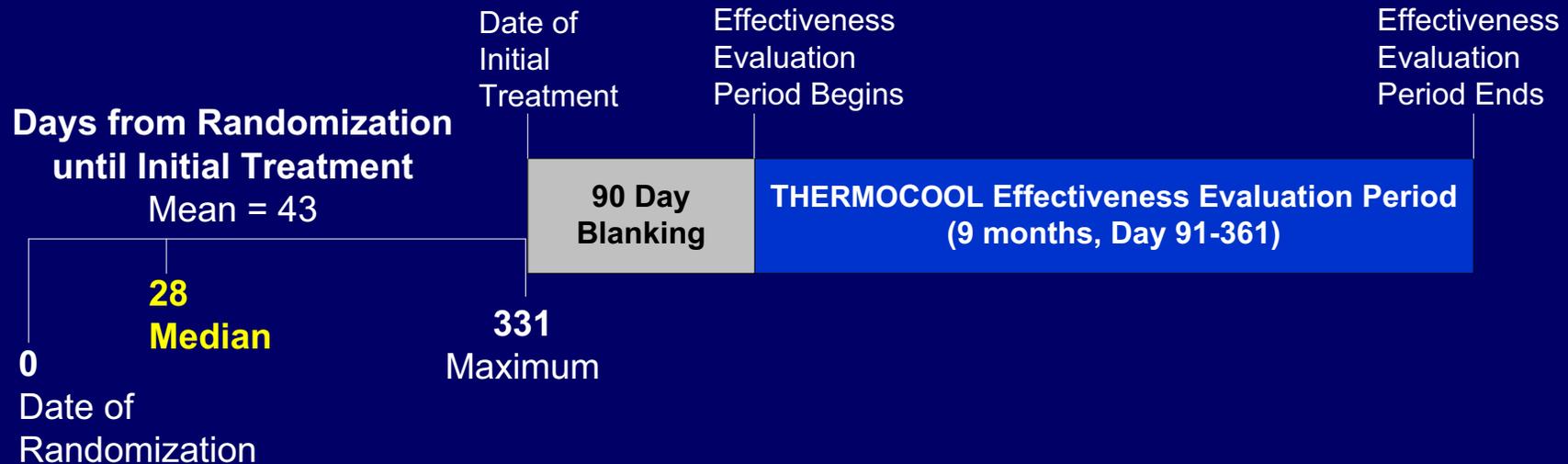
Route of Administration	Drug	Type	Minimum Recommended Dosage
Oral	Sotalol	III	240 mg
	Dofetilide	III	500 mcg
	Flecainide	IC	200 mg
	Propafenone	IC	450 mg
	Quinidine	IA	600 mg

- Prescribed AAD adjusted and dosed for maximum efficacy during the 14-day dosing period
- AAD medication and dose fixed during the effectiveness evaluation period (starting at day 15)
- Amiodarone therapy was not an option under this protocol (currently unapproved for treatment of AF)

THERMOCOOL Catheter Ablation Procedure

- Required
 - Circumferential anatomical approach to isolate all PVs
 - Electrophysiological Confirmation of Entrance Block into the PVs (procedural endpoint)
 - CARTO electroanatomical mapping
- Optional
 - Isolation of the Superior Vena Cava
 - Ablation of non-PV foci that initiate AF
 - LA Linear Lesions if AF can be induced
 - Left Inferior PV-Mitral Isthmus if LA flutter induced
 - Cavo-Tricuspid Isthmus (CTI) if right atrial flutter induced

Time from Randomization to Treatment Initiation



Acute Effectiveness Outcome for THERMOCOOL Group

- Acute Effectiveness Outcome per protocol definition

	THERMOCOOL n
Underwent RF Study procedure	103
Entrance Block Confirmed	103*
Ablation Procedure >80 days	2
Non-study Catheter Utilized for AF Targets	0
>2 Repeat Ablation Procedures	0
Acute Effectiveness Success	101 (98.0%)

* Confirmation in one subject received post-submission

Primary Effectiveness Chronic Success THERMOCOOL Group

Freedom from the following:

- Documented symptomatic AF recurrence (days 91-361)
- Acute procedural failure (irrespective of AF recurrence days 91-361)
 - Failure to confirm entrance block into each targeted PV
- Repeat AF ablation procedure after 80 days
- Protocol adjudicated AAD failure (irrespective of AF recurrence days 91-361)
 - New or increased dose of the following “protocol specified AADs” in the post-blanking period:
 - Class I / III AADs, beta blockers, calcium channel blockers, digitalis, ARBs or ACE inhibitors

Primary Effectiveness Chronic Success AAD (Control) Group

Freedom from the following:

- Documented symptomatic AF recurrence (15-285 days)
- Protocol adjudicated AAD failure (irrespective of AF recurrence days 15-285)
 - New or increased dose of the following “protocol specified AADs” in the post-dosing period:
 - Class I/III AADs, beta blockers, calcium channel blockers, digitalis, ARBs or ACE inhibitors
- Safety failure requiring discontinuation of the assigned AAD during days 0-285

Transtelephonic Monitor (TTM) Transmission and Blinded Review Process

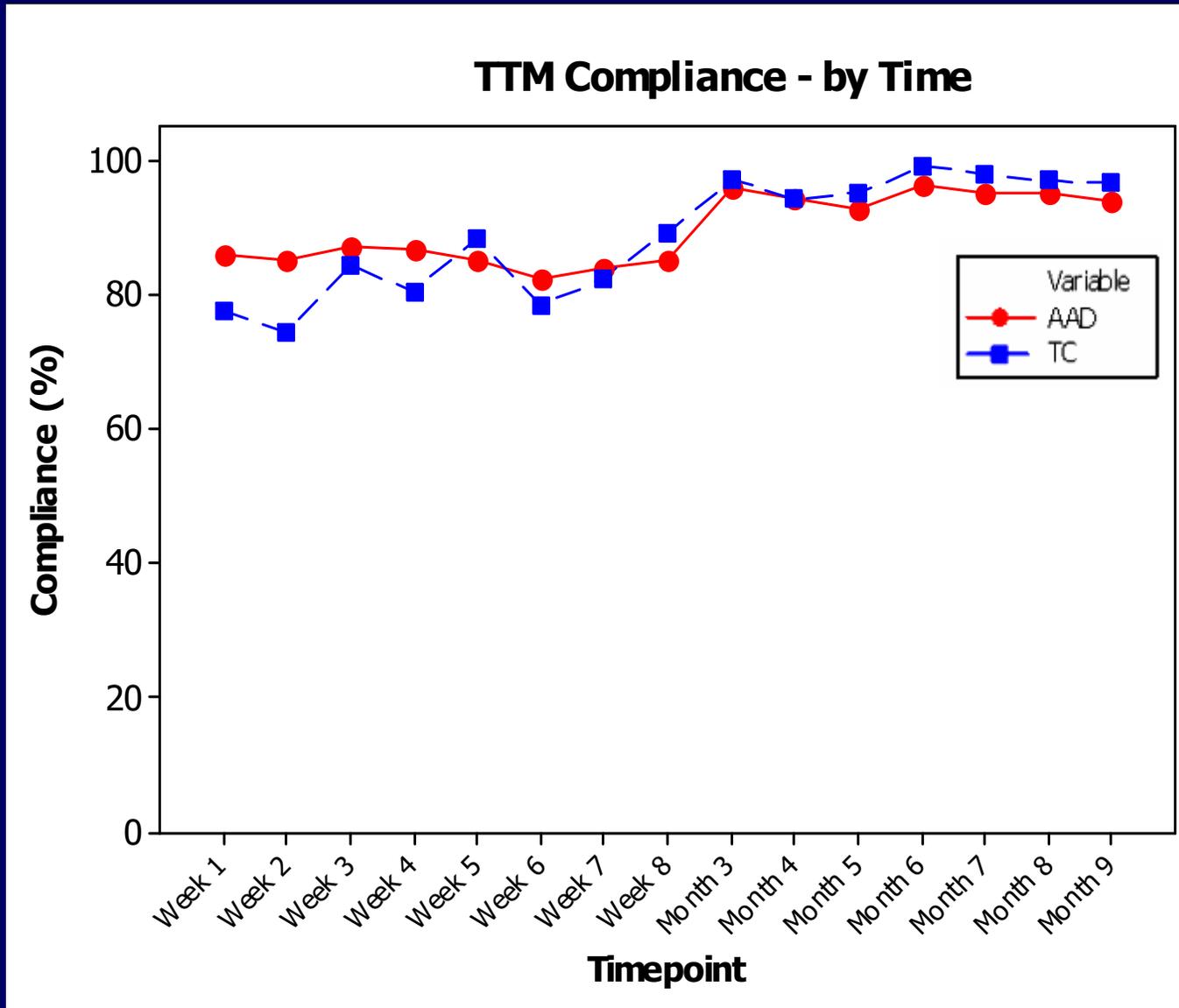
Subject - Transmits Cardiac Episodes to Core Lab

- Transmits once a week for the initial 8 weeks and monthly for the remaining 7 months
- Transmits ALL symptomatic cardiac episodes

Two core lab technicians - serially review and provide the initial interpretation

