P030031/S11 Panel-Track Supplement to add "Treatment of Atrial Fibrillation" indication to Biosense Webster ThermoCool Catheters.

1) Design – patient selection

   For inclusion in the study, patients need to have demonstrated three episodes of AF within the 6 months prior to enrollment. Only one of these episodes needed to be documented with electrocardiographic evidence prior to enrollment. Literature reports provide evidence that symptoms often do not correlate well with actual AF occurrence in this patient population.

   Please discuss whether the population studied is representative of patients with recurrent symptomatic paroxysmal AF.

2) Design – Comparison to Standard of Care and Generalizability of Results

   Therapy in the medical control arm was limited to drugs approved for treating AF. Per FDA recommendations, the list did not include amiodarone, a drug that is commonly used off-label in the treatment of AF.

   Please discuss the impact of exclusion of amiodarone from this trial. How does this affect the generalizability of the control arm to medical practice in the United States?

3) Poolability of US and OUS Sites

   Outside of the United States (OUS) sites enrolled 60% of all patients in the study. OUS sites generally performed better than US sites as evidenced by the chronic effectiveness result reported at the highest enrolling site. At this site, none of the 31 ThermoCool subjects failed during the nine month period, whereas the chronic success rate for ThermoCool subjects in the remaining sites combined was 47%. The respective control group success rates were 11% and 18%, for the highest enrolling site and remaining sites. In addition, there were some differences noted in patient treatment between the OUS and US subjects (refer to pgs. 25-27 of the FDA Executive Summary). However, the posterior probability that the ThermoCool ablation group is superior to the AAD group was 0.997 for the remaining sites alone.

   Please discuss the impact of these differences between OUS and US sites on generalizability of reported results to a solely US population.

4) Safety

   The seven-day Primary Adverse Event rate in the pivotal study was 10.8% with a 95% upper confidence bound of 16.1%. The adverse events included in the primary AE analysis are the following:

Description	**Number of Subjects with Primary AEs (%)**
Total Serious Primary AEs	**15 (10.8%, 95% UCB 16.1%)**
Hospitalization (initial and prolonged)	7 (5.0 %)
Vascular Access Complication	5 (3.6 %)

Pulmonary Edema	1 (0.7 %)
Pericarditis	1 (0.7 %)
Pericardial Effusion	1 (0.7 %)

In this study, no deaths, strokes, atrio-esophageal fistulae, myocardial infarctions, or thromboemboli occurred within 7 days of the ablation procedure. These SAEs have been reported in the literature for AF ablation procedures.

The pre-specified target upper confidence bound was 16.0%.

Please discuss whether the safety results demonstrate that there is a reasonable assurance that the device is safe for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

5) Effectiveness Results - General

The results of the study demonstrate freedom from symptomatic AF in the 9-month evaluation period in 53 out of 103 patients enrolled in the ablation arm (not including 14 censored patients who had not yet completed their nine-month follow-up) compared with 9 out of 56 patients in the medical control arm.

Enrollment Status for Each of the Enrolled Subjects (June 2008 dataset, n = 159)

Group	Success	Censored	Fail	N
ThermoCool	53	14	36	103
Control (AAD)	9	0	47	56

Using available data only, the posterior probability of increased effectiveness (i.e., superiority) of ablation over control for freedom from symptomatic AF at 9 months was greater than 0.999 This was in excess of the pre-specified criterion of 0.98. In addition, the predictive probability of concluding superiority of ablation over control had the full 230 subjects been enrolled and have outcomes is greater than 0.999.

Please discuss whether the chronic effectiveness results demonstrate that there is a reasonable assurance that the device is effective for the chronic treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

6) Device Labeling

One aspect of the premarket evaluation of a new product is the review of its labeling. The labeling must indicate which patients are appropriate for treatment, identify the products potential adverse events, and explain how the product should be used to maximize benefits and minimize adverse effects.

A,Please comment on whether the Indications section identifies the appropriate patient population for treatment with the device.

B. Heart failure and AF often occur together in patients. The premarket study specifically excluded patients with LVEF < 40% and NYHA class III/IV heart failure.

Please comment on whether the labeling should include a warning that the safety and effectiveness has not been demonstrated in this group.

C. The CARTO EP Navigation System was required as part of the investigational procedure to map the anatomical location of the pulmonary vein and the RF lesions. The PMA requests approval for several catheters that do not include a location sensor capable of generating electroanatomic maps with the CARTO EP Navigation System.

Please comment on whether the data collected in the IDE study can be generalized to devices that are not capable of generating electroanatomic maps. If not, please discuss whether the referenced scientific articles provide sufficient information to warrant approval of the requested change in Indications for Use for the non-CARTO equipped catheters

D. The study protocol allowed enrollment of patients that had failed a class II/IV AAD (rate-control therapy) in addition to patients who had failed a class I/III AAD (membrane active drugs). Of the enrolled patients, 16% (26/167) failed only rate-control therapy.

Please discuss whether the trial provides sufficient experience in a population that has failed only rate-control therapy such that the indication statement should include patients that have failed only rate-control medical therapy.

E. Please discuss any additional recommendations you have regarding the device labeling.

7) Post-Approval Study

The premarket data has provided evidence regarding the acute and mid-term safety and effectiveness of this device. Furthermore, one site included prophylactic application of a right atrial lesion, and that site had higher mid-term effectiveness results compared with the remaining sites.

Please discuss whether a post-approval study should be performed to address any issues that are unresolved but not essential to the approval of the device. Please comment on the major components of such a study including suggested hypotheses, study endpoints and study duration.