Medtronic Cardiac Ablation System

FDA Review of P100008

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Office of Device Evaluation

October 27, 2011
FDA Review Team Members

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- Felipe Aguel, PhD
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- Melissa Torres
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**Office of Surveillance and Biometrics**
- Yu Zhao, PhD
- Dale Tavris, MD
FDA Presentations

- Linda Ricci
  Introduction

- Dr. Yu Zhao
  Study Statistical Considerations and Conclusions

- Dr. Jun Dong
  Study Clinical Results and Considerations

- Dr. Dale Tavris
  Post-approval Study Considerations

- Linda Ricci
  Conclusions
Introduction Outline

- Proposed Indications for Use
- Key Regulatory Milestones
- Device Background
- Premarket Study Overview
- Discussion Points
The Medtronic Cardiac Ablation System is indicated for the treatment of symptomatic, drug refractory, persistent atrial fibrillation (AF) or longstanding persistent AF of up to four years in duration.
P100008
Key Regulatory Milestones
TTOP-AF Clinical Study

Feasibility Trial
Non-randomized 20 patient study
- February 2007 – received approval
- May 2007 – first patient enrolled

Pivotal Trial
Randomized, multi-center, unblinded, study
- November 2007 – received approval
- November 2007 – first patient enrolled
After initiation of the pivotal phase of the trial, FDA approved modifications to the TTOP-AF protocol for the following:

- **Inclusion of Interim Analysis**
  - Interim analysis could occur once all acute safety data had been collected for entire cohort and 50% of subjects had 6 month effectiveness data
  - Early stopping rules only included effectiveness goals

- **Modification of definition for “failed cardioversion”**
  - Changed wording from 30 days to 7 days

- Both of these items were approved after more than half of the patients were enrolled
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Device Background
The Medtronic Cardiac Ablation System is comprised of the following primary components:

- The Multi-Array Ablation Catheter (MAAC)
- The Multi-Array Septal Catheter (MASC)
- The Pulmonary Vein Ablation Catheter (PVAC)
- The GENius Multi-Channel RF Generator
Catheters

MAAC

MASC

PVAC
Preclinical Testing

- Extensive preclinical testing was performed:
  - Bench testing
  - Animal testing
  - Biocompatibility
  - Sterilization
  - Software Verification and Validation
  - Electrical Safety/Electromagnetic Compatibility

- All issues have been addressed. FDA has no remaining concerns on the preclinical results.
Primary Endpoints

- **Chronic effectiveness endpoint definition**
  - 90% reduction in clinically significant AF (> 10 minutes) on 48-hour Holter recording.
  - Off all Class I and III AADs at the six month follow-up (AM Arm Only).
  - Acute success of all procedures (AM Arm Only).

- **Acute safety endpoint definition**
  - Rate of 7-day acute serious procedure and/or device-related adverse events (AM Arm Only)

- **Chronic safety endpoint definition**
  - Rate of serious procedure and/or device related adverse events (AM Arm Only)
  - Rate of serious adverse events related to management of atrial fibrillation (MM Arm Only)
Secondary Endpoints

Subjective

No formal hypothesis was generated
P100008
Primary Discussion Points
Primary Discussion Points

- Overall Adverse Event Rate
- Observed Stroke Rate
- Observed PV Stenosis Rate
- Definition of Ablation Success
- Appropriateness of the Indication
- Long-term Ablation Success
- Post-approval Study Considerations
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FDA’s Statistical Review of Medtronic Ablation System

Yu (Audrey) Zhao, Ph.D.
Division of Biostatistics
Office of Surveillance and Biometrics
Center for Devices and Radiological Health
10/27/2011
Outline

- Pivotal Study Design
- Interim Analysis Results
- Analysis Results for All Enrolled Subjects
- Gender Analysis
- Summary
Pivotal Study Design

- Prospective, multi-center, randomized, unmasked, two-arm trial
  - Investigational device arm: Ablation Management
  - Concurrent control arm: Medical Management

- 2:1 Randomization (210 enrolled from 24 sites)
  - Ablation Management: n=138
  - Medical Management: n=72
Pivotal Study Design

- **Primary effectiveness endpoint**
  - Chronic effectiveness: \( H_0 : P_A^{CE} \leq P_M^{CE} \) vs. \( H_a : P_A^{CE} > P_M^{CE} \)

- **Primary safety endpoints:**
  - Acute safety: \( H_0 : P_A^{AS} \geq .16 \) vs. \( H_a : P_A^{AS} < .16 \)
  - Chronic safety: \( H_0 : P_A^{CS} \geq P_M^{CS} + .06 \) vs. \( H_a : P_A^{CS} < P_M^{CS} + .06 \)

- **Study Success Rule:**
  - Need to meet both the chronic effectiveness and the acute safety endpoints
One interim analysis for the chronic effectiveness endpoint when:
- all 210 planned subjects are enrolled; and
- at least 50% enrolled subjects have reached the chronic effectiveness endpoint; and
- 100% enrolled subjects have reached their acute safety endpoint

The O'Brien-Fleming method was used to preserve the overall one-sided Type I error rate 0.025:
- Interim analysis: significance level of 0.0015
- Final analysis: significance level of 0.0245

If the chronic effectiveness endpoint is met at the interim analysis, a PMA using the interim results would be filed.
Pivotal Study Design