Independent Cardiologist - final blinded adjudication of the transmission

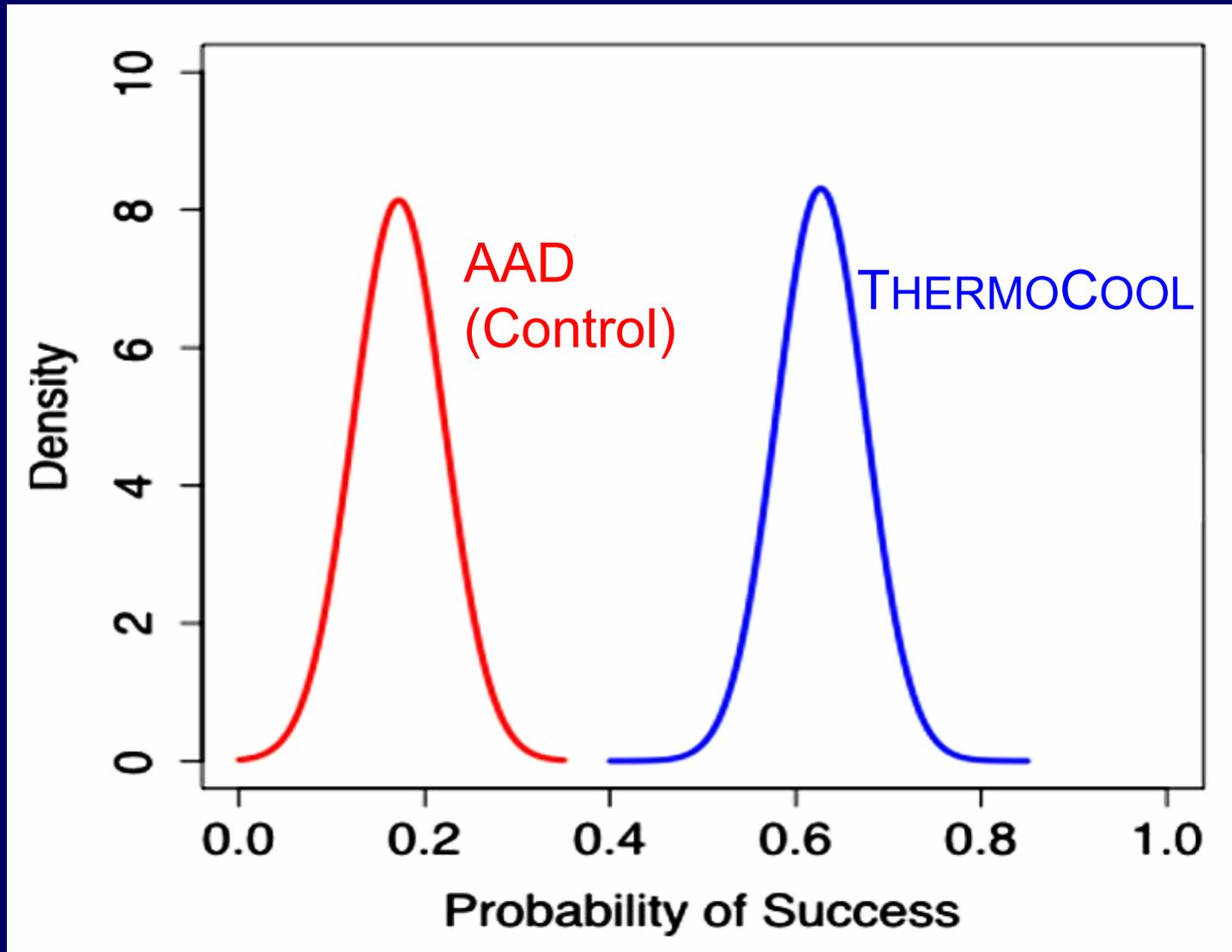
Overall Mean TTM Compliance Over Time (Effectiveness Cohort, n=159) 88.8%



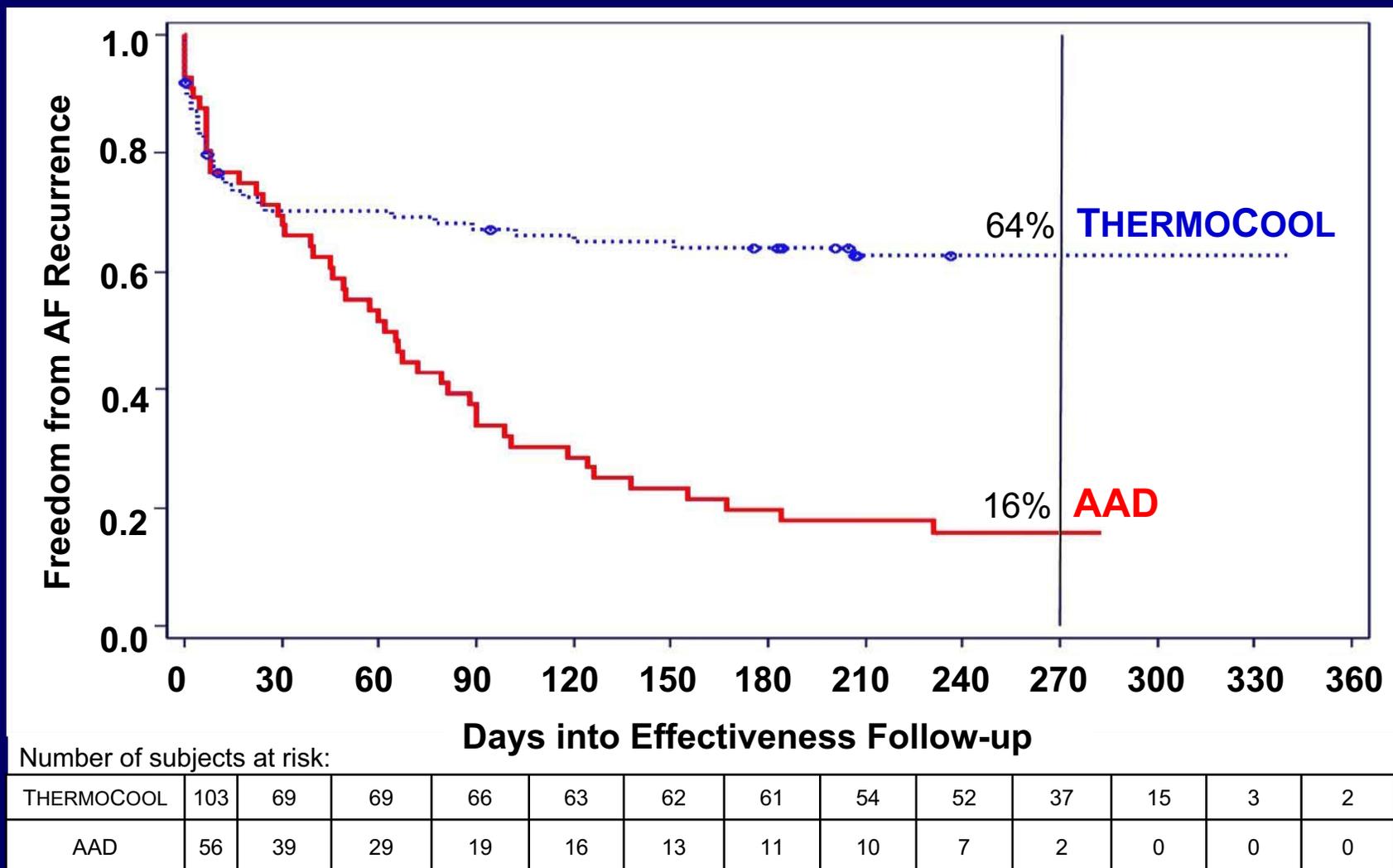
Chronic Effectiveness Outcomes June 2008 Dataset

- The critical results of this analysis are the **predictive probability of study success for 230 patients** and the posterior probability of superiority for the THERMOCOOL group
 - Posterior **probability that the THERMOCOOL group is superior to the AAD (Control) group is essentially 1 (>0.9999)**
 - Probability of success for a subject in the THERMOCOOL group is **62.7% ± 4.8%**
 - Probability of success for a subject in the AAD (Control) group is **17.2% ± 4.9%**

THERMOCOOL Group is Superior to AAD Group in Probability of Success at 9 Months



KM Curve of Time to Chronic Failures By Randomization Group (Effectiveness Cohort, n=159)



- Circles in the graph represent 14 censored THERMOCOOL subjects

Chronic Effectiveness Failures THERMOCOOL Group

36 failures in the THERMOCOOL group

24
Symptomatic AF Recurrence in the
Effectiveness Evaluation Period (*days 91-361*)

12
No Symptomatic AF Recurrence in the
Effectiveness Evaluation Period (*days 91-361*)

2
Reablation Between
80-90 Days

10
Protocol Adjudicated
AAD Failure

7 - Failed due to use of
BB, CCB, or ACE "AAD"
3 - BB or CCB
2 - BB
1 - BB, ACE
1 - ACE
3 - Failed Class I/III AAD

