Expanded Indication for AtriCure Synergy Ablation System to Include Treatment of Persistent and Longstanding Persistent AF in the Concomitant Surgical Setting

FDA Review of P100046

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FDA Review Team Members

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FDA Presentations

- Dr. Soma Kalb
  Introduction
- Dr. Weihua Cao
  Statistical Considerations
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  Conclusions

Introduction Outline

- Indications for Use
- Device Background
- Regulatory History
- Overview of Pivotal Study
- Target Population
- Discussion Points

Current Indications for Use

- K063630 (January 26, 2007):

  The AtriCure Ablation System is intended to ablate soft tissues during general surgery using radiofrequency energy.

- K101174 (November 12, 2010):

  The AtriCure Bipolar System including Synergy Dual Electrode Clamps is intended for the ablation of cardiac tissue during surgery.

Use of Device for Treatment of AF

- Current indication does not include treatment of atrial fibrillation (AF)

- FDA does not regulate practice of medicine
  - Federal Food, Drug and Cosmetic Act

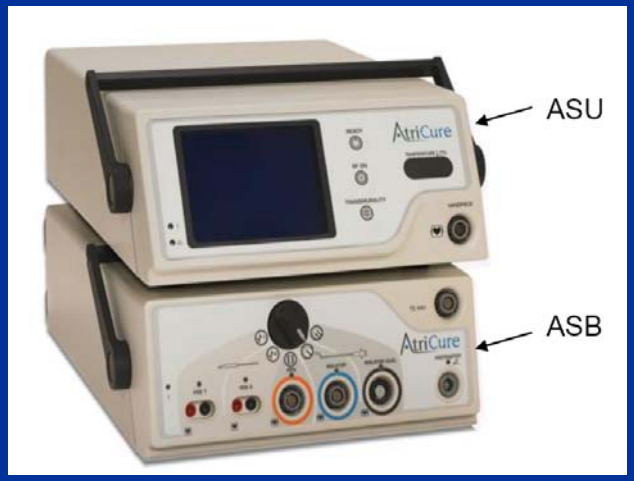
    Sec. 906 (21 USC § 396)

    Nothing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship

Proposed Indications for Use

The AtriCure Synergy Ablation System is intended to ablate cardiac tissue for the treatment of persistent or longstanding persistent atrial fibrillation in patients who are undergoing open concomitant coronary artery bypass grafting and/or valve replacement or repair.

Device Background

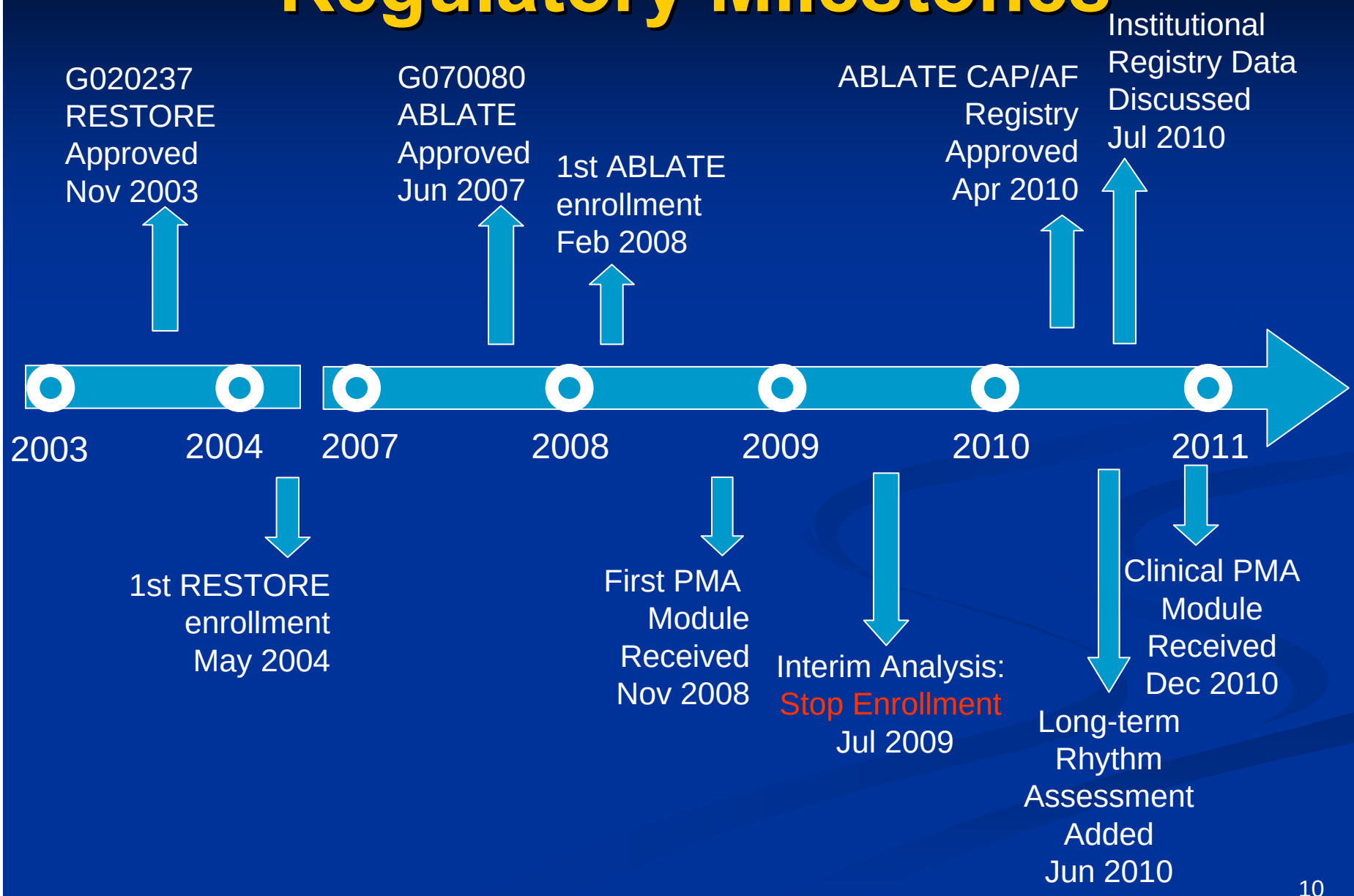


- AtriCure Synergy Ablation System
  - Synergy Ablation Clamp
  - Ablation and Sensing Unit (ASU)
  - Isolator Switch Matrix
- No device changes introduced in this PMA

Regulatory History: Surgical Ablation Studies

- 10-year history of Cox Maze IV procedure
- Difficult enrollment in randomized controlled trials
- Alternative designs attempted
  - RESTORE study – matched concurrent controls without AF
- FDA and sponsor agreed to single arm-study
  - ABLATE study

Regulatory Milestones



Pre-Clinical Review

- Pre-clinical testing included
  - Biocompatibility testing
  - Electrical, mechanical, and environmental *in-vitro* bench testing
  - Sterilization testing
  - Packaging and Shelf-life testing
  - Animal testing
- No outstanding pre-clinical issues

ABLATE Study Overview

- Single arm, nonrandomized
  - Permanent AF, concomitant CABG and/or valve surgery
- 9 centers
- 50-100 subjects
- Bayesian adaptive design with a non-informative prior for sample size determination
- Primary effectiveness endpoint
  - Rate of freedom from AF while off Class I or III anti-arrhythmic drugs at 6 months post procedure assessed with a 24-hr Holter
  - Performance goal: 60%
- Primary safety endpoint
  - Rate of major adverse events (death, stroke, MI, TIA or bleed) at 30 days post procedure
  - Performance goal: 18.95%

Target Population

- ABLATE inclusion criterion:

  Subject has history of permanent atrial fibrillation (AF in which cardioversion (electrical and/or pharmacologic) has failed or has not been attempted) as defined by the 2006 ACC/AHA/ESC Guidelines.