- **Primary analysis population:**
  The Intent-to-Treat (ITT) population

- **Primary missing data imputation method:**
  All missing endpoints are imputed as failures
Interim Analysis Results

For the chronic effectiveness endpoint:

- The data cutoff date: July 31, 2009
- Analysis population (ITT): n=136
  - 79 Ablation Management subjects
  - 57 Medical Management subjects

<table>
<thead>
<tr>
<th></th>
<th>Ablation Management (n=79)</th>
<th>Medical Management (n=57)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>44 (56%)</td>
<td>14 (25%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Failure</td>
<td>26 (33%)</td>
<td>32 (56%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>9 (11%)</td>
<td>11 (19%)</td>
<td></td>
</tr>
</tbody>
</table>

- The chronic effectiveness endpoint was met
Interim Analysis Results

For the acute safety endpoint:

- **Analysis population (ITT):**
  138 (100%) Ablation Management subjects

<table>
<thead>
<tr>
<th>Ablation Management n=138</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of subjects having one or more acute serious adverse events related to the device or procedure (SADEs) (Failures)</td>
</tr>
<tr>
<td>Missing</td>
</tr>
<tr>
<td>95% Exact Binomial CI</td>
</tr>
<tr>
<td>P-value</td>
</tr>
</tbody>
</table>

- The acute safety endpoint was not met against PG of 16%
Interim Analysis Results

For the chronic safety endpoint:

- Analysis population (ITT): n=136
  - 79 Ablation Management subjects
  - 57 Medical Management subjects

- Only reported descriptively since the primary acute safety endpoint was not met at the interim analysis

<table>
<thead>
<tr>
<th></th>
<th>Ablation Management</th>
<th>Medical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=79</td>
<td>n=57</td>
</tr>
<tr>
<td>Failure</td>
<td>5 (6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Non-Failure</td>
<td>70 (89%)</td>
<td>47 (82%)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (5%)</td>
<td>9 (16%)</td>
</tr>
</tbody>
</table>
Interim Analysis Results

Summary:

- The chronic effectiveness endpoint was met
- The acute safety endpoint was NOT met
- The overall study success was NOT met at the interim analysis
- The sponsor decided to use the interim analysis to support the PMA application
Analysis Results for All Enrolled Subjects

- By FDA’s request, the analysis results based on all enrolled subjects were submitted to the agency for review.

- The data cutoff date: March 30, 2011

- Analysis population (ITT):
  - 138 Ablation Management subjects
  - 72 Medical Management subjects
## Analysis Results for All Enrolled Subjects

For the chronic effectiveness endpoint:

<table>
<thead>
<tr>
<th></th>
<th>Ablation Management (n=138)</th>
<th>Medical Management (n=72)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
<td>77 (56%)</td>
<td>19 (26%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Failure</td>
<td>44 (32%)</td>
<td>38 (53%)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>17 (12%)</td>
<td>15 (21%)</td>
<td></td>
</tr>
</tbody>
</table>

- The chronic effectiveness endpoint was met
Analysis Results for All Enrolled Subjects

Tipping point analysis for the chronic effectiveness endpoint:
### Analysis Results for All Enrolled Subjects

For the acute safety endpoint:

<table>
<thead>
<tr>
<th>Number of subjects having one or more acute SADEs (Failures)</th>
<th>Ablation Management n=138</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>0</td>
</tr>
<tr>
<td>95% Exact Binomial CI</td>
<td>(7%, 19%)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.14</td>
</tr>
</tbody>
</table>

- The acute safety endpoint was not met against PG of 16%
Analysis Results for All Enrolled Subjects

For the chronic safety endpoint:

- Only reported descriptively since the acute safety endpoint was not met based on all enrolled subjects

<table>
<thead>
<tr>
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<th>Ablation Management</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=138</td>
<td>n=72</td>
</tr>
<tr>
<td>Failure</td>
<td>9 (7%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Non-Failure</td>
<td>123 (89%)</td>
<td>58 (81%)</td>
</tr>
<tr>
<td>Missing</td>
<td>6 (4%)</td>
<td>11 (15%)</td>
</tr>
</tbody>
</table>
Analysis Results for All Enrolled Subjects

Summary:

- The chronic effectiveness endpoint was met
- The acute safety endpoint was **NOT** met
- The overall study success was **NOT** met based on all enrolled subjects
Gender Analysis

- Males accounted for the majority of enrolled subjects

<table>
<thead>
<tr>
<th></th>
<th>Ablation Management n=138</th>
<th>Medical Management n=72</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>115 (83%)</td>
<td>60 (83%)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (17%)</td>
<td>12 (17%)</td>
</tr>
</tbody>
</table>
Gender Analysis

For the chronic effectiveness endpoint:

- Males seemed to perform better under the Ablation Management
- Females seemed to perform similar between two arms
- Test of interaction: $p$-value = 0.07

<table>
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<th>Medical Management</th>
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<tbody>
<tr>
<td></td>
<td>n=138</td>
<td>n=72</td>
</tr>
<tr>
<td>Male</td>
<td>58% (67/115)</td>
<td>23% (14/60)</td>
</tr>
<tr>
<td>Female</td>
<td>43% (10/23)</td>
<td>42% (5/12)</td>
</tr>
</tbody>
</table>
Gender Analysis

For the acute safety endpoint:

<table>
<thead>
<tr>
<th>Acute Safety</th>
<th>Ablation Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male n=115</td>
<td>Female n=23</td>
</tr>
<tr>
<td>Number of subjects having one or more acute SADEs (Failures)</td>
<td>12 (10%)</td>
</tr>
</tbody>
</table>

- Fisher’s exact test to compare males and females: p-value=0.16
- No conclusion about the gender difference can be drawn due to limited number of females enrolled
Summary

- At the interim analysis, the chronic effectiveness endpoint was met but not the acute safety endpoint. Therefore, the pre-specified study success rule was not met.