- 23% (24/103) of THERMOCOOL subjects failed due to symptomatic AF recurrence

Chronic Effectiveness Failures AAD (Control) Group

47 failures in the **AAD (Control)** group

40

Symptomatic AF Recurrence
in the Effectiveness
Evaluation Period

7

No Symptomatic AF Recurrence in
the Effectiveness Evaluation Period

*All 7 failed due to intolerance to the
prescribed AAD*

- 71% of Control (AAD) subjects (40/56) failed due to symptomatic AF recurrence

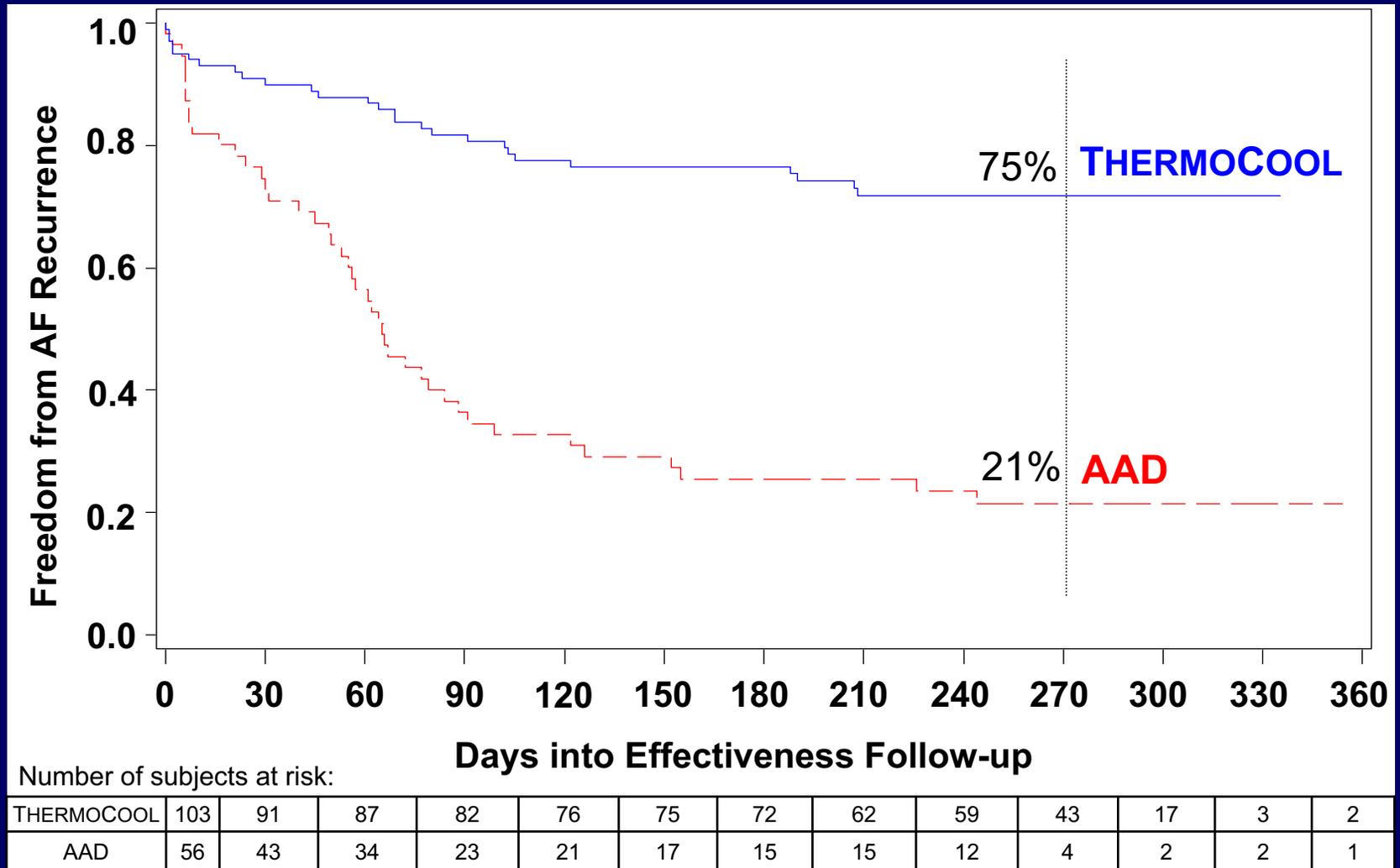
Additional Considerations

- THERMOCOOL Group
 - 50% PV isolation alone
 - Other procedures (more than one in single subject)
 - CTI ablation for RA flutter: 34% (prophylactic in 24/103, 23.3%)
 - SVC 16%, other focal driver 17%, LIPV-MA line 21%, other LA lines 20%
 - 13 subjects (12%) underwent 2nd procedure within first 80 days of blanking period
 - Protocol allowed use of previously failed AAD during follow-up: use limited to 7% of subjects classified as success during last 6 months of follow-up
- AAD (Control) Group
 - Flecainide 36%, Propafenone 41%, Sotalol 20%, Dofetilide 3%
 - 64% of AAD group had an ablation procedure after symptomatic recurrence and classification as treatment failure

Additional Effectiveness Analyses Demonstrate Benefit of THERMOCOOL AF Ablation

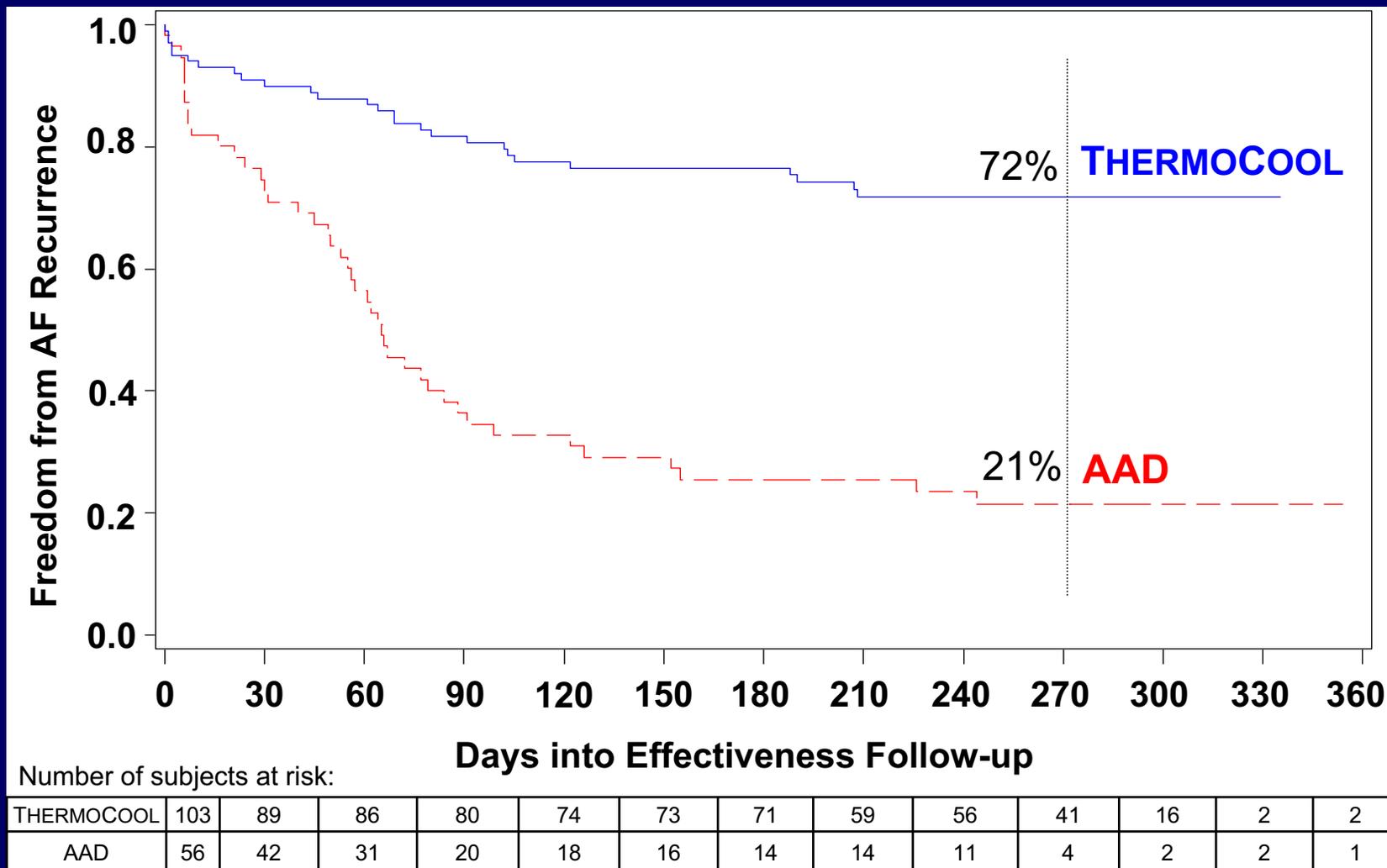
- To further characterize the effectiveness results, the following post-hoc KM analyses were conducted:
 - Freedom from symptomatic AF recurrence
 - Freedom from any AF recurrence (symptomatic or asymptomatic)

Symptomatic AF Recurrence* Dramatically Reduced for THERMOCOOL Group vs. AAD Group (n=159)



*Subject to monitoring provisions of the protocol

Total Observed AF Recurrence* Dramatically Reduced for THERMOCOOL Group vs. AAD Group (n=159)



*Subject to monitoring provisions of the protocol

Robustness of AAD (Control) Group Effectiveness Results

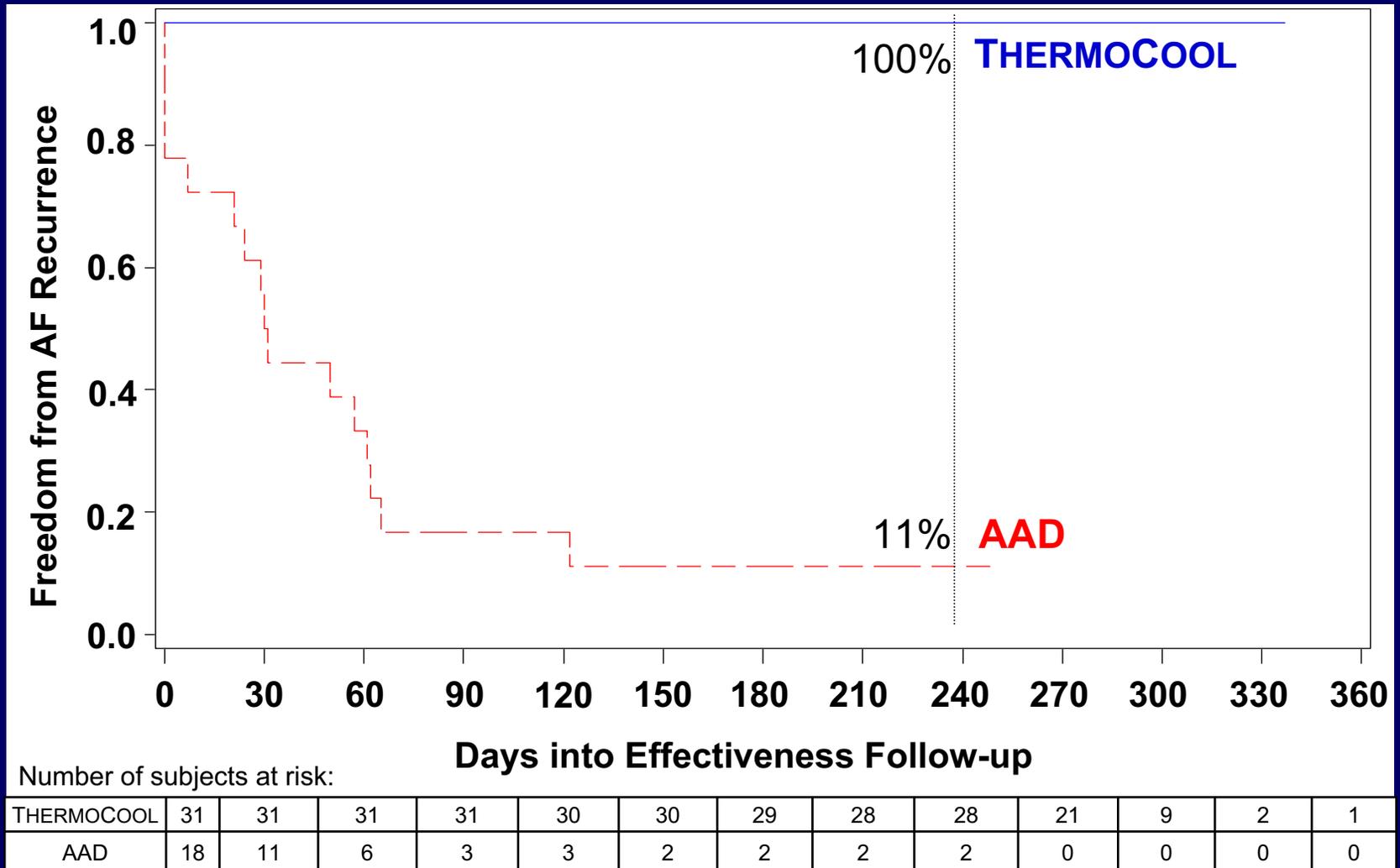
- 11 AAD (Control) subjects were prescribed *the same or higher* dose of a previously failed drug
 - Sensitivity Analysis performed removing these 11 subjects from the AAD (Control) group; results consistent with primary analysis showing superiority for the THERMOCOOL group (p-value < 0.0001)
- 4 AAD (Control) subjects received *less than* the protocol-recommended AAD dosage (1 subject included in the above group)
- Bayesian multiple imputations analysis was conducted for these 14 subjects receiving less than the protocol-specified AAD dosage
 - **Superiority was still demonstrated**