AF Classification in Clinical Guidelines

AF Classification	2006 ACC/AHA/ESC Guidelines	2007 HRS Consensus Statement
Paroxysmal	Self-terminating within 7 days	Recurrent episodes that terminate spontaneously within 7 days
Persistent	Not self-terminating within 7 days, or is terminated electrically or pharmacologically	Sustained beyond 7 days, or necessitating pharmacologic or electrical cardioversion
Longstanding persistent		Continuous, > 1-year duration
Permanent	Cardioversion has failed or has not been attempted	A decision has been made not to pursue sinus rhythm

Enrolled Population

- FDA interpretation of “Permanent AF” (per 2006 ACC guidelines):

  continuous AF of long duration (e.g., greater than one year) in which cardioversion has failed or has not been attempted

- Sponsor had enrolled subjects with paroxysmal, persistent and longstanding persistent AF (2007 HRS definitions)

- Sponsor formally classified subjects per current 2007 HRS definitions
  - 4 paroxysmal
  - 22 persistent
  - 29 longstanding persistent

Proposed Target Population

The AtriCure Synergy Ablation System is intended to ablate cardiac tissue for the treatment of persistent or longstanding persistent atrial fibrillation in patients who are undergoing open concomitant coronary artery bypass grafting and/or valve replacement or repair.

- Data are presented for all Treated subjects and Non-Paroxysmal AF (persistent and longstanding persistent AF) subjects

Primary Discussion Points

- Interpretation of safety results
- Interpretation of effectiveness results
  - Late antiarrhythmic drug (AAD) washout
  - Late cardioversion
  - Current definitions of AF treatment success
  - Non-compliance with ablation procedure
- Long-term effectiveness
- Appropriate target population
- Post-approval study considerations

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ABLATE Study Statistical Considerations

Weihua Cao, Ph.D.
Division of Biostatistics
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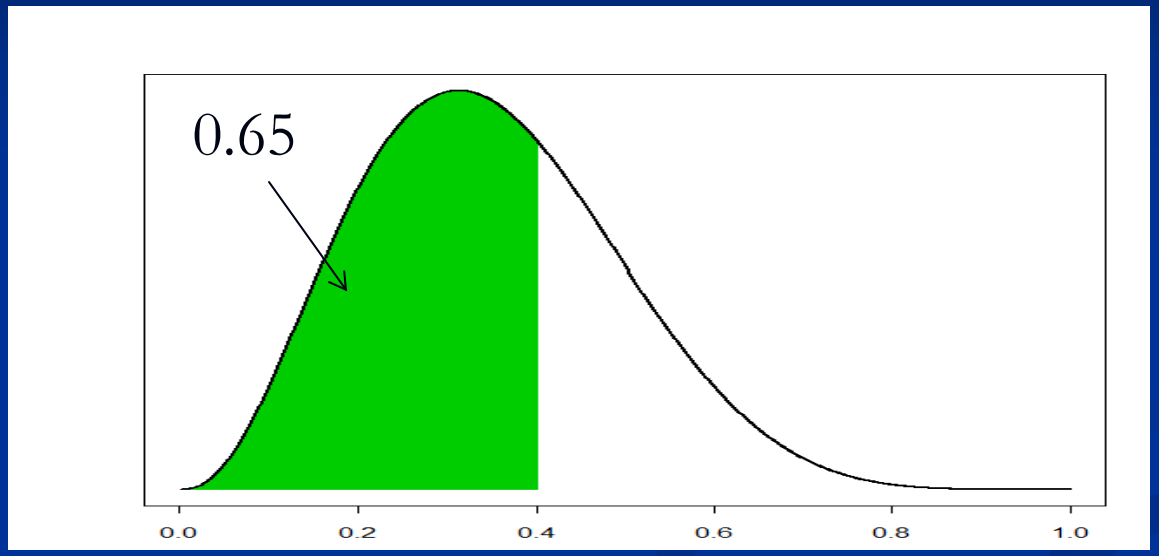
Outline

- Overview of Bayesian statistics
- Study design
- Pre-specified hypotheses for primary endpoints
- Sample size adaptation
- Interim analyses
- Study results
- Summary

Bayesian Statistics Overview

- An approach for learning from evidence as it accumulates.
- *Bayes' Theorem*: combine prior information with current information on a quantity of interest (e.g., AE rate).
- At the conclusion of the current study, the information about the quantity of interest is summarized by a posterior distribution, and Bayesian inferences are based on it.
- Prior information on quantity of interest comes from:
  - Information from previous comparable studies
  - subjective ideas prior to running the study
  - "No" prior information: non-informative prior can represent lack of information.

Hypothetical Prior Distribution on an Adverse Event Rate



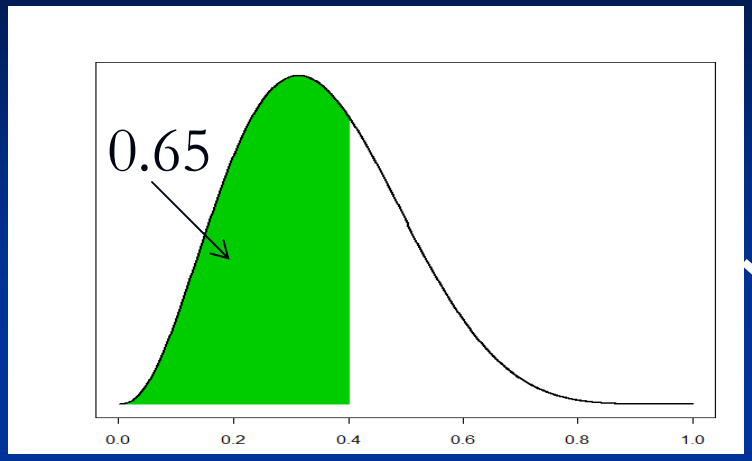
Adverse Event Rate

Hypothetical target = 0.40

Prior Probability that AE [illegible] – 0.65

Learning from Data

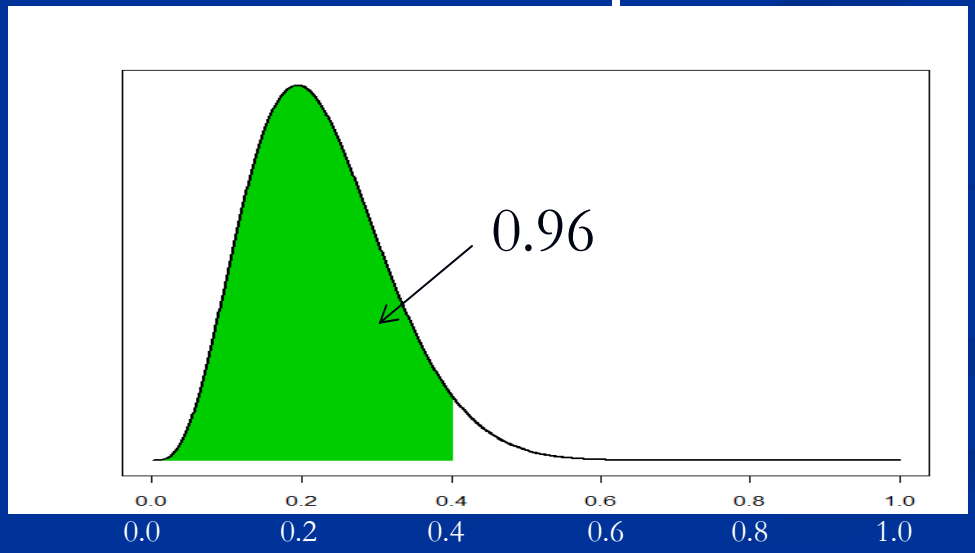
Prior



Study (n=10)

Data: 1 in 10 patients with AEs

Bayes Theorem



Posterior:
the updated prior distribution after seeing the current data

Study Design

- Prospective, single-arm, unblinded, multicenter trial
- IDE sites: up to 20 US sites (9 enrolled)
- Primary safety endpoint: rate of MAEs (death, stroke, MI, TIA and excessive bleeding) occurring within the initial 30 days post procedure or discharge (whichever is later) --- q_T

Study Design (Cont')

- Primary effectiveness endpoint: the proportion of subjects that are free of atrial fibrillation while off of any antiarrhythmic medication (Class I or III) at six months post procedure --- p_+

Statistical Hypothesis

- Primary safety endpoint:
  - H_0: $q_T \geq 18.95\%$ *vs.* H_a: $q_T < 18.95\%$
  - The null hypothesis is rejected if the posterior probability that the MAE rate q_T is less than 18.95% exceeds 0.95

$$P(q_T < 18.95\% \mid data) \geq 0.95$$

- Prior distribution on q_T: non-informative (uniform)

Statistical Hypothesis (Cont')

- Primary effectiveness endpoint:
  - H_0: $p_T \leq 60\%$ *vs.* H_a: $p_T > 60\%$
  - The null hypothesis is rejected if the posterior probability that the six-month success rate p_T exceeds 60% is greater than 0.975

$$P(p_T > 60\% \mid data) \geq 0.975$$

- Prior distribution on p_T: non-informative (uniform)

Sample Size Adaptation

- Sample size targeted between 50 and 100 subjects
- Bayesian adaptive design to determine sample size
  - First interim analysis: 50 patients enrolled, 20 patients reached 6-month endpoint
  - Repeated after every five patients were through 30 days
  - A maximum of 10 interim looks

Sample Size Adaptation (Cont')

- At each interim analysis, calculate the predictive probability of trial success for two scenarios:
  1) assuming enrollment stops and all currently enrolled patients are followed to six months (for success)
  2) assuming enrollment continues to the maximum sample size, 100 patients, and all are followed to six months (for futility)

- Trial success requires meeting both the primary effectiveness and safety endpoints.