- Based on all enrolled subjects, the chronic effectiveness endpoint was met but not the acute safety endpoint. Therefore, the pre-specified study success rule was not met.

- Males accounted for the majority of the enrolled subjects.

- For males, Ablation Management seemed to be superior in chronic effectiveness compared to Medical Management.

- For females, there was no evidence showing that Ablation Management was superior in chronic effectiveness compared to Medical Management.
FDA Presentations

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Medtronic Cardiac Ablation System PMA

FDA Clinical Review

Jun Dong, MD PhD
Cardiac Electrophysiology and Monitoring Branch
Division of Cardiovascular Devices
Office of Device Evaluation

October 27, 2011
## Atrial Fibrillation Classification

<table>
<thead>
<tr>
<th>AF Types</th>
<th>2006 ACC/AHA/ESC Guidelines</th>
<th>2007 HRS Expert Consensus Statement</th>
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<tr>
<td>Paroxysmal</td>
<td>self-terminating within 7 days of recognized onset</td>
<td>Recurrent AF (&gt;2 episodes) that terminates spontaneously within 7 days</td>
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<td>Persistent</td>
<td>not self-terminating within 7 days, or is terminated electrically or pharmacologically</td>
<td>AF which is sustained beyond 7 days, or lasting less than 7 days but necessitating cardioversion</td>
</tr>
<tr>
<td>Longstanding Persistent</td>
<td></td>
<td>Continuous AF of greater than one-year duration</td>
</tr>
<tr>
<td>Permanent</td>
<td>AF in which cardioversion has failed or has not been attempted</td>
<td>Patients for whom a decision has been made not to pursue restoration of sinus rhythm by any means</td>
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# Atrial Fibrillation Classification

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<td>Patients where a decision has been made not to pursue restoration of sinus rhythm by any means</td>
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</table>
AF Ablation Strategies

- Pulmonary vein (PV) isolation for paroxysmal AF
- PV isolation plus substrate modification (e.g. CFAE ablation) for persistent and longstanding persistent AF
AF Ablation with Medtronic Cardiac Ablation System

PVAC

PV Isolation

MAAC

+CFAE Ablation

MASC
Pivotal Study Design

- Prospective, multi-center, randomized, unblinded study
- 2:1 Randomization to Ablation Management and Medical Management arms
- Primary effectiveness compared between two arms
- Primary acute safety endpoint compared to a performance goal
Key Inclusion Criteria

- History of symptomatic permanent AF
  - Continuous AF of 1-4 years duration, OR
  - Non self-terminating AF lasting 7 days to 1 year, with at least one failed DC cardioversion
  - AF symptoms: palpitations, fatigue, exertional dyspnea, and exercise intolerance

- Age between 18-70

- Failure of at least one Class I or III AAD
Key Exclusion Criteria

- NYHA Class III or IV
- LVEF < 40%
- LA diameter > 55 mm
- History of stroke or TIA
- Substantial co-morbidity
- Left atrial thrombus
Study Overview

Ablation Management Arm

- Study Eligibility Met
- Randomization (2:1)
- Procedure and Pre-discharge Follow-up
  - 1 Month Follow-up Visit
  - 3 Month Follow-up Visit
  - 6 Month Follow-up Visit
    - Repeat Ablation Procedure
- Medical Management Arm
  - 1 Month Follow-up Visit
  - 3 Month Follow-up Visit
  - 6 Month Follow-up Visit
    - Crossover to Ablation (~4 months from randomization)
Subject Accountability

242 Consented and Assessed for Eligibility

210 Underwent randomization

138 to Ablation Management Arm
- 5 Withdrawn prior to procedure
- 133 Underwent a study procedure
- 1 Withdrawn during procedure
- 7 Withdrawn (3 after repeat ablation)
- 1 Died after repeat ablation
- 48 Underwent repeated ablation

124 Completed 6-month F/U

72 to Medical Management Arm
- 3 Withdrawn w/o receiving medical therapy
- 69 Received medical therapy
- 3 Lost to F/U or withdrawn
- 43 Received crossover ablation
- 12 Underwent repeat ablation

66 Completed 6-month F/U
Baseline Demographics

- Mean Age: 60 years
- Male: 83%
- Mean LA size: 45 mm
- Mean LVEF: 55%
- History of CAD, cardiomyopathy and valvular disease in 19%, 9%, and 7.1%
- Hypertension: 59%
- Diabetes: 14%
- Average CHADS\textsubscript{2} score: 0.8; CHADS\textsubscript{2} score ≥2: 16.7%
AF History