Analysis of Site / Regional Variability

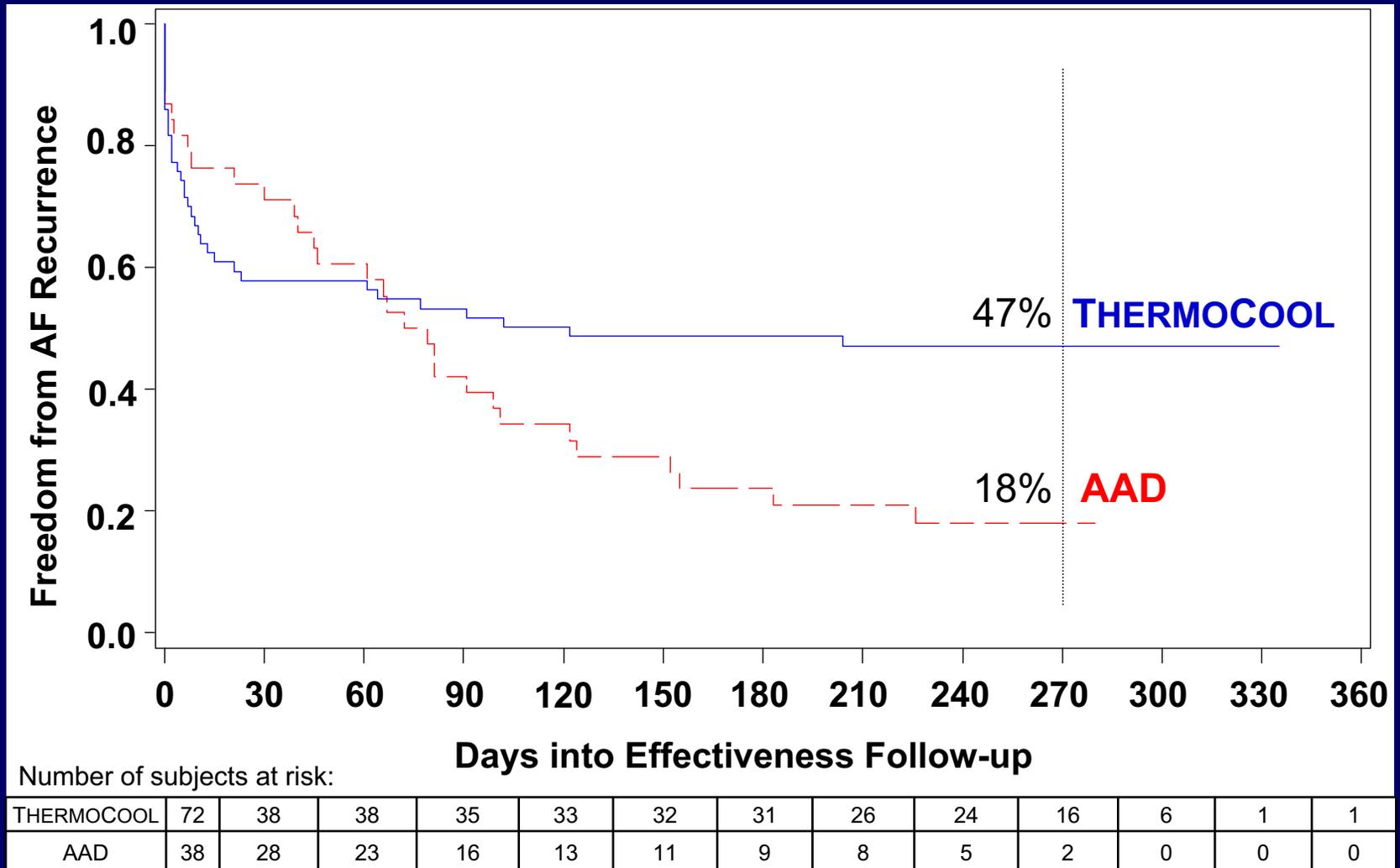
- Effectiveness outcomes stratified by site and/or region
 - OUS-1 vs. Remaining sites
 - Non-US vs. US sites

Time to Chronic Failure (per Protocol)

OUS-1 Site (n=49)



Time to Chronic Failure (per Protocol) Excluding OUS-1 Site (n=110)

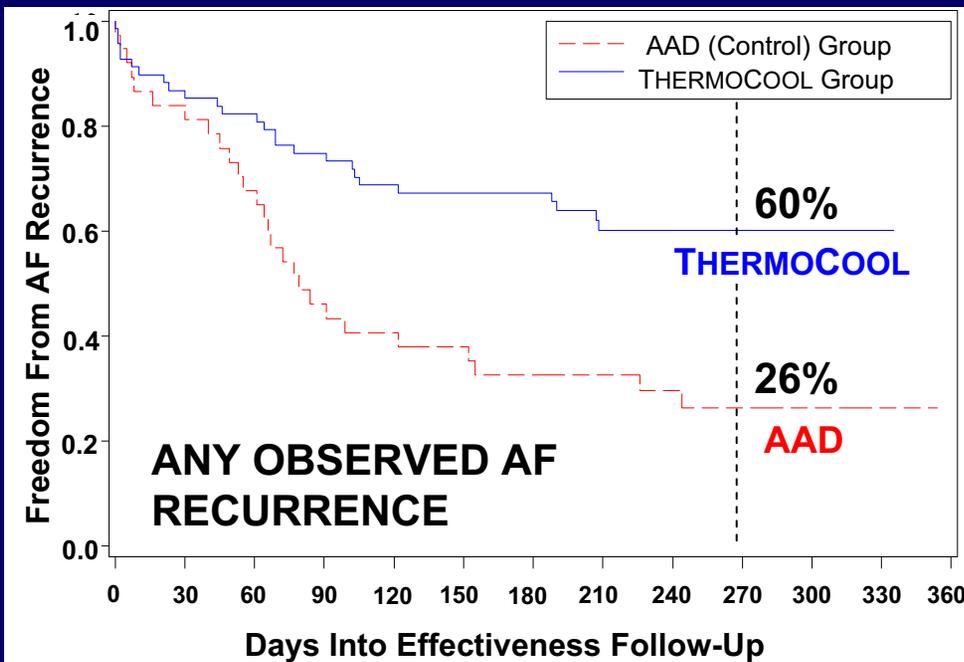
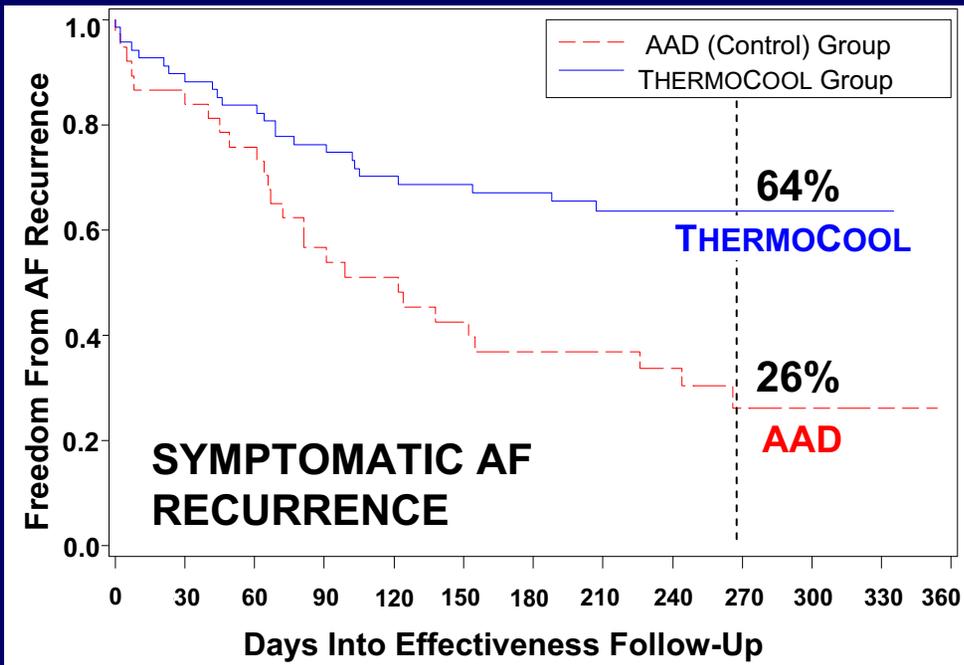


Potential Contributors to OUS-1 Site Variation

- One of the highest volume AF ablation centers worldwide
- Access to THERMOCOOL catheter since 1999
- Minor differences in baseline demographics (smaller atrial size, less hypertension, younger subjects)
- Procedural Practice
 - Cavotricuspid isthmus ablation (23/31 at OUS-1 vs. 13/72)
 - Left atrial linear lesions (20/31 at OUS-1 vs. 9/72)
- THERMOCOOL subjects with early AF recurrence underwent ablation within 80 days (4/31 at OUS-1 vs. 9/72)
- Medical Management Post-Ablation
 - Administration of previously failed Class I/III AADs post-ablation (typically continued for 3 - 6 months)
 - Strict protocol compliance - absence of protocol adjudicated failures in both randomization groups