Predictive Probability

- Predictive probability was used to decide:
  - Stop enrollment, wait 6 months and do final analysis
  - Stop trial for futility
  - Continue enrollment

- Predictive probability is calculated according to pre-specified rules agreed upon between FDA and the sponsor.

- Predictive probability is only for sample size adaptation, not for making of study success decision.

Predictive Probability at 55-patients

- First interim look conducted when 55 patients had been enrolled
- All 55 patients had 30-day safety outcomes
  - the primary safety endpoint was met
- The predictive probability of meeting the effectiveness endpoint with the current sample size was calculated to be 0.988
- The predictive probability of trial success is 0.988, which exceeds the threshold of 0.9, and accrual was stopped for probable success.

Predictive Probability with Non-paroxysmal Subjects

- In order to determine the effect of having enrolled paroxysmal patients on stopping the trial, a retrospective interim analysis was conducted when the 50th non-paroxysmal subject was enrolled in the trial.

	Pred prob of meeting effectiveness	Pred prob of meeting safety	Pred prob of trial success
Current n (Test for probable success)	0.550	0.000	0.000
Maximum n (Test for futility)	0.826	0.682	0.564

- Had we only used non-paroxysmal subjects at the first interim look, enrollment would have continued.

Type I Error Rate

- Due to interim looks, Type I error rate may be inflated.
- Type I error rate for the primary safety endpoint was inflated from 5% to 6.1%.
- Type I error rate for primary effectiveness endpoint was inflated from 2.5% to 2.6%.
- However, study conclusions for the primary safety and effectiveness endpoints are not affected.

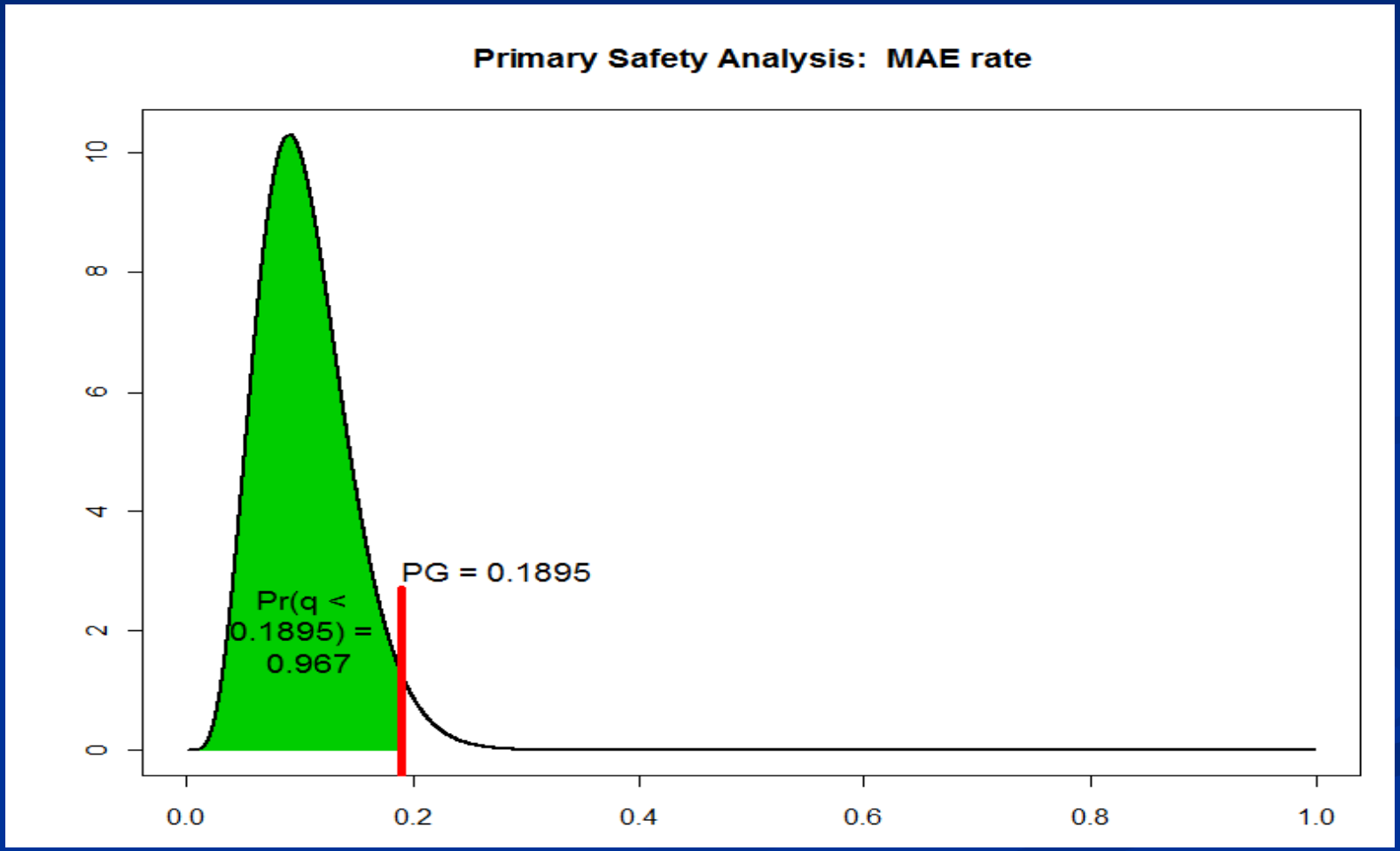
Primary Safety Endpoint Result

- Treated patients: 55 subjects
  - 5 MAEs: 2 deaths, 2 excessive bleedings, and 1 stroke (9.1%)
  - Posterior probability

    $P(q_T < 18.95\% \mid \text{trial data}) = 0.967 > 0.95$

  - Upper bound of the one-sided 95% Bayesian credible interval for q_T: 17.9%

Primary Safety Endpoint Result (Cont')



Safety Rate

Primary Safety Endpoint Result: Non-paroxysmal

- Non-paroxysmal AF: 51 subjects
  - 5 MAEs: 2 deaths, 2 excessive bleedings, and 1 stroke (9.8%)
  - Posterior probability