- Diagnosis of persistent/permanent AF: 9.9 +/- 10.4 months
- Persistent AF: 73%; longstanding persistent AF: 27%
- Number of failed Class I or III AADs:
  - 1.4 +/- 0.9 for Ablation Management arm
  - 1.1 +/- 0.5 for Medical Management arm
- Number of prior cardioversions: 2.1 +/- 2.3
Ablation Procedure

- **Required**
  - PV isolation with PVAC
  - LA septum CFAE ablation with MASC
  - CFAE ablation at other LA locations with MAAC
  - DC cardioversion if AF continued after ablations above

- **Optional**
  - SVC ablation using PVAC
  - Other RA ablation including isthmus ablation
Anticoagulation Protocol

- Two peri-procedural anticoagulation strategies*
  - Bridging with intravenous or low molecular weight heparin (LMWH)
  - Continuation of warfarin without bridging
- During the procedure: ACT > 300 seconds
- Oral anticoagulation continued for the whole follow-up period

* Peri-procedural anticoagulation strategy was not a data collection point.
Bridging with IV or LMW Heparin

Warfarin withdrawn 3-5 days before procedure

3-5 days post ablation, LMWH stopped

3-6 hrs after sheath removal, Warfarin restarted

INR

Time

IV or LMW Heparin

IV Heparin

Procedure

IV or LMW Heparin

54
Treatments for Medical Management Arm

- Initiation of new AADs or titration of existing AAD

- DC cardioversions
  - Separated by at least 30 days
  - ECG 30 days after each cardioversion
  - Two failed DC cardioversions constituted an effectiveness failure
## AAD Dose Ranges

<table>
<thead>
<tr>
<th>Medication</th>
<th>Class</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>III</td>
<td>200 mg/day (Increased to 300mg/day for 30 days if 200 mg/day at baseline)</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>III</td>
<td>0.125-0.5 mg BID</td>
</tr>
<tr>
<td>Sotalol</td>
<td>III</td>
<td>120-160 mg BID</td>
</tr>
<tr>
<td>Flecainide</td>
<td>IC</td>
<td>100-150 mg BID</td>
</tr>
<tr>
<td>Propafenone</td>
<td>IC</td>
<td>150-300 mg TID</td>
</tr>
<tr>
<td>Rhythmol Extended Release</td>
<td>IC</td>
<td>225-425 mg BID</td>
</tr>
</tbody>
</table>
Safety Results
Safety Analyses

- Ancillary Analysis
- Protocol Specified Analyses

**Ablation Management**
- Primary Endpoint: PG 16%
- Acute SADE ≤7 days
- Chronic SADE >7 days

**Medical Management**
- Primary Endpoint (not powered)
- Cross-Over Safety SADE

**Safety Analyses**

- Acute SADE ≤7 days
- Chronic SADE >7 days
- Cross-Over Safety SADE
Acute Safety Primary Endpoint

- Definition: Proportion of Ablation Management (AM) subjects with at least one serious procedure and/or device related event (SADE) through 7 days post procedure (acute SADE)

- Included all subjects randomized to the AM arm

- PV stenosis identified on follow-up CT/MRI not considered an acute safety event

- Protocol included a performance goal of 16% (95% UCB) of subjects that could experience an acute SADE
Acute Safety Primary Endpoint

- 21 acute (≤ 7 days) serious adverse device/procedure related events (SADEs) in 17 of 138 AM subjects
- Observed proportion 12.3% with 95% UCB of 19%
- Performance goal was 16.0%
- Acute safety primary endpoint was not met
## Acute Safety Events

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of Patients with Acute SADE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (2.9%)</td>
</tr>
<tr>
<td>Tamponade</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Vascular complications</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
<td>1 (0.7%)**</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>17/138 (12.3%, UCB 19%)</td>
</tr>
</tbody>
</table>

**One subject experienced 2 episodes of pulmonary infiltrates**
# Acute Safety Events + PV Stenosis

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of Patients with Acute SADE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (2.9%)</td>
</tr>
<tr>
<td>PV stenosis/symptomatic PV narrowing</td>
<td>5 (3.6%)</td>
</tr>
<tr>
<td>Tamponade</td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (0.7%)</td>
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<td>Acute respiratory failure</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>3 (2.2%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>22/138 (15.9%, UCB 23.1%)</strong></td>
</tr>
</tbody>
</table>
Chronic Safety Endpoint

Definition

- AM arm: Proportion of subjects with at least one SADE during the 6 month follow-up period (excluding the first 7 days post procedure)

- MM arm: Proportion of subjects with at least one serious adverse event (SAE) related to AAD therapy or AF during 6 months post randomization
<table>
<thead>
<tr>
<th>Description</th>
<th>Number of Patients with Chronic SADE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>PV stenosis (&gt; 70% diameter reduction)</td>
<td>4 (2.9%)</td>
</tr>
<tr>
<td>Symptomatic PV narrowing (50-70% diameter reduction)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Pericarditis/Pleuritis</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Persistent ASD</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>9/138 (6.5%)</strong></td>
</tr>
</tbody>
</table>
### SAEs Related to AF or AAD Therapy in MM Arm (ITT population)

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of Patients with SAE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI bleed secondary to anticoagulation</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Hospitalization for AF with RVR</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3/72 (4.2%)</strong></td>
</tr>
</tbody>
</table>
### All SAEs in MM Arm (as treated population)