Superiority of THERMOCOOL Ablation vs. AAD Independent of the Contribution of the OUS-1 site

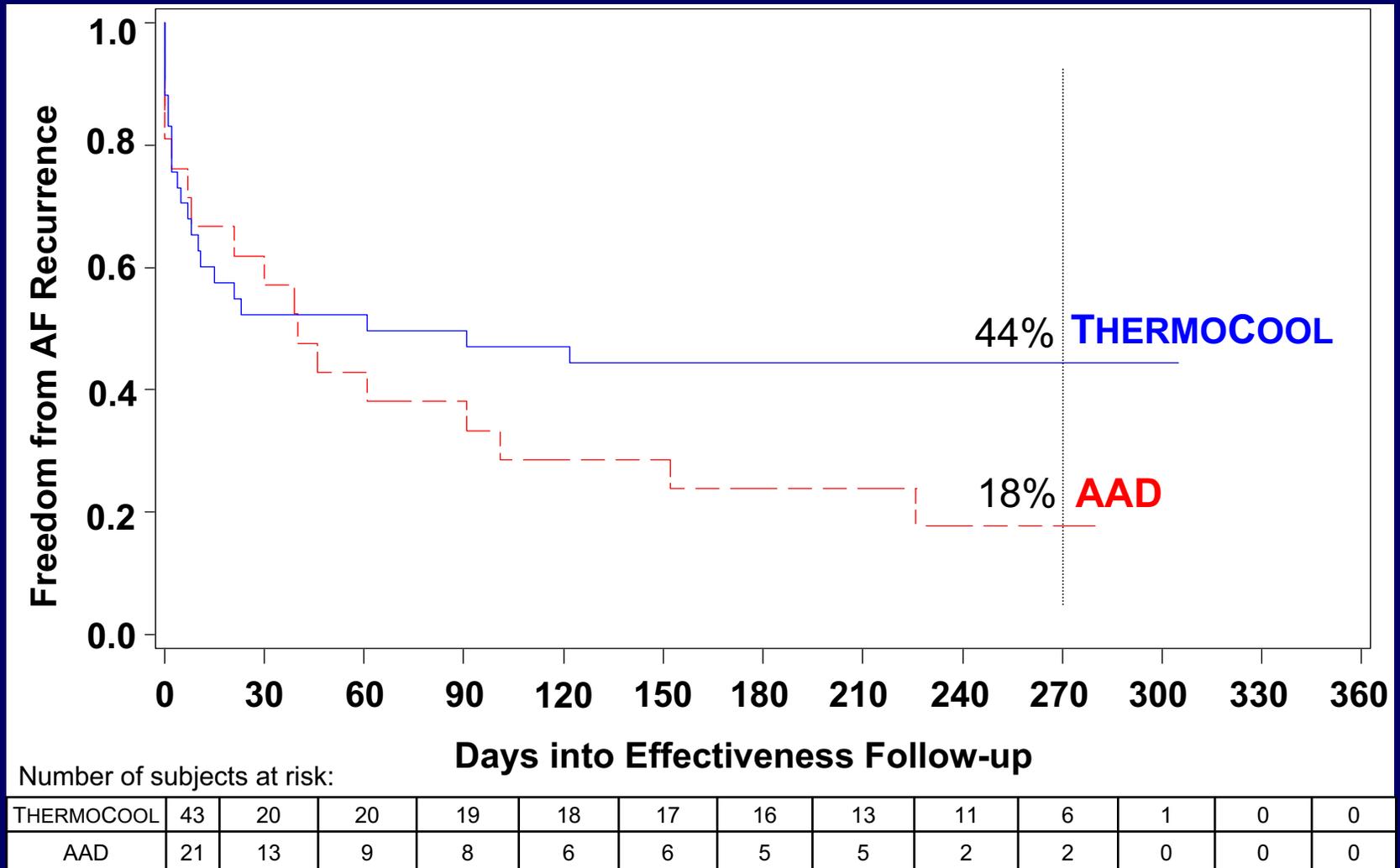
- Bayesian analysis conducted excluding subjects from the OUS-1 site
 - Resulting posterior mean probabilities of success
 - 46% THERMOCOOL Group
 - 20% AAD Group
 - The posterior probability that the THERMOCOOL group is superior to the AAD (Control) group is 0.9975
- Sensitivity analyses conducted varying strengths of borrowing of OUS-1 and remaining OUS sites
 - Even if one heavily discounts OUS-1 and remaining OUS sites, the result is still very compelling
 - e.g. if one borrows 20% (discounts by 80%) OUS-1 and remaining OUS sites, the probability of superiority is 0.991

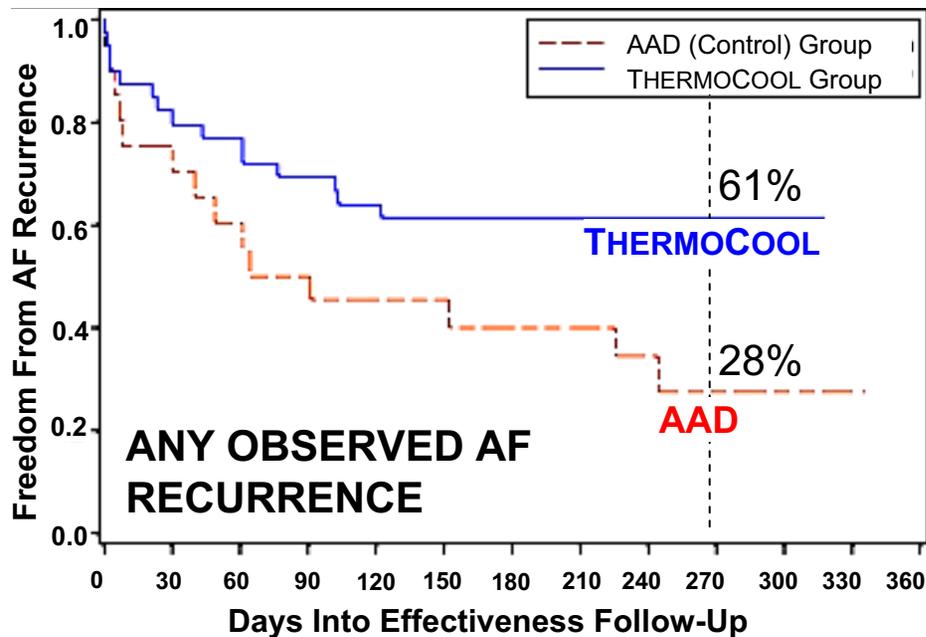
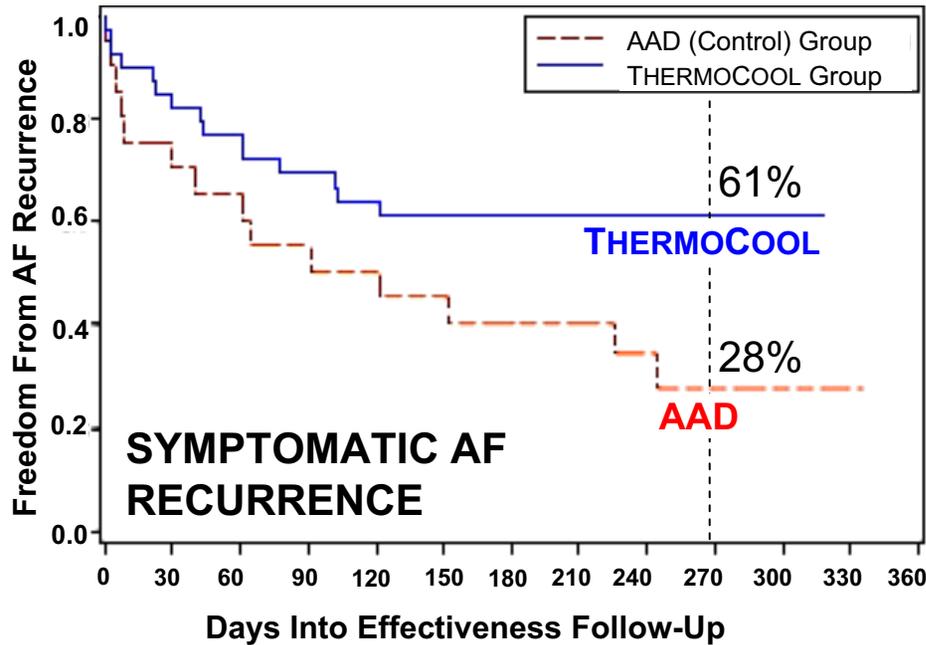


Additional Effectiveness Outcomes Excluding OUS-1

- Differences between treatment groups remain clinically meaningful

Time to Chronic Failure (per Protocol) US Sites (n=64)





Additional Effectiveness Outcomes – US Sites only

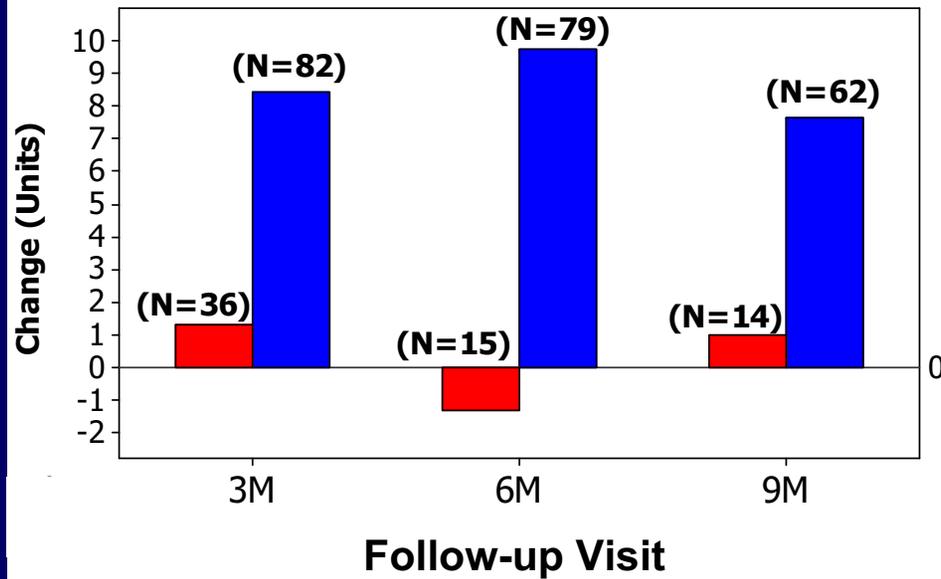
- Clinically important treatment effect observed for the US site subset