$$P(q_T < 18.95\% \mid \text{trial data}) = 0.946 < 0.95$$

  - Upper bound of the one-sided 95% Bayesian credible interval for q_T: 19.2%

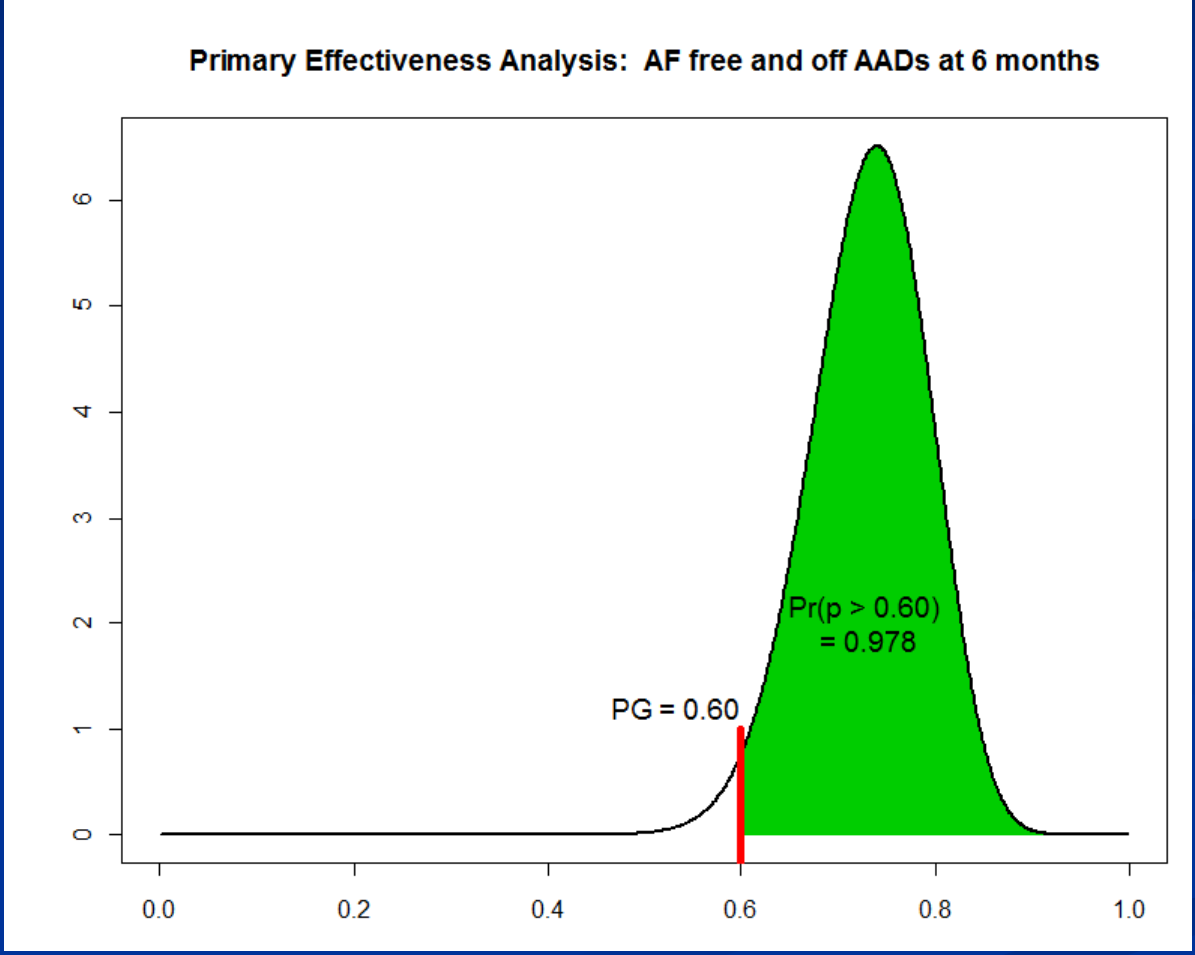
Primary Effectiveness Endpoint Result

- Treated patients: 50 subjects with 6-month data
  - 37 effectiveness successes (74%)
  - Posterior probability

    $P(p_T > 60\% \mid \textit{trial data}) = 0.978 > 0.975$

  - Lower bound of the one-sided 97.5% Bayesian credible interval for p_T: 60.4%

Primary Effectiveness Endpoint Result (Cont')



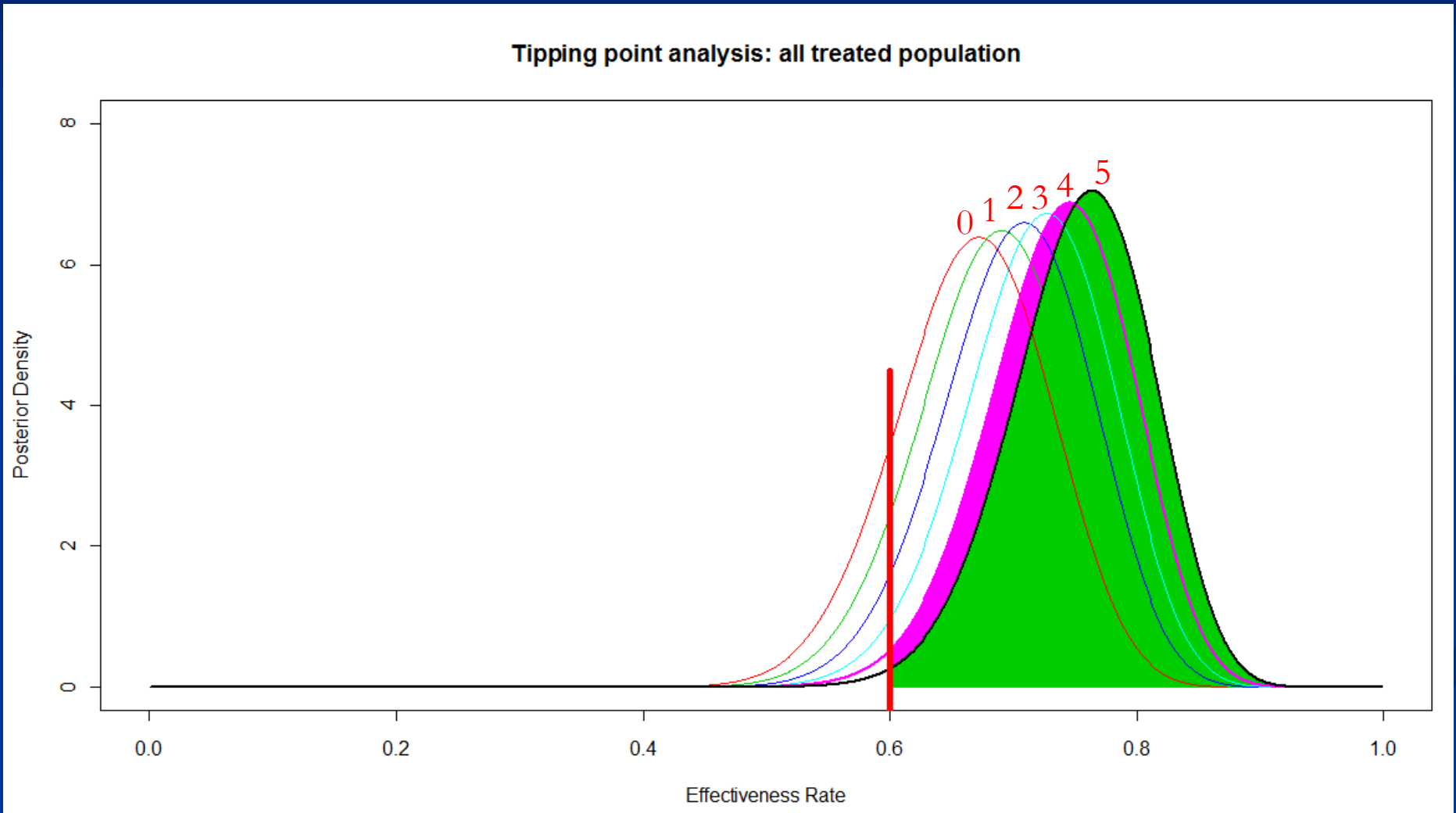
Effectiveness Rate

Primary Effectiveness Endpoint Result: Impact of Missing Data

- 5 subjects excluded from the analysis: 2 deaths < 30 days, 2 deaths between 30 days and 6 month, and 1 withdrawal at 30 days.