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of Patients with SAE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI bleed secondary to anticoagulation</td>
<td>2 (2.9%)</td>
</tr>
<tr>
<td>Hospitalization for AF with RVR</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td>Chest discomfort related to CAD</td>
<td>1 (1.4%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>4*/69 (5.8%)</td>
</tr>
</tbody>
</table>

* One patient experienced two events

No death, stroke, TIA, myocardial infarction, or other thromboembolic events.
### Acute + Chronic SADEs for subjects with at least one study procedure

**(133 AM + 43 Crossovers)**

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of Patients with SADE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (2.8%)</td>
</tr>
<tr>
<td>TIA</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Tamponade</td>
<td>3 (1.7%)</td>
</tr>
<tr>
<td>PV stenosis/symptomatic PV narrowing</td>
<td>7 (4.0%)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>3 (1.7%)</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>3 (1.7%)</td>
</tr>
<tr>
<td>Pericardial effusion</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Vascular complications</td>
<td>5 (2.8%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Pulmonary infiltrates</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Acute respiratory failure</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Persistent ASD</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>4 (2.3%)</td>
</tr>
<tr>
<td>Hyperesthesia in right leg and neuropathy</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38/176 (21.6%, UCB 28.4%)</strong></td>
</tr>
</tbody>
</table>
Peri-Procedural Stroke

- **5 strokes within one month of a procedure, giving a peri-procedural stroke rate of 2.8% (UCB 6.5%)**
  - 4 strokes occurred within 12 hours post procedure
  - One stroke subject was evaluated for visual field defect on day 31 post procedure but symptoms occurred shortly post ablation

- All stroke subjects received LMWH bridging peri-procedurally

- Not surprisingly, INR < 2 in 4 of 5 stroke subjects at the time of stroke

- Complete resolution of neurological deficits occurred in two stroke subjects by the 6 months follow-up visit

- All 5 strokes were adjudicated as SADEs
# Patient Characteristics, Stroke Symptoms and Outcome

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Age/ Gender</th>
<th>CHADS&lt;sub&gt;2&lt;/sub&gt; Score</th>
<th>LA size (cm)</th>
<th>Event Onset</th>
<th>Symptoms/Signs</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>07-315</td>
<td>59/M</td>
<td>1 (HTN)</td>
<td>5.5</td>
<td>&lt; 12 hrs</td>
<td>Dysarthria, right leg weakness, right hand apraxia</td>
<td>Complete recovery by 6 mos</td>
</tr>
<tr>
<td>18-305</td>
<td>56/M</td>
<td>1 (HTN)</td>
<td>5.0</td>
<td>12 hrs post ablation</td>
<td>Diplopia, partial gaze palsy, mild dysarthria</td>
<td>Diplopia unresolved by 6 mos</td>
</tr>
<tr>
<td>28-304</td>
<td>67/M</td>
<td>2 (HTN, DM)</td>
<td>4.9</td>
<td>&lt; 12 hrs</td>
<td>Anomia, visual field deficits, right hemiparesis</td>
<td>Anomia unresolved by 6 mos</td>
</tr>
<tr>
<td>31-305</td>
<td>49/M</td>
<td>1 (HTN)</td>
<td>4.4</td>
<td>12 hrs post ablation</td>
<td>Left arm weakness, loss of fine motor skills, left facial paresis</td>
<td>Complete recovery by 6 mos</td>
</tr>
<tr>
<td>28-305</td>
<td>69/M</td>
<td>3 (DM, HTN, CHF)</td>
<td>4.6</td>
<td>Shortly post ablation</td>
<td>Visual field defect</td>
<td>Unchanged at 6 mos</td>
</tr>
<tr>
<td>Subject ID</td>
<td>Age/Gender</td>
<td>CHADS$_2$ Score</td>
<td>LA size (cm)</td>
<td>Event Onset</td>
<td>Symptoms/Signs</td>
<td>Outcome</td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>------------------</td>
<td>-------------</td>
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<td>Shortly post ablation</td>
<td>Visual field defect</td>
<td>Unchanged at 6 mos</td>
</tr>
</tbody>
</table>
Stroke subject 28-305

- 69-year-old male with CAD, DM, HTN and CHF
- Uneventful repeat procedure on 3/6/2009
- On therapeutic anticoagulation post procedure
- Sinus rhythm at 1-month visit (3/23/2009)
- Ophthalmology evaluation on 4/6/2009
  - Complaint: seeing images in right eye periphery that occurred shortly post ablation
  - Exam: right eye temporal visual field defect of 20%
- Ophthalmology evaluation on 5/15/2009
  - Complaint: fixed temporal peripheral vision difficulty in right eye
  - Exam: > 50% inferotemporal visual field defect
  - Impression: occipital stroke
- MRI on 6/8/2009 (3 months post ablation): chronic left occipital infarct

- Diagnosed as peri-procedural embolic stroke by an independent neurologist after reviewing source documents and MR images
- CEC/DSMB re-adjudicated it as device/procedure related stroke
Incidence of Stroke Between the Two Study Arms

- Ablation Management arm: 6/138 (4.3%)
  - 5 peri-procedural strokes, all device/procedure related by CEC/DSMB
  - One stroke 40 days post ablation, not related to device/procedure, but subtherapeutic anticoagulation.