Improved Quality of Life Post-THERMOCOOL AF Ablation

- Quality of life was assessed at baseline and 3, 6, and 9-months post-blanking/dosing
- Instruments used:
 - SF36-v2
 - Atrial Fibrillation Symptom Frequency and Severity Checklist

Mental Component Summary (MCS)

Mean Absolute Change from Baseline

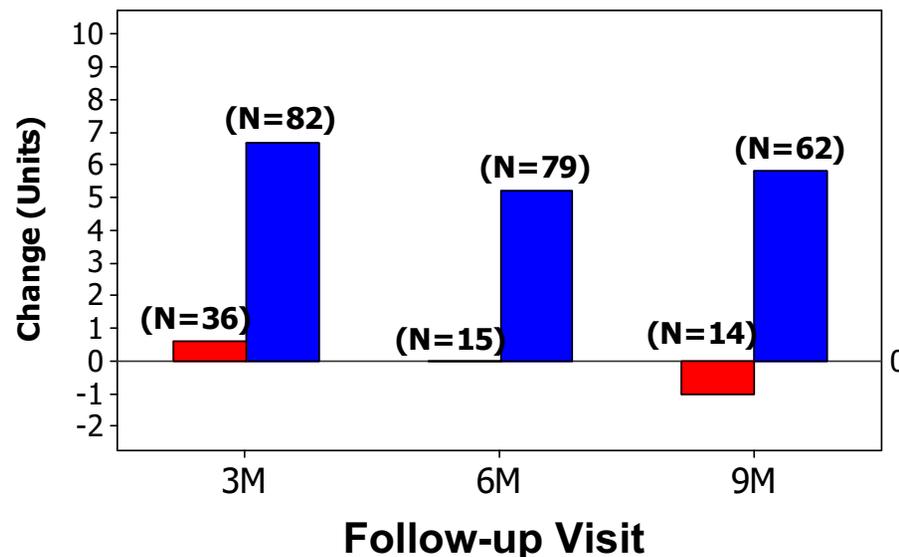


QOL: SF-36

- Baseline values for both groups similar, and below population norm of 50
 - MCS 45 ± 11 THERMOCOOL
44 ± 12 AAD
 - PCS 46 ± 9 THERMOCOOL
48 ± 9 AAD

Physical Component Summary (PCS)

Mean Absolute Change from Baseline

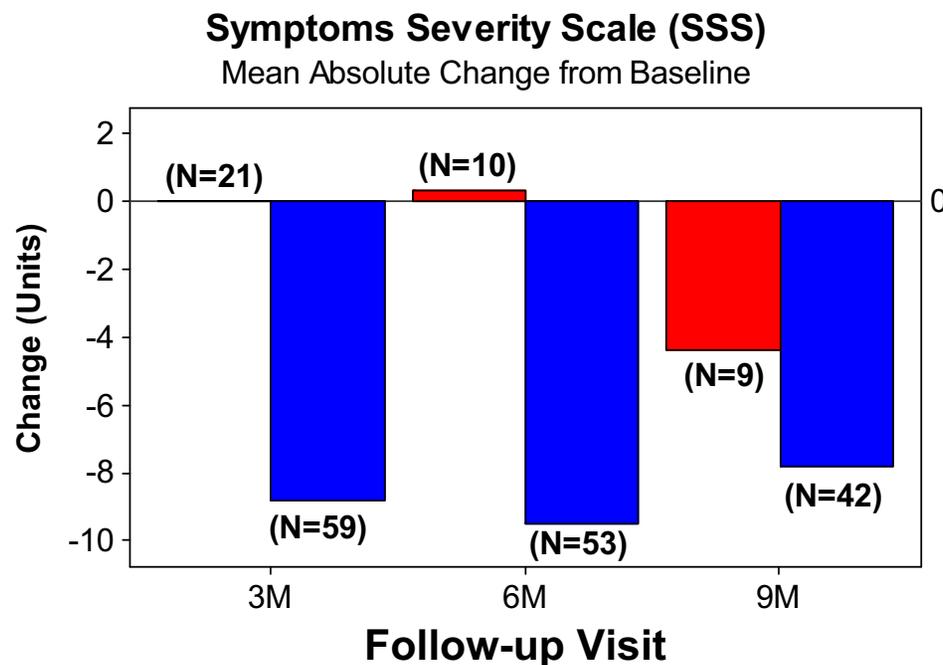
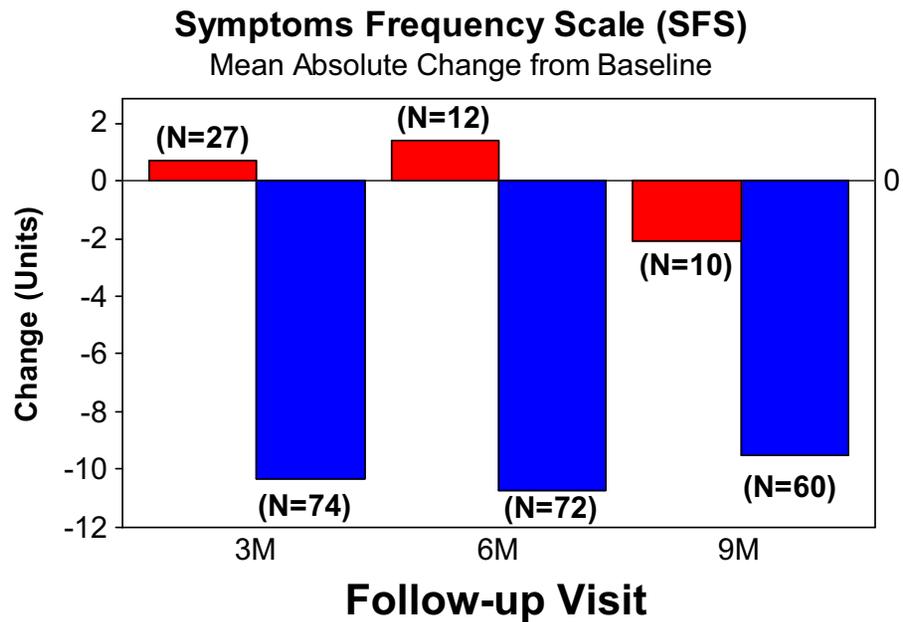


- AAD pts undergoing ablation excluded from subsequent QOL analysis
- 3-5 unit change considered clinically significant

■ AAD (Control)

■ THERMOCOOL

Clinically Meaningful Reduction in Symptoms for THERMOCOOL Subjects



- Decrease in score correlate with decrease in symptoms
- $\geq 50\%$ decrease in symptom frequency and severity scores from baseline in the THERMOCOOL group at all time points
- AAD group at 9 months reflect a small number remaining without ablation

■ AAD (Control)

■ THERMOCOOL

Heart Failure

- Only NYHA Class I & II subjects were eligible for study inclusion
 - 5 subjects (THERMOCOOL=3, AAD=2) enrolled with a history of CHF at baseline
 - No HF related Primary AEs reported in any of the 3 THERMOCOOL subjects
 - Safety and effectiveness inference challenging due to small number of subjects
- Safety of THERMOCOOL catheter adequately characterized in the VT population (PMA P040036)
 - 56.7% (131/231) enrolled subjects with CHF
- Restoration of sinus rhythm by ablation in subjects with CHF and AF significantly improves cardiac function, symptoms, exercise capacity, and quality of life with low complication rate (Hsu et. al *NEJM* 2004)

Subjects Failing Only Class II/IV AADs

- 16% (27/167) of subjects enrolled based on failure of class II or IV AADs only
 - 20 THERMOCOOL group
 - 7 AAD group
- Chronic effectiveness success
 - 39% (5/13) THERMOCOOL group
 - Remaining 7 subjects still within the effectiveness evaluation period at the time of the analysis
 - 29% (2/7) AAD group
- Small numbers make inference difficult

Effectiveness Results Generalizable to the US Population

- 15 US sites contributed to study population
- Statistical results insensitive to exclusion of OUS-1 and to discounting of all OUS sites
- Analyses of time to symptomatic AF recurrence and any observed AF recurrence demonstrate substantial treatment effect in the US population alone
- While amiodarone use was excluded by protocol, it is considered an unacceptable option by many patients and practitioners for paroxysmal atrial fibrillation due to potential long-term side effects

Additional Considerations

Electroanatomical Mapping

- In this study, electroanatomical mapping was incorporated as part of the ablation procedure
- Alternative mapping guides for AF ablation including fluoroscopy, intracardiac echocardiography, and circular mapping catheters are documented in literature
- This study does not address whether electroanatomical mapping is superior to these alternative approaches

Effectiveness Conclusions

- Superiority for THERMOCOOL ablation vs. AAD demonstrated in achieving primary effectiveness endpoint
 - Randomized, controlled trial
 - Conservative effectiveness endpoint definition
 - Excellent TTM compliance and rigorous adjudication
 - Statistical conclusions robust to deviations
 - Directionality of treatment effect robust across subsets
- Clinically meaningful treatment effects also in favor of THERMOCOOL arm
 - Freedom from symptomatic AF or any observed AF recurrence
 - QOL improvement

Albert L. Waldo, M.D., FACC, FAHA, FHRS

The Walter H. Pritchard Professor of Cardiology,
Professor of Medicine & Professor Biomedical Engineering;
Case Western Reserve University

Associate Chief of Cardiology for Academic Affairs
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Primary Safety Analysis

- The primary safety endpoint for this study was defined as the incidence of early onset (within 7 days of the ablation procedure) of Primary AEs. Including the following:
 - Death
 - Atrio- esophageal fistula
 - Atrial perforation
 - Cardiac Tamponade
 - Myocardial infarction (MI)
 - Stroke
 - Cerebrovascular accident (CVA)
 - Thromboembolism
 - Transient Ischemic Attack (TIA)
 - Diaphragmatic paralysis
 - Pneumothorax
 - Heart block
 - Pulmonary vein (PV) stenosis
 - Pulmonary edema
 - Pericarditis
 - Hospitalization (initial and prolonged)
 - Pericardial effusion
 - Vascular access complications