- Tipping point analysis conducted
  - need at least 4 successes out of the 5 unobservable subjects to meet the effectiveness objective

Tipping Point Analysis for All Treated Patients



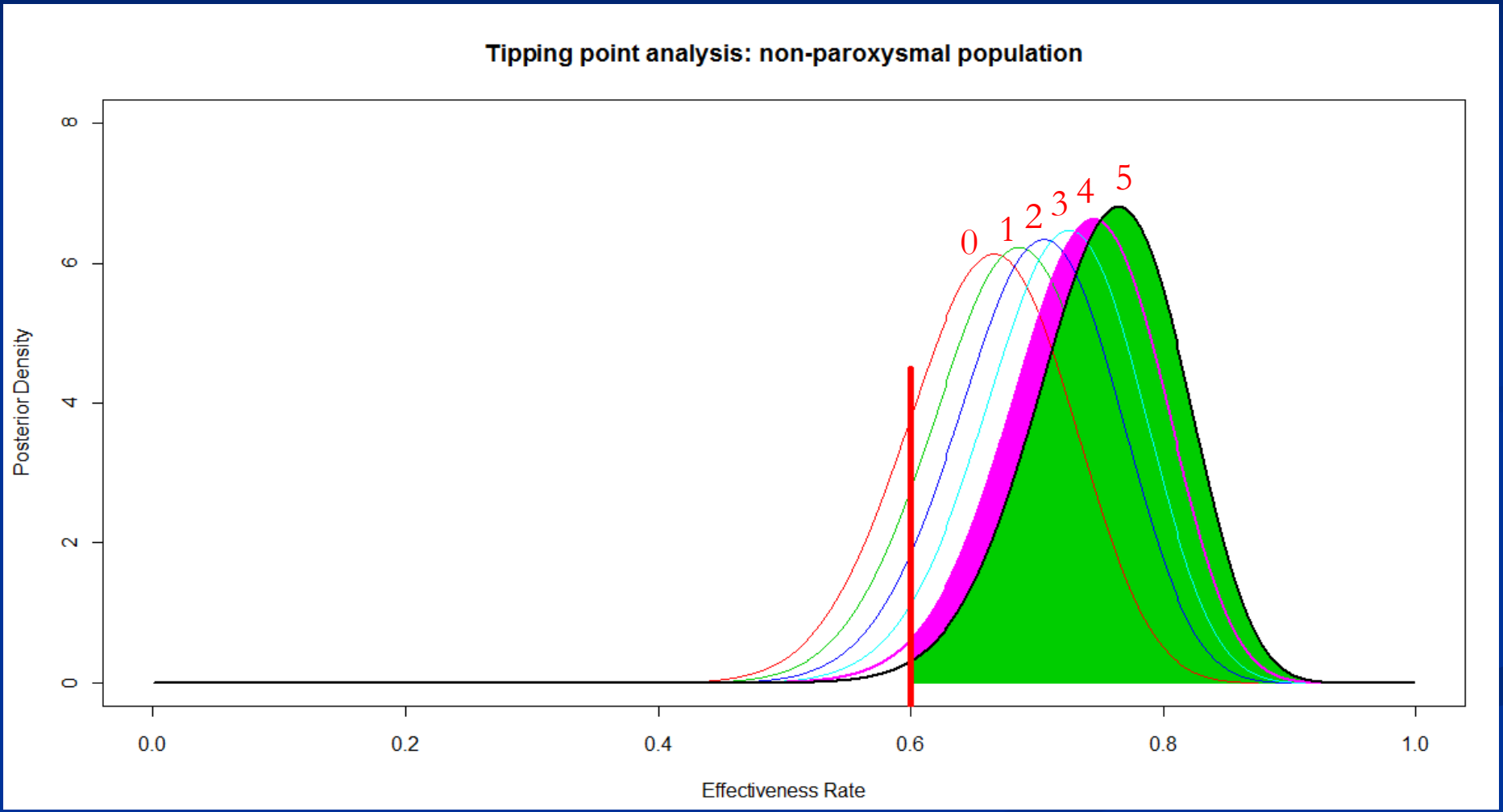
Primary Effectiveness Endpoint Result: Non-paroxysmal

- 46 non-paroxysmal subjects with 6-month data
  - 34 effectiveness successes (73.9%)
  - Posterior probability

    $P(p_T > 60\% \mid \text{trial data}) = 0.972 < 0.975$

  - Lower bound of the one-sided 97.5% Bayesian credible interval for p_T: 59.7%
- 5 missing observations were excluded
- Tipping point analysis: need 4 successes out of 5 unobservable subjects

Tipping Point Analysis for Non-paroxysmal Patients



Sponsor's Analysis of Non-paroxysmal patients

- The sponsor analyzed the non-paroxysmal patients by combining ABLATE and the ABLATE AF registry together.

- FDA finds this combined analysis problematic and the statistical inference un-interpretable (as the combined analysis is post-hoc and no alpha was allocated for this analysis).

Summary

- Enrollment would have continued if only non-paroxysmal subjects were used at the first interim look.
- The primary safety and effectiveness endpoints were met, ignoring the effect of missing data.
- The primary safety and effectiveness endpoints were not met for non-paroxysmal patients.

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FDA Presentation to the Advisory Panel on Circulatory Devices: Clinical Aspects

PMA P100046
AtriCure Synergy Ablation System

Adam E. Saltman, M.D., Ph.D.
Medical Officer, CDRH/ODE/DCD

PAR=Paroxysmal, PER = Persistent,
LSP = Longstanding Persistent

Some Clinical Experience

	Procedure	N	PAR	PER	LSP	Success	F/U
Akpinar 2006	CABG	33	36%		64%	PRM: 58.1%	6 mo
Beyer 2009	Lone	100	39%	29%	32%	PRS: 96% PRM: 71%	13.6 mo
Doty 2007	CABG, MVR, AVR, TVR	65	32%		68%	79.6%	6 mo
Edgerton 2006	Lone	47	74%		26%	PRM: 71.4%	6 mo
Edgerton 2010	Lone	52	100%			86.3%	6 mo
Gillinov 2004	MVR	108	25%	26%	49%	85%	3 mo
Melby 2006	Lone 32%, Concomitant 68%	100	59%	7%	34%	91%	12 mo
Mokadam 2005	Lone 57%, Concomitant 43%	30	63%	37%		96%	12 mo
Sternik 2010	MVR	192	15%	37%	49%	86%	6 mos
Sternik 2006	Lone	60		54%	46%	80%	?
Suwalski 2007	Lone	6	100%			100%	3 mos
Weimar 2011	Lone	100	31%	6%	63%	93%	6 mos

IDE Clinical Study

- ABLATE: AtriCure Synergy Bipolar RF Energy Lesions for Permanent Atrial Fibrillation Treatment during Concomitant, On-Pump, Endo/Epicardial Cardiac Surgery

IDE Clinical Study

- Key I/E criteria
- Analysis population
- Endpoints
  - Primary Effectiveness
  - Primary Safety
  - Secondary Effectiveness and Safety
- Procedures
- Results and Additional analyses

Inclusion / Exclusion Criteria

- ✓ Inclusion
  - ✓ History of permanent AF (2006 Guidelines)
  - ✓ Elective cardiac surgical procedure
    - ✓ CABG, mitral valve, aortic valve, tricuspid valve
- ✗ Exclusion
  - ✗ Previous ablation (including catheter)
  - ✗ LA diameter > 8 cm
  - ✗ Inotrope / IABP usage
  - ✗ Redo surgery

Analysis Populations

AF Classification	2006 ACC/AHA/ESC Guidelines	2007 HRS Statement
Paroxysmal	Self-terminating within 7 days	Recurrent episodes that terminate spontaneously within 7 days
Persistent	Not self-terminating within 7 days, or is terminated electrically or pharmacologically	Sustained beyond 7 days, or necessitating pharmacologic or electrical cardioversion
Long-standing persistent		Continuous, > 1-year duration
Permanent	Cardioversion has failed or has not been attempted	A decision has been made not to pursue sinus rhythm

Analysis Populations

- Are the study design and enrolled population appropriate for persistent and long-standing persistent AF subjects?