- Medical Management arm: 0%
  - No stroke
  - 2 TIAs within 7 days post crossover ablation
<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Pts with nonPAF (n)</th>
<th>Pts with Stroke (n)</th>
<th>Overall stroke rate</th>
<th>95% UCB</th>
<th>nonPAF pts with stroke (n)</th>
<th>Stroke rate in nonPAF Pts</th>
<th>95% UCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTOP-AF</td>
<td></td>
<td>176</td>
<td>176</td>
<td>5</td>
<td>2.8%</td>
<td>6.5%</td>
<td>5</td>
<td>2.8%</td>
<td>6.5%</td>
</tr>
<tr>
<td>Spragg</td>
<td>2008</td>
<td>517</td>
<td>240</td>
<td>7</td>
<td>1.4%</td>
<td>2.8%</td>
<td>4</td>
<td>1.7%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Patel</td>
<td>2010</td>
<td>3060</td>
<td>1209</td>
<td>25</td>
<td>0.8%</td>
<td>1.2%</td>
<td>22*</td>
<td>1.8%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Oral</td>
<td>2006</td>
<td>755</td>
<td>265</td>
<td>7**</td>
<td>0.9%</td>
<td>1.9%</td>
<td>1</td>
<td>0.4%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Bertaglia</td>
<td>2007</td>
<td>1011</td>
<td>404</td>
<td>4</td>
<td>0.4%</td>
<td>1.0%</td>
<td>0</td>
<td>0</td>
<td>0.7%</td>
</tr>
<tr>
<td>Tilz</td>
<td>2010</td>
<td>205</td>
<td>205</td>
<td>2</td>
<td>1%</td>
<td>3.5%</td>
<td>2</td>
<td>1%</td>
<td>3.5%</td>
</tr>
<tr>
<td>Oral</td>
<td>2007</td>
<td>100</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>3%</td>
<td>0</td>
<td>0</td>
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</tr>
</tbody>
</table>

*Might have included one TIA.*  **Might have included three TIAs.
## Peri-procedural Stroke

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<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Pts with nonPAF (n)</th>
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<td></td>
</tr>
</tbody>
</table>

*Might have included one TIA.* *Might have included three TIAs.*
Peri-procedural stroke and anti-coagulation strategy

Warfarin withdrawn 3-5 days before procedure

INR

IV or LMW Heparin

Warfarin withdrawn 3-5 days before procedure

IV Heparin

Procedure

IV or LMW Heparin

3-6 hrs after sheath removal, Warfarin restarted

3-5 days post ablation, LMWH stopped
## Peri-procedural stroke and anti-coagulation strategy

<table>
<thead>
<tr>
<th>Authors</th>
<th>Anti-coagulation strategy</th>
<th>Pts (n)</th>
<th>Pts with Stroke (n)</th>
<th>Overall stroke rate</th>
<th>95% UCB</th>
<th>nonPAF pts with stroke (n)</th>
<th>Stroke rate in nonPAF Pts</th>
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</tr>
</thead>
<tbody>
<tr>
<td>TTOP-AF</td>
<td>Bridging or on warfarin</td>
<td>176</td>
<td>5</td>
<td>2.8%</td>
<td>6.5%</td>
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<td>3%</td>
<td>0</td>
<td>0</td>
<td>3%</td>
</tr>
</tbody>
</table>

*Might have included one TIA.**Might have included three TIAs
Asymptomatic Cerebral Embolism

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Medtronic Cardiac Ablation System (subject of this PMA)</th>
<th>Irrigated RF</th>
<th>Cryoballoon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Siklody</td>
<td>2011</td>
<td>9/24 (37.5%)</td>
<td>2/27 (7.4%)</td>
<td>1/23 (4.3%)</td>
</tr>
<tr>
<td>Gaita</td>
<td>2011</td>
<td>14/36 (38.9%)</td>
<td>3/36 (8.3%)</td>
<td>2/36 (5.6%)</td>
</tr>
<tr>
<td>Deneke</td>
<td>2011</td>
<td>30/72 (41.7%)</td>
<td>3/14 (21.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Siklody C et al.. J Am Coll Cardiol 2011.
Deneke T et al. Heart Rhythm 2011
Peri-Procedure Stroke Summary

- Observed rate: 2.8%, UCB 6.5%.
- No strokes observed in control group
- Observed rate higher than literature reports
- High stroke rate cannot be definitively attributed to anti-coagulation strategy
- External reports indicate a high incidence of asymptomatic cerebral embolism associated with the subject device
Discussion Item: Peri-Procedure Stroke

- FDA will request panel input on the significance of the high peri-procedural stroke rate observed in this trial.