Accountability for Primary Safety Analysis: All Subjects Undergoing Ablation

Subject Disposition	Treatment Group		Total
	THERMOCOOL	AAD (Control)	
Total Number of Subjects Enrolled	106	61	167
Subjects Excluded	3	4	7
Overall Safety Cohort	103	57	160
Subjects Discontinued	0	1	1
Subjects not Undergoing Ablation	0	20	20
Primary Safety Cohort (Subjects undergoing ablation)	103	36	139

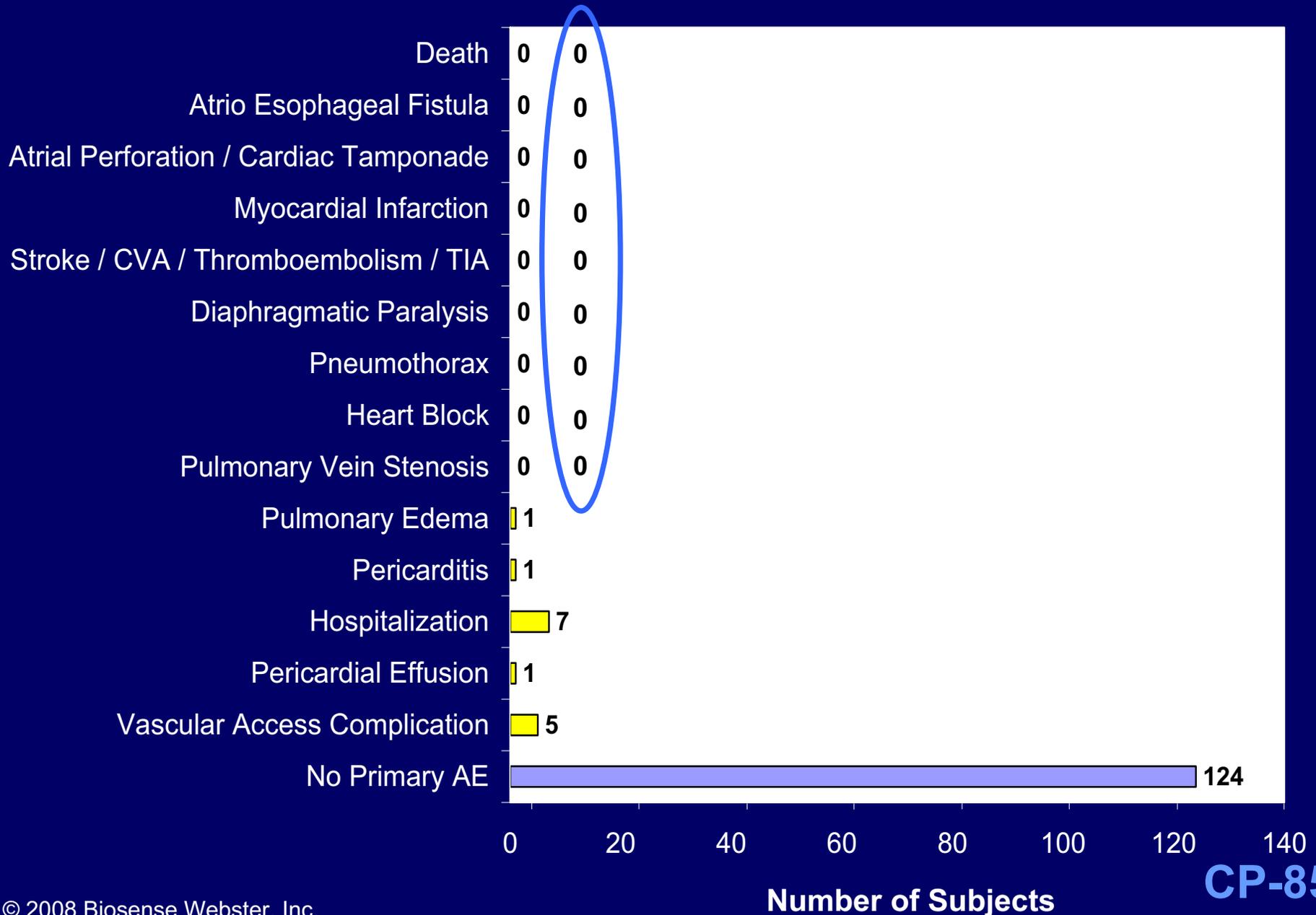
Primary Adverse Events

- Primary Safety Endpoint (Early Onset \leq 7 days)
- Primary AEs compared to performance goal of 16.0%

	Study Results
Number of Subjects in Safety Cohort	139
Number of Subjects with Primary AEs	15
% Subjects with Primary AEs	10.8 %
95% Upper Confidence Bound*	16.1 %

* Exact binomial using a commercially available software package.

Low Incidence of Primary Adverse Events



All Primary Adverse Events: Resolved or Improved

- Primary Safety Endpoint – Early-Onset (≤ 7 Days)
Primary AE Outcomes

Description	Number of Primary AEs (n = 16)	Outcome
Pulmonary Edema	1	Resolved
Pericarditis	1	Improved
Hospitalization (initial and prolonged)	8*	All Resolved
Pericardial Effusion	1	Resolved
Vascular Access Complication	5	All Resolved

* Two (2) events in one subject, 15 total subjects experienced primary AE

Primary Adverse Events: Hospitalizations

Hospitalizations

- Extended Stay
 - 1 subject for decrease in hemoglobin level*
 - 1 subject for hematuria (traumatic Foley catheter insertion)
 - 1 subject for atrial flutter
- Re-admission during 1st week
 - 3 subjects developed AF recurrence
 - 1 subject for pneumonia
 - 1 subject for shortness of breath*

*Same subject was hospitalized 2 times

No Device-Related Primary Adverse Events

- Primary Adverse Events by Causality
(Primary Safety Cohort, n=139)

Description	Number of Subjects Experiencing Primary AEs	% Subjects Experiencing Primary AEs	Total No. of Primary AEs
All Primary Adverse Events	15	10.8	16
Device-related	0	0.0	0
Possibly Device-related	1	0.7	1
Procedure-related	9	6.5	10
Possibly Procedure-related	0	0.0	0
Unrelated to Device or Procedure	5	3.6	5

Primary Safety Analysis: Pulmonary Vein Stenosis

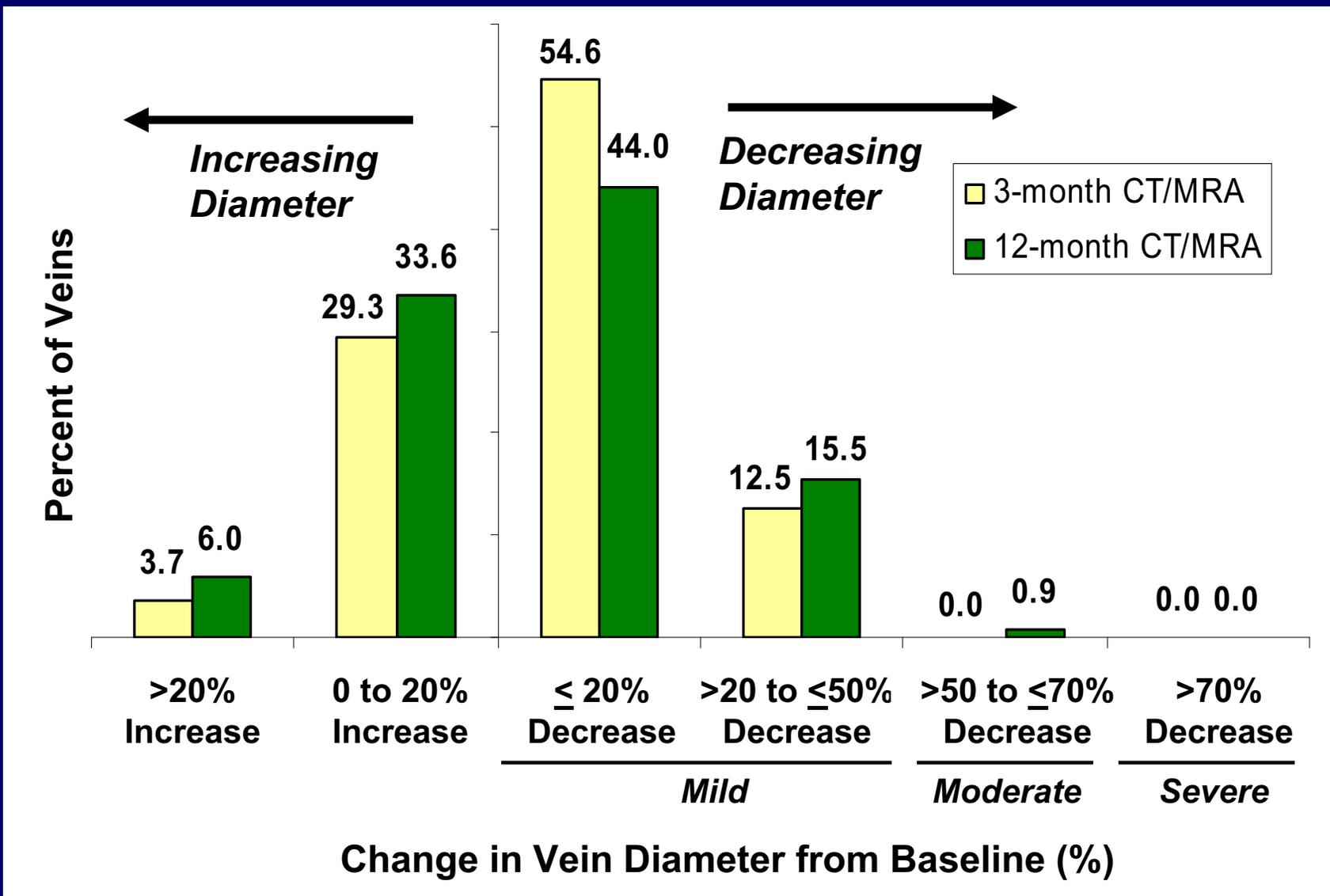
- Pulmonary vein stenosis was defined in the study protocol as $\geq 70\%$ reduction in the diameter of the pulmonary vein from baseline
- Subject cohort included all subjects undergoing an ablation procedure (with follow-up CT/MRA)