Endpoints

- Primary effectiveness
  - Proportion of subjects free of AF while off of any AAD at 6 months post procedure
    - Recordings: 24-hour Holter or permanent pacemaker (PPM) interrogation
    - "Freedom from AF": No episode > 5 minutes, and total AF < 1 hour / 24 hours
  - Performance goal: 60%

Endpoints

- Primary safety
  - Rate of MAEs within the initial 30 days post procedure or discharge
    - Death
    - Bleeding > 2 units of RBCs with reoperation
    - Stroke
    - Transient ischemic attack
    - Myocardial infarction
  - Performance goal: 18.95%

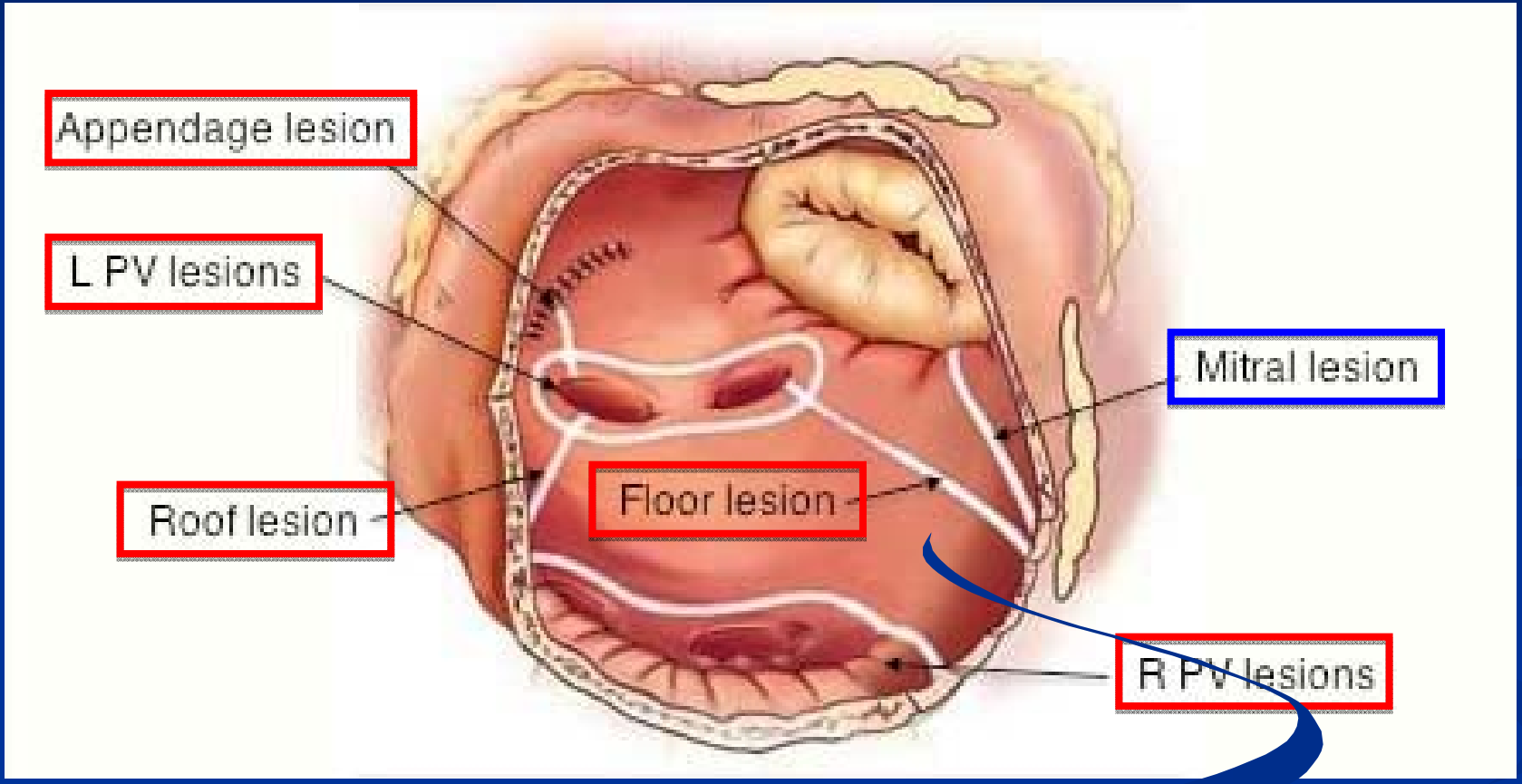
Endpoints

- Secondary effectiveness
  - Intraoperative pulmonary vein isolation
  - Freedom from AF at 6 months, independent of AADs
  - AF burden at 6 months
- Secondary safety
  - MAE at 6 months
  - All AE at 6 months
    - Device- and procedure-related AE and SAE

Additional Analyses

- Rate of pacemaker implantation
- Freedom from AF and off AADs at 12+ months
- Overall freedom from AF at 12+ months
- AF burden at 12+ months

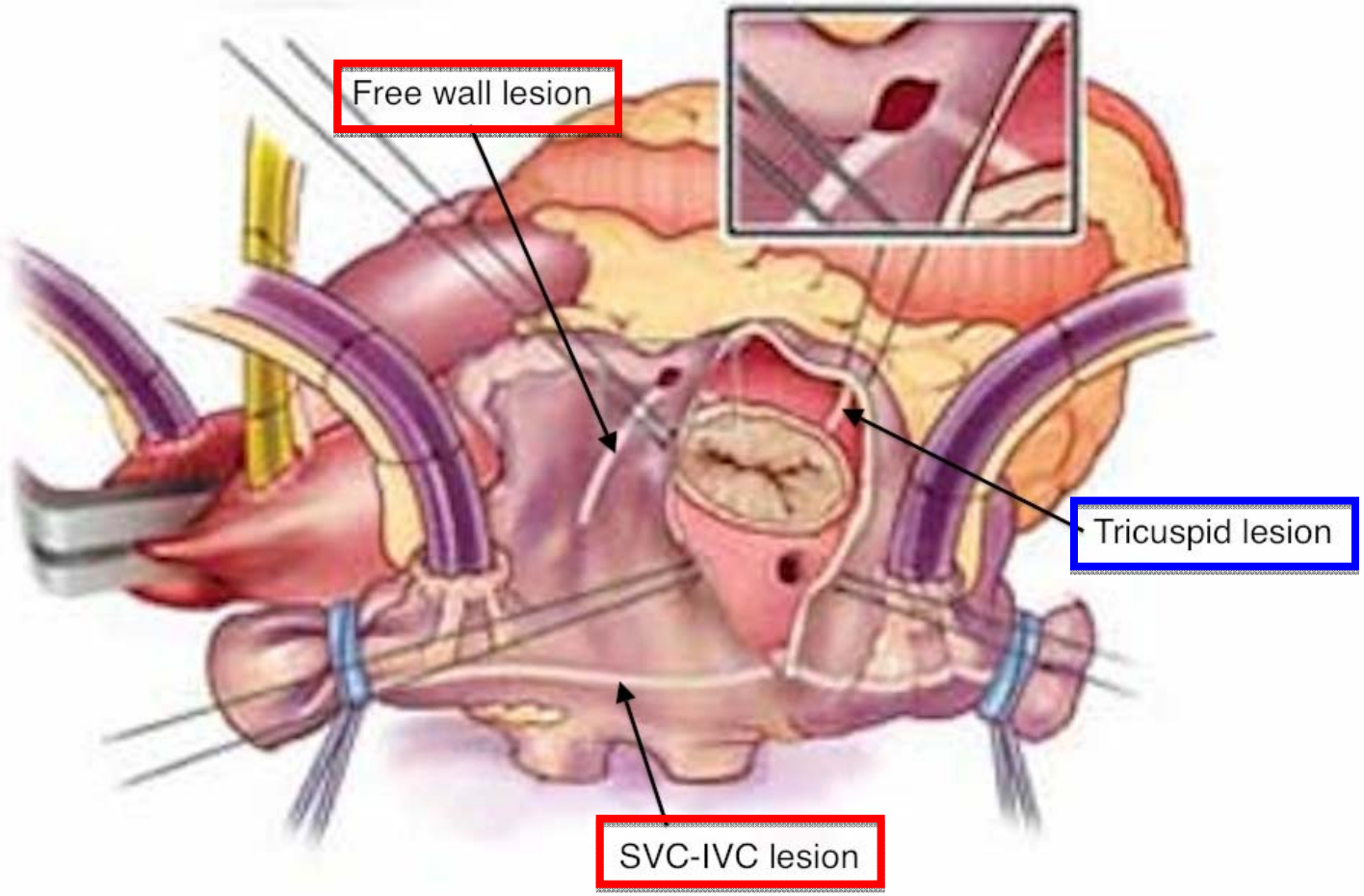
Procedures – Left Atrium



= Synergy handpiece only

= Start with Synergy h[illegible]e, complete with cryothermy or RF pen

Procedures – Right Atrium



= Synergy handpiece only

= Synergy handpiece, cryothermy, or RF pen

Lesion Requirements

Lesion	Device Recommended
R and L Pulmonary Veins	Clamp only
Roof line	Clamp only
Floor line	Clamp only
LA appendage to pulmonary vein	Clamp only
Mitral valve connecting	Clamp ➔ Pen or cryosurgical device
SVC to IVC	Clamp only
Free wall to appendage tip	Clamp only
RA appendage to tricuspid annulus	Clamp ➔ Pen or cryosurgical device
Tricuspid valve	Any device

