

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

1) 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’s recommendation, the list did not include amiodarone, which is commonly used off-label to treat AF.

Please discuss the impact of excluding amiodarone as a treatment option in the medical control arm. How does this affect the generalizability of the control arm to medical practice in the United States?

2) 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 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 differences between OUS and US sites on generalizability of reported results to a solely US population.

3) 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 %)

This study reported no occurrences of death, stroke, atrio-esophageal fistula, myocardial infarction, or thromboemboli within 7 days of the ablation procedure. These serious adverse events (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.

4) 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, which exceeded 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 treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation.

5) 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 discuss whether the proposed Indications identify the appropriate patient population for treatment with the device.

B. AF often occurs in patients with heart failure. At the September 2007 advisory committee meeting on the general topic of trial design issues for the study of devices intended to treat

AF, panel recommended that patients with structural heart disease be studied as a separate group. The clinical study specifically excluded patients with advanced heart failure (LVEF < 40% and NYHA class III/IV).

Please comment on whether the labeling should include a warning that the safety and effectiveness has not been demonstrated in patients with heart failure.

C. In the clinical study and protocol, the CARTO EP Navigation System was required to map the anatomical location of the pulmonary vein and the RF lesions. The PMA application 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 clinical 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 sensor equipped catheters.

D. The study protocol allowed enrollment of patients who failed a class II/IV anti-arrhythmic drug (AAD) (rate-control therapy) in addition to patients who 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.

6) Post-Approval Study

The premarket clinical data has provided evidence regarding the safety and effectiveness of this device in the acute phase and up to 12 months post-ablation. The study was performed at recognized centers of excellence. The purpose of ablation therapy is to produce a permanent change to the structure of the heart, generally thought to be a non-regenerative organ. One clinical site performed prophylactic application of a right atrial (cavo-tricuspid isthmus [CTI]) lesion that was not done in the remaining clinical sites, and that site had higher effectiveness results 12 months post-ablation compared with the remaining sites.

A. Please discuss the appropriate trial design for determining the procedural safety profile in a broader patient and provider population. Please comment on what may be an appropriate hypothesis, endpoint, duration of follow-up, and control group.

B. Please discuss the appropriate trial design for evaluating the long-term safety of patients treated with the device. Please comment on what may be an appropriate hypothesis, endpoint, duration of follow-up, and control group.

C. Please discuss the appropriate trial design for evaluating the durability of effectiveness in patients treated with the device. Please comment on what may be an appropriate hypothesis, endpoint, duration of follow-up, and control group.

D. Please discuss the impact of CTI ablation on the premarket effectiveness results and discuss whether this issue should be investigated in a postapproval study. Please comment on whether it is appropriate to randomize patients to prophylactic CTI ablation.