- FDA will request panel input on the emphasis that should be given to external findings of asymptomatic cerebral embolism for assessing the approvability of this application.
PV Stenosis

- PV stenosis: > 70% reduction in the diameter of the PV from baseline
- PV narrowing: 50 – 70% reduction in the diameter of PV from baseline
### PV Stenosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Subjects who underwent at least one study procedure (n = 176)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV Stenosis</td>
<td>6 (3.4%)</td>
</tr>
<tr>
<td>PV Narrowing</td>
<td>12 (6.8%)</td>
</tr>
<tr>
<td>Symptomatic PV stenosis</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Symptomatic PV narrowing</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>PV stenosis/Symptomatic PV narrowing</td>
<td>7 (4%, UCB 8%)</td>
</tr>
</tbody>
</table>
## PV Stenosis: Comparison to STOP-AF Trial

<table>
<thead>
<tr>
<th>Patients with PV stenosis (&gt; 75% reduction from baseline cross-sectional area)</th>
<th>TTOP-AF Trial (n = 176)</th>
<th>STOP-AF Trial* (n = 228)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 (7.4%)</td>
<td>7 (3.1%)</td>
<td></td>
</tr>
</tbody>
</table>

*Arctic Front Cryoballoon Catheter Instruction for Use*
# PV Stenosis in Literature

<table>
<thead>
<tr>
<th></th>
<th>TTOP-AF Trial (n = 176)</th>
<th>Meta-Analysis* (n = 5831)</th>
<th>ThermoCool AF Trial** (n = 103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with PV stenosis (&gt; 70% diameter reduction)</td>
<td>6 (3.4%)</td>
<td>91 (1.6%)</td>
<td>0</td>
</tr>
</tbody>
</table>


**Wilber et al. JAMA. 2010.
Discussion Item: PV Stenosis

- FDA is concerned about the high PV stenosis event rate (4%, UCB 8%) observed in this trial.

- FDA will request panel input on the significance of the PV stenosis event rate observed in this trial.
Effectiveness Results
## Effectiveness Analyses

<table>
<thead>
<tr>
<th>Ablation Management</th>
<th>Medical Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>90% ↓ AF @ 6 Months</td>
<td>90% ↓ AF @ 6 Months</td>
</tr>
<tr>
<td>HRS AF-Free @ 6 Months</td>
<td>HRS AF-Free @ 6 Months</td>
</tr>
<tr>
<td>90% ↓ AF @ 12 Months</td>
<td>90% ↓ AF @ 12 Months</td>
</tr>
</tbody>
</table>

**Primary Endpoint**

- 90% ↓ AF @ 6 Months
- HRS AF-Free @ 6 Months
- 90% ↓ AF @ 12 Months
- HRS AF-Free @ 12 Months
### Acute Effectiveness Endpoint

<table>
<thead>
<tr>
<th>Acute Effectiveness Success Criteria</th>
<th>Ablation Management (n = 138)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study catheters used to achieve acute success</td>
<td>129</td>
</tr>
<tr>
<td>Isolation of all accessible PVs</td>
<td>129</td>
</tr>
<tr>
<td>≥ 50% reduction of CFAEs amplitude</td>
<td>131</td>
</tr>
<tr>
<td>SR at completion of procedure</td>
<td>128</td>
</tr>
<tr>
<td><strong>Acute effectiveness</strong></td>
<td><strong>128 (92.8%)</strong></td>
</tr>
</tbody>
</table>
Primary Effectiveness Endpoint

- Chronic effectiveness definition
  - 90% reduction in clinically significant AF (> 10 minutes) on 6-month Holter recording
  - Off all Class I and III AADs at the six month follow-up (Ablation Management arm only)
    - Amiodarone: discontinued 28 days prior to Holter recording
    - Other AADs: discontinued 5 days prior to Holter recording
  - Acute success of all procedures (ablation arm only)
### 6 Months Chronic Effectiveness Results

<table>
<thead>
<tr>
<th>Subjects meeting all success criteria</th>
<th>Ablation Management Arm (n = 138)</th>
<th>Medical Management Arm (n = 72)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>77 (55.8%)</td>
<td>19 (26.4%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

The primary effectiveness endpoint was met.
6 months Chronic Effectiveness
Stratified by AF Type

<table>
<thead>
<tr>
<th></th>
<th>Ablation Management Arm (n = 138)</th>
<th>Medical Management Arm (n = 72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent AF (n = 97)</td>
<td>53 (54.6%)</td>
<td>16 (28.1%)</td>
</tr>
<tr>
<td>Longstanding persistent AF (n = 41)</td>
<td>24 (58.5%)</td>
<td>Longstanding persistent AF (n = 15)</td>
</tr>
</tbody>
</table>

- The trial was not powered to examine the treatment effect across AF populations
- FDA will ask the panel to comment on whether the study results demonstrated a treatment effect for both the persistent AF population and the longstanding persistent AF population
Ablation Success per HRS Expert Consensus Statement Definition

- Ablation success: Freedom from AF/AFL/AT of ≥ 30 seconds in the absence of Class I and III AAD therapy following a 3 month blanking period

- Failure if any of the followings applies:
  - ECG documented AF/AFL/AT recurrences following 3 month post ablation;
  - DC cardioversion or ablation for AF/AFL/AT following 3 month post ablation;
  - ≥ 30 seconds of continuous AF/AFL/AT on 6-month Holter;
  - On Class I or III AAD following 3 month post ablation
Chronic Effectiveness as Analyzed by HRS Expert Consensus Statement Definition

Ablation Management
n = 138

77 (55.8%)
Chronic successes by protocol definition

66 (47.8%)
No AF/AFL ≥ 30 s on 6-month Holter
No AF/AFL/AT, no CV/ablation after 3 mos

51 (37%)
No AF/AFL ≥ 30 s on 6-month Holter
No AF/AFL/AT, no CV/ablation after 3 mos
off Class I and III AAD after 3 mos

chronic success per HRS definition
Chronic Effectiveness for Medical Management Arm Using 30 Seconds Criterion

Medical Management  
n = 72

19 (26.4%)  
Chronic successes by protocol definition:  
≥ 90% AF burden reduction on 6-month Holter

19 (26.4%)  
No AF/AFL ≥ 30 s on 6-month Holter
Discussion Item: Chronic Success

- The prespecified primary effectiveness endpoint was achieved in 55.8% of Ablation Management subjects.