No Pulmonary Vein Stenosis Observed

- Incidence of Pulmonary Vein Stenosis ($\geq 70\%$ from baseline) in any targeted vein by subject

	THERMOCOOL Subjects n / N	AAD (Control) Subjects Undergoing Ablation n / N	Total n / N
PV Stenosis \geq 70% at 3 Months	0 / 67	0 / 15	0 / 82
PV Stenosis \geq 70% at 12 Months	0 / 25	0 / 4	0 / 29

PV Diameter Changes at 3 and 12 Months by Pulmonary Vein



Secondary Safety Analysis: Comparison of Randomization Groups

Biosense Webster developed a hierarchical classification of AEs based on 2 categories of level of severity:

Category 1 - Resulted in **Permanent Injury or Impairment**

- Death
- Cerebrovascular Accident
- Myocardial Infarction
- Pulmonary Vein Stenosis
- Diaphragmatic Paralysis
- Left Atrial/Esophageal Fistula

Category 2 - AE was **Temporary or Reversible**

- Transient Ischemic Attack
- Cardiac Tamponade
- Pericarditis
- Life-Threatening Arrhythmia
- Bradycardia with Hemodynamic Compromise
- Anaphylactic Reaction
- Respiratory Insufficiency
- Pneumothorax
- Hospitalization (Initial or Prolonged)
- Emergency Department (ED) Visit
- Major Bleeding
- Vascular Access Complications
- Abnormal Liver-Function Tests
- Prolonged QT Interval
- Neurologic Side-Effects
- Disabling Exercise Intolerance
- Disabling Fatigue
- Disabling Visual Disturbance
- Disabling GI Upset

Early Onset Serious Adverse Events About Half as Likely for THERMOCOOL Subjects (Overall Safety Cohort, n=160)

- Secondary safety endpoint: Early-onset serious adverse events within 90 days of initial treatment

Group	Early-Onset of Serious Adverse Events	
	Category 1 Permanent Injury or Impairment	Category 2 Temporary or Reversible
THERMOCOOL (n=103)	0 (0.0%)	19 (18.4%)
AAD (Control) (n=57)	0 (0.0%)	20 (35.1%)
p-value*	N/A	0.0221

* Fisher's Exact test, unpowered secondary endpoint without multiplicity adjustment

Late Onset Serious Adverse Events Less Likely for THERMOCOOL Group (Overall Safety Cohort, n=160)

- Secondary Safety Analysis: Late-onset serious adverse events after 90 days of initial treatment

Group	Late-Onset of Serious Adverse Events			
	Category 1 Permanent Injury or Impairment	Category 2 Temporary or Reversible	Other	Total*
THERMOCOOL (n=103)	1 (1.0%)	8 (7.8%)	4 (3.9%)	11 (10.7%)
AAD (Control) (n=57)	0 (0.0%)	8 (14.0%)	1 (1.8%)	9 (15.8%)

* Two (2) subjects in the THERMOCOOL group are represented in more than one category

Safety Conclusions

- Excellent safety profile for THERMOCOOL AF catheter ablation
- Primary AE incidence
 - Performance goal 16.0%; observed UCB 16.1%
 - 1 possibly device-related event
 - No death, MI, stroke, CVA, heart block, atrial perforation, etc., within 7 days
- No clinically significant PV stenosis
- Early-onset serious adverse events
 - Lower incidence in the THERMOCOOL group (18.4%) compared with the AAD group (35.1%)
- Late-onset serious adverse events
 - Lower incidence in the THERMOCOOL group (10.7%) compared to the AAD group (15.8%)

Marcia S. Yaross, Ph.D.

Vice President, Clinical, Regulatory, and Health Policy,
Biosense Webster, Inc.

Results Constitute Valid Scientific Evidence

- Randomized Control Trial (RCT) Design
- Bayesian analysis methods have allowed efficient, timely study completion
- Rigorously conducted
 - TTM adjudication process
 - Excellent TTM compliance
- Thoroughly vetted study dataset
 - Sponsor monitoring
 - FDA Bioresearch Monitoring audits
 - No Form 483 inspectional observations

Clinical Trial Demonstrates Safety and Effectiveness for Treatment of AF

- Primary trial objectives met
 - **Superior chronic effectiveness of THERMOCOOL AF ablation** vs. AADs, per strict protocol definitions
 - Posterior probability of superiority > 0.999 using all available data
 - Robust conclusion: probability 0.9975 without OUS-1
 - **Clinically Acceptable safety profile**
- Additional important results for THERMOCOOL AF ablation subjects vs. AAD control subjects
 - More likely to be AF recurrence free
 - Improved quality of life
 - Fewer serious adverse events

Both Genders Well-Represented in THERMOCOOL AF Trial

- Women represented 33.5% of the enrolled population
- Regression analyses determined that gender was not a predictor of chronic success outcome or of primary AEs in this study
- Therefore, it is concluded from this study that the product is equally safe and effective when used in males and females

Need for AF-specific THERMOCOOL labeling

- Public interest best served by the rapid communication of THERMOCOOL AF study results, AF ablation risks and benefits, in FDA-approved device labeling
- Additional AF indication to current THERMOCOOL labeling to help ensure that physicians use THERMOCOOL catheters in the most safe and effective manner for treatment of AF
- Biosense Webster, Inc. is committed to formal training program
 - THERMOCOOL training required prior to first shipment
 - Unable to train on AF in the absence of indication-specific approval

THERMOCOOL Catheter Instructions for Use

- Current PMA Approved Indications for Use
 - Catheter-based cardiac electrophysiological mapping and for the treatment of:
 - a) **Type I atrial flutter** in patients age 18 or older (NAVISTAR and CELSIUS)
 - b) Recurrent drug/device refractory sustained monomorphic **ventricular tachycardia (VT)** due to prior myocardial infarction (MI) in adults (NAVISTAR only)
 - The NAVISTAR THERMOCOOL Catheter provides location information when used with the CARTO[®] EP Navigation System
- Proposed additions to current indications for use
 - c) **Drug refractory symptomatic paroxysmal atrial fibrillation** (NAVISTAR and CELSIUS)

Post-Approval Study Commitment

- Biosense Webster, Inc. proposes to conduct a Post-Approval Registry Study to confirm:
 - device performance in the post-market setting
 - long term safety and effectiveness

Proposed Post-Approval Registry Study

Study Design	Prospective, multicenter, non-randomized clinical evaluation
Study Hypothesis	The safety of the device in post-market setting is non-inferior compared to IDE study results (P030031/S11)
Sample Size	145 subjects from 10 to 20 sites with $\geq 50\%$ of new sites
Duration of Study	6 – 7 years (including enrollment phase) with 5 years of follow-up
Primary Safety Endpoint	Occurrence of primary AEs within 7 days of an ablation procedure
Secondary Endpoints	A) Effectiveness Long term (5 year) symptomatic AF Recurrence Evaluate effectiveness outcomes in subjects in whom cavo-tricuspid ablation lines are placed in addition to PV isolation B) Safety Long term (5 year) occurrence of Serious Adverse Events (Death, Stroke, MI, etc.)

Statutory Burden for Pre-Market Approval Met (21 CFR 860.7)

- Study constitutes “valid scientific evidence”
- Probable benefits outweigh risks of AF ablation with THERMOCOOL catheter when used as directed in the symptomatic, paroxysmal AF population
- Biosense Webster, Inc. respectfully requests that the Panel recommend P030031/S11 for approval

Sensitivity Analyses Varying Strengths of Borrowing OUS-1 and Remaining OUS Sites Data

Probability of Superiority		OUS-1 Site											
		0	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90	1	
Remaining OUS Sites	0	0.892	0.957	0.984	0.995	0.998	1	1	1	1	1	1	1
	0.10	0.915	0.966	0.988	0.996	0.999	1	1	1	1	1	1	1
	0.20	0.933	0.974	0.991	0.997	0.999	1	1	1	1	1	1	1
	0.30	0.947	0.980	0.993	0.998	0.999	1	1	1	1	1	1	1
	0.40	0.958	0.984	0.994	0.998	0.999	1	1	1	1	1	1	1
	0.50	0.967	0.987	0.996	0.998	1	1	1	1	1	1	1	1
	0.60	0.974	0.990	0.997	0.999	1	1	1	1	1	1	1	1
	0.70	0.980	0.992	0.997	0.999	1	1	1	1	1	1	1	1
	0.80	0.984	0.994	0.998	0.999	1	1	1	1	1	1	1	1
	0.90	0.987	0.995	0.998	0.999	1	1	1	1	1	1	1	1
	1	0.990	0.996	0.999	1	1	1	1	1	1	1	1	1

Demographics for Site OUS-1 vs. Remaining Sites

*New presentation of data

	OUS-1 n/50 (%)	Remaining Sites n/117 (%)	p-Value
Gender			1.0000
Female	17 / 50 (34.0)	39 / 117 (33.3)	
Male	33 / 50 (66.0)	78 / 117 (66.7)	
Age (years)			0.5165
Mean	54.9	56.1	
Standard Deviation	10.86	10.69	
Median	57	57	
Range	35 - 75	19 - 77	

Baseline Medical History for Site OUS-1 vs. Remaining Sites

***New presentation of data**

Medical History	OUS-1 n/N (%)	Remaining Sites n/N (%)	p-value
Hypertension	22 / 50 (44.0)	59 / 115 (51.3)	0.4027
Diabetes	3 / 50 (6.0)	14 / 115 (12.2)	0.2780
Congestive Heart Failure	2 / 50 (4.0)	3 / 114 (2.6)	0.6411
Deep Vein Thrombus	0 / 50 (0.0)	2 / 114 (1.8)	1.0000
Ejection Fraction < 40%	0 / 50 (0.0)	1 / 115 (0.9)	1.0000
Arrhythmias			
Atrial Flutter	8 / 50 (16.0)	36 / 109 (33.0)	0.0350
Atrial Tachycardia	0 / 50 (0.0)	13 / 113 (11.5)	0.0101
AV Node Re-entry Tachycardia	0 / 50 (0.0)	4 / 115 (3.5)	0.3156
Accessory Pathway	0 / 50 (0.0)	0 / 115 (0.0)	N/A
Ventricular Tachycardia	0 / 50 (0.0)	1 / 115 (0.9)	1.0000
Ventricular Fibrillation	0 / 50 (0.0)	0 / 115 (0.0)	N/A