LEFT

RIGHT

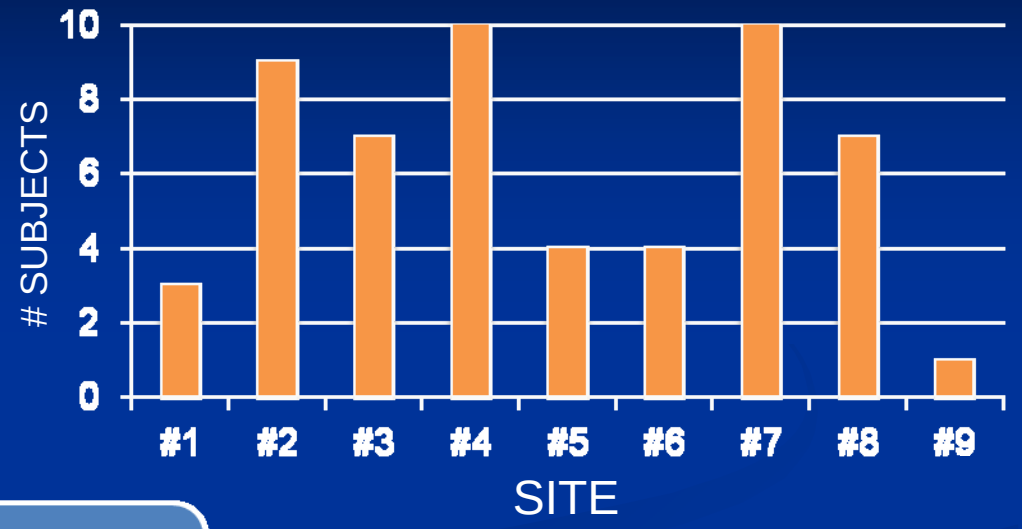
Procedures – Postoperative

- After surgery, subjects given AAD
- Anticoagulation by MD preference
- Follow up
  - D/C, 30 days, 3 mo, 6 mo, 12 mo, 18 mo, 2 yr
- Stop AAD before 6 month assessment
  - Amiodarone: 12 weeks earlier
  - Others: 4 weeks earlier
- Cardioversions any time up to 6 mo visit

Results

- Subject accountability
- Demographics
- Procedures performed
- Primary safety
- Primary effectiveness
- Secondary endpoints
- Additional analyses

Treated Population



57 Subjects consented

- 1 Large atrium
- 1 Expired

55 Subjects treated

- 2 Expired
- (1 Withdrew but was assessed)

53 subjects @ 30 days

- 2 Expired

50 Subjects @ 6 months

- 2 Expired

48 Subjects @ 12 months

Non-Paroxysmal Subset

56 Subjects consented

- 1 Large atrium
- 4 Paroxysmal AF
- 1 Expired

51 NP subjects treated

- 2 Expired
- (1 Withdrew but was assessed)

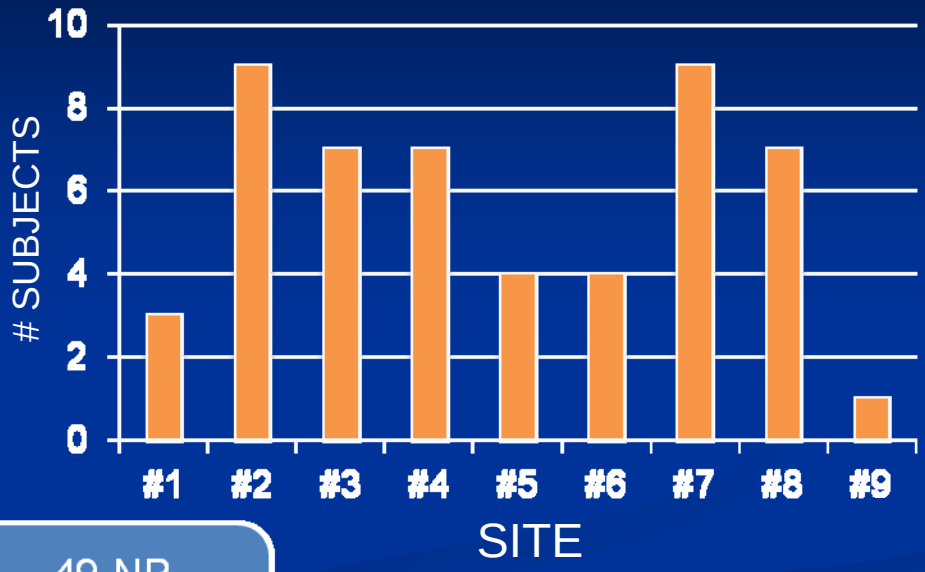
49 NP subjects @ 30 days

- 2 Expired

46 NP subjects @ 6 months

- 1 Expired

45 NP subjects @ 12 months



Subject Demographics

	Treated Population N = 55		Non-paroxysmal Subset N = 51	
	Mean	Range	Mean	Range
Age (yrs)	70.5 ± 9.3	45 – 88	70.8 ± 9.6	45 - 88
Male	58.2%		[illegible]%	
AF Duration (mos)	61.2 ± 49.5	1.8 – 188.	61.7 ± 51.1	1.8 – 188.4
Hx AF > 1 yr	85.5%		84.3%	
Ejection fraction (%)	50.0 ± 10.3	20 – 77	49.6 ± 10.6	20 – 77
LA size (cm)	5.9 ± 1.0	3.9 – 7.7	6.0 ± 1.0	3.9 – 7.7

Procedures Performed

Concomitant Procedures	Treated Population	Non-paroxysmal Subset
Valve only	40.0%	37.2%
Mitral valve	18.2%	17.6%
Aortic valve	21.8%	19.6%
Double valve	16.4%	17.6%
Aortic & Mitral	7.3%	7.8%
Mitral & Tricuspid	9.1%	9.8%
CABG & valve	16.4%	15.7%
CABG & mitral	10.9%	9.8%
CABG & aortic	5.5%	5.9%
CABG & double valve	9.1%	9.8%
Aortic & mitral	5.5%	5.9%
Mitral & tricuspid	3.6%	3.9%
CABG only	18.2%	19.6%

Primary Safety

	Treated Population N=55	Non-paroxysmal Subset N=51
Composite MAE <= 30 days	9.1% (5)	[illegible] (5)
95% BCI	0.00 – [illegible]	0.00 – 0.192
Posterior Pr (safety event rate < 0.1895)	[illegible]6.7%	94.6%

Posterior probability threshold = 95%

Primary Effectiveness

	Treated Population N=50	Non-paroxysmal Subset N=46
Primary success rate	74.0% (37)	[illegible] (34)
95% Bayesian Credible Interval	0.604 - [illegible]	0.597 – 1.00
Posterior Pr (effectiveness > 60%)	[illegible].8%	97.2%

Posterior probability threshold = 97.5%

Secondary Safety Endpoints

	Treated Population N = 55	Non-paroxysmal Subset N = 51
MAE through 6 months	10.9% (6)	11.8% (6)
Any AE through 6 months	90.9% (50)	[illegible] (48)
Any SAE	74.5% [illegible]	76.5% (39)
Any AF procedure related AE	16.[illegible]% (9)	17.6% (9)
Any device-related AE	0.0% (0)	0.0% (0)
Any serious procedure-related AE	14.5% (8)	15.7% (8)
Any serious device related AE	0.0% (0)	0.0% (0)

Procedure-Related Events

	Total Population N=55
AV block	5.4% (3)
Bradycardia	3.6% (2)
Left atrial tear	1.8% (1)
Inferior vena cava cannulation site injury	1.8% (1)
Pulmonary vein tear	1.8% (1)
Cardiac akinesis	1.8% (1)

Secondary Effectiveness

At 6 Months	Treated Population N = 50	Non-paroxysmal Subset N = 46
Free of AF, Regardless of AADs	84.0% (42)	82.6% (38)
AF Burden		
0 minutes	82.0% (41)	82.6% (38)
<= 5 minutes	2.0% (1)	0.0% (0)
>5 min – 1 hour	2.0% (1)	0.0% (0)
> 1 hour	14.0% (7)	15.2% (7)
Bilateral PV Isolation	100.0% (23/23)	