- Chronic success rate for the Ablation Management arm drops to 37% when retrospectively applying success definition by the HRS Consensus Statement.

- FDA will ask the panel to comment on the chronic success rates observed in the trial using the definition of ablation success from both the approved clinical study protocol and the 2007 HRS Consensus Statement.
At FDA’s request, the sponsor made an effort to obtain 12 month follow-up data from as many study subjects as possible.

12-month follow-up visit with Holter recordings was completed from 106 subjects, accounting for about half of all randomized subjects.
## Change in AF Burden Reduction at 12 Months

<table>
<thead>
<tr>
<th>Subjects with ≥ 90% AF burden reduction on 6-month Holter post ablation</th>
<th>Ablation Management (n = 48)</th>
<th>Crossovers (n = 14)</th>
<th>Total (n = 62)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with ≥ 90% AF burden reduction on 12-month Holter post ablation</td>
<td>41 (85.4%)</td>
<td>12 (85.7%)</td>
<td>53 (85.5%)</td>
</tr>
</tbody>
</table>
Discussion Item: 12 Month Success

- Given the limitations of the long term effectiveness data, FDA requests panel input on the emphasis that should be given to the incomplete 12-month data
Summary

- The primary effectiveness endpoint was met, but the primary safety endpoint was not met

- FDA is particularly concerned about the high incidence of peri-procedural stroke observed in the trial (2.8% with UCB of 6.5%)

- FDA is concerned about the high rate of PV stenosis events (4% with UCB of 8%)

- FDA is also concerned about the high overall procedure/device related serious adverse event rate of 21.6% observed in the trial
Summary (Cont.)

- 6 months chronic success rate decreases from 55.8% to 37% when the HRS Expert Consensus Statement definition of ablation success is applied retrospectively.

- Analysis of available 12 month effectiveness data suggests a reduction in chronic success after 6 months post ablation.
FDA Presentations

- Linda Ricci
  Introduction

- Dr. Yu Zhao
  Study Statistical Considerations and Conclusions

- Dr. Jun Dong
  Study Clinical Results and Considerations

- Dr. Dale Tavris
  Post-approval Study Considerations

- Linda Ricci
  Conclusions
Post-Approval Study (PAS) Considerations

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

October 27, 2011
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.
Post-Approval Study Components

- Fundamental study question or hypothesis
- Well specified study population and study design
- Safety endpoints and methods of assessment
- Acute and chronic effectiveness endpoints and methods of assessment
- Duration of follow-up
Important Postmarket Issues

- Long-term performance of the device
  - Chronic effectiveness in the premarket study was assessed only at 6-months
  - Little knowledge of effectiveness beyond that
- 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
Sponsor’s Proposed Post-Approval Study (PAS): Design and Primary Endpoint

- Prospective multi-site observational study
- Eligibility criteria
  - Symptomatic permanent or long-standing persistent AF
  - Intolerance to or failure of AADs
  - 18 -70 years of age
- 3-year follow-up
- Primary endpoints
  - Chronic treatment success at 3 years
  - Serious procedure- or device-related adverse events at one year
Sponsor’s Proposed PAS: Secondary Endpoints

- Major atrial fibrillation events (MAFE)
  - Evaluated at 1, 2, and 3
  - Defined as a non-procedure- or device-related event, including:
    - Cardiovascular death
    - Myocardial infarction
    - All strokes
    - Hospitalization for:
      - AF recurrence or ablation
      - Atrial flutter ablation (excluding Type I)
      - Systemic embolization
      - Congestive heart failure
      - Hemorrhagic event
      - Anti-arrhythmic drug initiation, adjustment or complication
Sponsor’s Proposed PAS: Hypotheses

- **Effectiveness hypothesis:**
  3-year treatment success > 20%
  - Cited studies showing approximately 30% success at 20-40 months
  - Cite recurrence rate of 7-9% per year
  - 10% margin

- **Safety hypothesis:**
  Serious procedure- and device-related AE < 19% at 1-year
  - Based on 12.3% rate in premarket study
  - Increase in duration of AE reporting
  - PV stenosis rate of 3.9% at 6 months
  - Margin of 3.1%
FDA Assessment of Sponsor’s Proposed PAS

- **Effectiveness hypothesis:**
  - It is unclear whether the proposed effectiveness success criteria represent clinically acceptable device performance
  - Not clear if treatment success definition is in line with current best practices

- **Safety hypothesis**
  - It is unclear whether the proposed safety success criteria represent clinically acceptable device performance

- Questions for panel this afternoon will address these issues
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Conclusions

- The acute safety endpoint was not met
  - Overall Adverse Event Rate
  - Observed Stroke Rate
  - Observed PV Stenosis Rate
- The chronic effectiveness endpoint was met
  - Definition of ablation success
- Appropriateness of the indication
- Long-term outcomes
- Risk/Benefit Profile
Thank you