

Presentation to FDA Circulatory Systems Advisory Panel September 20, 2007

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Disclosures

- **Consultant** to **Biosense Webster**, who paid travel costs to this meeting
- **Consultant** to additional **drug** (Astellas Pharma US, sanofi-aventis U.S., Solvay Pharmaceuticals) and **device** (Biotronik, CryoCor, St. Jude Medical) companies with products used to treat arrhythmias
- **Speakers Bureau** for **Reliant Pharmaceuticals**
- **Research Contract** with **Boehringer-Ingelheim Pharmaceuticals**

NaviStar® ThermoCool® Catheter for the Radiofrequency Ablation of Paroxysmal AF

- Presenting on Biosense Webster's experiences as sponsor of this IDE trial
- Chair of Data Safety/Adverse Events Committee for THERMOCOOL® catheter IDE Studies
- Previously chaired similar committees for previous Biosense Webster studies
 - THERMOCOOL® Atrial Flutter and Ventricular Tachycardia IDE studies for BW
 - Both indications now approved. THERMOCOOL® catheter widely used for right- and left-sided procedures worldwide



Biosense Webster's Commitment to AF IDE

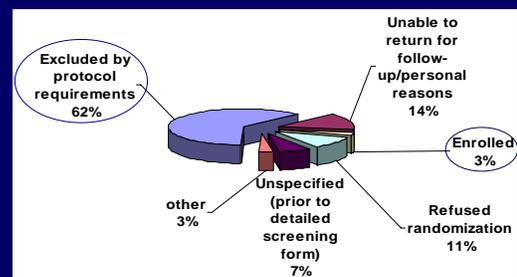
- The Company recognizes the potential benefit to public health and to practitioners of on-label procedures, with attendant arrhythmia-specific instructions for use.
- The Company also recognizes the importance and value of a rigorous, critical examination of both efficacy and safety of the product by the FDA
- Currently enrolling patients in a 3rd IDE ablation trial using the NAVI STAR® THERMOCOOL® Diagnostic/Ablation Deflectable Tip Catheter
 - this time, seeking to demonstrate its efficacy and safety in the **treatment of paroxysmal AF**
 - but **encountering major challenges not seen previously** in the AFL and VT ablation studies

ThermoCool® AF IDE Study Design

- RF ablation using the THERMOCOOL® ablation catheter randomized against AAD therapy, all in accordance with current FDA guidance
- Inclusion/exclusion criteria specify minimum number and frequency of pre-enrollment AF episodes, need for previous AAD usage except no amiodarone in past 6 months
- Ablation arm treatment approach and procedural endpoint specified in the protocol
- Study designs, based on current FDA guidance, directly cause the majority of screening "failures," thereby prolonging trials – some of this is inevitable, but some seem reasonable to modify

Patient Screening Results

It has taken 3 plus years of intensive effort to approach the required number of study patients



Slide 3

ALW3 indicate other disclosures?

Albert Waldo, 9/13/2007

aw2 ? what about DSMB?events committee?

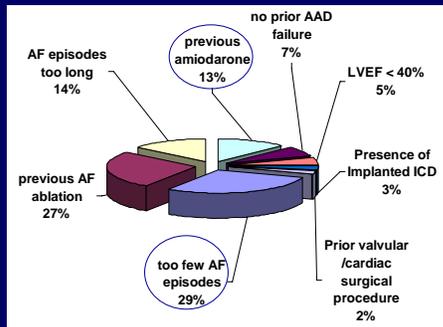
awaldox1, 9/17/2007

Slide 6

aw3 need to fix the "n" in refused randomization

awaldox1, 9/17/2007

Reasons for Protocol Exclusion



ALW21

Additional Trial Difficulties

- The ACC/AHA/ESC 2006 AF treatment guidelines elevated ablation of AF to a secondary treatment option
- The mechanism(s) of AF is (are) incompletely understood, such that an exquisite ablation target(s), well known for AVRT, AVNRT, and AFL, is (are) not identified for AF
- Ablation techniques have continued to evolve, so that over the course of a clinical trial, we should anticipate that further evolution will continue

BW7

Recruitment Outreach

- **Patient Directed:** IRB-approved direct-to-patient initiatives:
 - newspaper ads
 - Internet ads
 - opt-in email networks
 - clinical trial websites, etc.
- **Physician Directed:** Thousands of cardiologists, other physicians contacted:
 - Letters from study's Principal Investigator
 - Opt-in email networks
 - ACC booth
- **Results:**
 - Spent >\$500,000
 - Screened 100's of resulting referrals
 - Enrolled 3 additional subjects

ALW22

Recommendations

- **Perfect is the enemy of good.**
- Greater flexibility needed in AF IDE study designs
- Inclusion/exclusion criteria – permit companies to tailor them to reflect better the current AF ablation patient populations
- Recognize that catheters are tools; don't use registration studies to try to answer questions comparing ablation lesion patterns, etc.