Pacemaker Implantations

	In Hospital	≤ 30 Days	≤ 6 Months	≤ 12 Months
PPM implantations	25.0% (12)	25.0% (12)	33.3% (16)	33.3% (16)
AVN dysfunction	8.3% (4)	8.3% (4)	8.3% (4)	8.3% (4)
SAN dysfunction	16.7% (8)	16.7% (8)	[illegible] (12)	25.0% (12)

Pacemaker Implantations

Subject	6 Month Rhythm	12+ Month Rhythm
04-03	Paced	Paced
05-03	Paced	Paced
07-01	Sinus	Paced
07-03	AF	AF
07-04	Paced	Sinus
08-02	Sinus	Paced
08-03	AF	AF
11-06	AF	Paced
11-07	-	-
11-10	Sinus	Paced*
13-06	AFL	Paced
19-01	Paced	AF*

Effectiveness Endpoints at 12+ Months

At 12+ months	Treated Population	Non-paroxysmal Subset
Free of AF	75.0% (36/48)	73.3% (33/45)
Free of AF, off AAD's	62.5% (30/48)	62.2% (28/45)
AF Burden		
0 minutes	77.5% (31/40)	76.3% (29/38)
<= 5 minutes	0.0% (0/40)	0.0% (0/38)
> 5 min – 1 hour	0.0% (0/40)	0.0% (0/38)
> 1 hour	22.5% (9/40)	23.7% (9/38)

Ancillary Considerations

- Inadequate drug washout at 6 months
- Cardioversions performed after 3 months
- Lesion set deviations
- Current (2007) clinical consensus document
- Overall

Inadequate Drug Washout

	Treated Population N=50	Non-paroxysmal Subset N=46
Primary effectiveness proportion	72.0% (36)	[illegible] (33)
97.5% Bayesian Credible Interval	0.583 – [illegible]	0.574 – 1.00

Cardioversions

Primary Effectiveness Status	CV Before 6 Months	CV Between 3 – 6 Months	Days Between CV and 6-month Evaluation
AF Free, Off AAD's	6	1	77
AF Free, On AAD's	2	1	9
In AF	4	2	29, 61

	Treated Population N=50	Non-paroxysmal Subset N=46
Primary success, no CV within 3 months	72.0% (36)	71.7% (33)
97.5% Bayesian Credible Interval	0.583 – 1.00	0.57[illegible] – 1.00

Using the Newest Consensus For Rhythm Failure

Effectiveness	Treated Population	Non-paroxysmal Subset
At 6 months:		
No AF/AFL/AT, Off AADs	70.0% (35/50)	[illegible]% (33/46)
97.5% Bayesian Credible Interv.	0.562 – [illegible]	0.574 – 1.00
No AF/AFL/AT	78.0[illegible] (39/50)	78.3% (36/46)
At 12+ months:		
No AF/AFL/AT, Off AADs	58.3% (28/48)	57.8% (26/45)
No AF/AFL/AT	70.8% (34/48)	68.9% (31/45)

Lesion Deviations

Lesion	Deviations	Omitted	Alterative Used
Floor	8	1	Cut & sew – 6, RF pen – 1
RA free wall	5	5	0
LA appendage	3	1	Cryoablation – 2
Roof	2	1	RF pen – 1
Mitral annulus	2	1	Cryoablation – 1
RA appendage	2	2	0
Tricuspid valve	1	1	0
SVC-to-IVC line	1	1	0

	Treated Population	Non-paroxysmal Subset
Primary success with lesions per protocol	58.0% (29/50)	[illegible] (25/46)
97.5% Bayesian Credible Interval	0.422 – 1.00	0.422 – 1.00

Modified Effectiveness

Reason for Failure	Treated Population N=50	Non-paroxysmal Subset N=46
Rhythm	11	10
AAD	6	5
Cardioversion	4	4
No AF/AFL/AT, off AADs, Not cardioverted	33 (66.0%)	31 (67.4%)
Lesion set deviation	8	8
No AF/AFL/AT, off AADs, Not cardioverted, Correct lesions	25 (50.0%)	23 (50.0%)

Additional Data Sources

- ABLATE AF
- RESTORE
- Baylor / Plano
- Washington University

Additional Data Sources

	Primary Safety	Primary Effectiveness
ABLATE-AF	0.0% (0/14)	81.8% (9/11)
RESTORE	10.3% (4/39)	66.7% (20/30)
Baylor / Plano	25.0% (2/8)	0.0% (0/2)
Washington University	14.3% (8/56)	74.4% (35/47)
"TOTAL"	11.9% (14/117)	71.1% (64/90)
ABLATE	9.1% (5/55)	74.0% (34/50)

Conclusions

- ABLATE was conducted according to the 2006 protocol
  - Enrolled 55 subjects with “permanent” AF
    - 4 Paroxysmal
    - 22 Persistent
    - 29 Long-standing persistent
- Met its safety and effectiveness endpoints
  - Albeit by a small margin

Conclusions

- Matching the trial population to the intended target patient group, by removing 4 paroxysmal subjects, reduced the subject pool
  - In retrospect, enrollment would have continued

Conclusions

- With the non-paroxysmal subset, ABLATE now fails its endpoints
  - Originally by a minimal margin
  - With additional considerations, the margin increases significantly

Conclusions

- Additional provided data are generally consistent with ABLATE

FDA Presentations

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  Conclusions

Post-Approval Study (PAS) Considerations

Dale R. Tavris, MD, MPH
Division of Epidemiology
Office of Surveillance and Biometrics

Reminder

- The discussion of a PAS prior to FDA determination of device approvability should not be interpreted to mean FDA is suggesting that the device is safe and effective.
- The plan to conduct a PAS does not decrease the threshold of evidence required by FDA for device approval.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness and an appropriate risk/benefit balance.

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

- Gather postmarket information
  - » Long-term performance including effects of re-treatments & device changes
  - » Real-world device performance (patients and clinicians)
  - » Effectiveness of training programs
  - » Sub-group performance
  - » Outcomes of concern (safety and effectiveness)
- 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

Important Postmarket Issues

- Long-term (3 years) performance of the device
  - Effectiveness declined from 74% at 6 months to 62.5% at 12 + months.
- Device performance in a representative population of providers and patients
  - Providers in the premarket study may be more skilled in the use of the device than a more representative sample of providers

Proposed PAS: General Design and Endpoints

- Prospective multi-site observational study
- Eligibility criteria
  - Persistent or long-standing persistent AF
  - Scheduled for CABG and/or valve surgery
- 3-year follow-up
- Primary endpoints
  - Freedom from AF at 36 months
  - Serious ablation procedure- or device-related adverse event
- Secondary endpoints

Proposed Postapproval Study: Hypotheses

- **Effectiveness hypothesis:**

  3-year freedom from AF is greater than 47.8%
  - 57.8% freedom from AF at 20 months in ABLATE trial
  - Margin of 10%

- **Safety hypothesis:**

  Serious ablation procedure- and device-related AE is less than 17.5%
  - 12.5% is rate in the ABLATE trial
  - Margin of 5%

FDA Assessment

- No concerns about general study design, population, or endpoints.
- Effectiveness hypothesis not clinically justified.
  - 3-year success criterion (47.8%),based on premarket data and unexplained subtraction of 10%.
- Safety hypothesis not clinically justified.
  - 17.5% serious procedure- and device-related adverse events based on premarket data, with an unexplained addition of 5%.

Issues for Panel Discussion

- FDA will have questions for the panel this afternoon on important issues regarding the PAS study. Those issues include:
  - The appropriateness of the primary effectiveness success criterion
  - The appropriateness of the primary safety success endpoint and criterion
  - The need for a Clinical Events Committee to adjudicate the device- and procedure-relatedness of adverse events

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Conclusions

- The population studied in ABLATE included a heterogeneous population.
  - The desired indication is based on the persistent and longstanding persistent population in the study.
- The ABLATE study met the pre-specified primary safety and effectiveness endpoints
- No major safety concerns; pacemaker implantation rate may be high
- Approximate 10% drop in effectiveness rate over 2 years
- Device effectiveness is reduced when considering late cardioversion, late AAD washout, current definitions of AF treatment success, and deviations to the lesion set
- Additional data sources are consistent with ABLATE

Thank you.