Suggestions for Trial Design Modification

- Since the techniques of ablation continue to evolve and are very likely to continue to evolve, consider allowing the investigator to use a "whatever works" approach, the endpoint being apparent effective treatment of AF
- Since FDA guidance permits use of a previously ineffective antiarrhythmic agent, consider modifying current restrictions on use of amiodarone
- Other alternatives to consider:
 - use decreased burden of AF post ablation as an acceptable endpoint
 - use patient as own control after obtaining appropriate baseline data
 - use more liberal ways for patients to qualify with enough AF episodes per unit time

Slide 8

ALW21 DELETE "BURDENS"
Albert Waldo, 9/17/2007

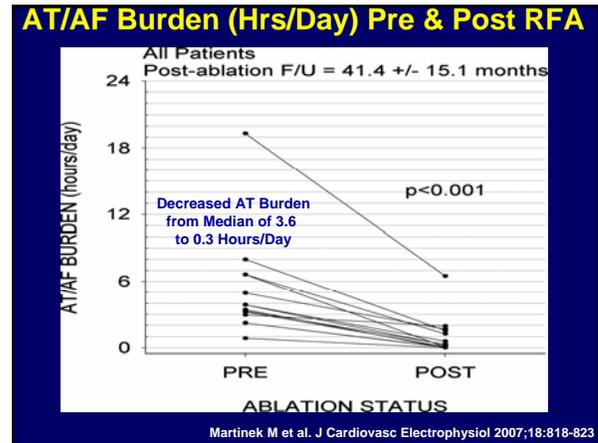
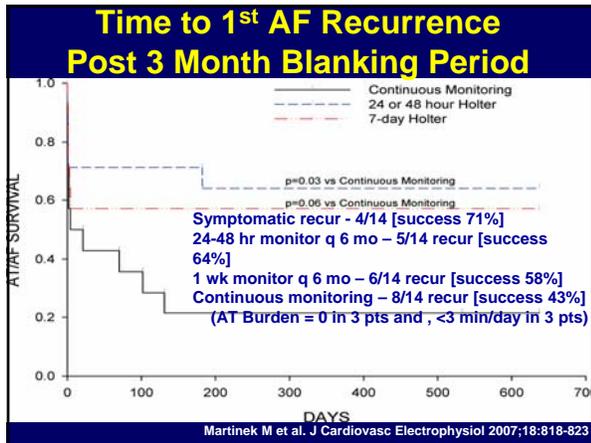
Slide 9

aw7 ?use - only because too many slides
awaldox1, 9/17/2007

Slide 10

aw6 still needs some work - the concepts are important
awaldox1, 9/17/2007

ALW22 DELETE PREVIOUS EXPERIENCE
Albert Waldo, 9/17/2007



- ### Recommendations, cont.
- Be sensitive to the efforts of sponsors who have persevered against the enormous obstacles of the current study designs
 - First-to-market approvals should not be used to raise or lower the threshold for approval
 - Nonetheless, recognition of alternative types of valid scientific evidence of safety & effectiveness is warranted
 - All trial designs have strengths and weaknesses. “One-size-fits-all” should apply no more to study design than to the care of our patients.

- ### Currently Inherent Trial Difficulties
- The ACC/AHA/ESC 2006 AF treatment guidelines elevated ablation of AF to a secondary treatment option, but the mechanism(s) of AF is (are) incompletely understood, such that an exquisite ablation target(s), well known for AVRT, AVNRT, and AFL, is (are) not identified for AF
 - Ablation techniques have continued to evolve, so that over the course of a clinical trial, we should anticipate that further evolution will continue
 - Amiodarone is the most commonly used antiarrhythmic agent in the Western world
 - The crafting of inclusion/exclusion criteria
 - Perfect is the enemy of good

Slide 16

ALW21 DELETE "BURDENS"
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