Summary of Safety and Effectiveness Data (SSED)

I. General Information

Device Generic Name:
Irrigated Diagnostic/Ablation Catheter and Accessories

Device Trade Names:
NaviStar ThermoCool Catheter and EZ Steer ThermoCool NAV Catheter

Applicant's Name and Address:
Biosense Webster Inc.
3333 Diamond Canyon Road
Diamond Bar, CA 91765

Date of Panel Recommendation:
November 20, 2008

Pre-market Approval Application (PMA) Number:
P030031 / S011

Date of Notice of Approval to Applicant: February 06, 2009

Expedited: Granted expedited review status on September 17, 2008, because we believe that ablation catheters may provide a novel approach for the treatment of atrial fibrillation, which present a risk of serious morbidity. Because no legally marketed ablation catheter is available for the treatment of atrial fibrillation, FDA has decided to grant expedited review for this application.

Table 1 provides a listing of the device and accessory model numbers:

Table 1: Device and Accessory Model Numbers

Family Name	Mfg. Part Number	Catalog Number	Curve	Temperature Sensor
NaviStar ThermoCool Catheter	D-1208-05	NI75TBH	B	Thermistor 3.5mm
	D-1208-06	NI75TCH	C	Thermistor 3.5mm
	D-1208-07	NI75TDH	D	Thermistor 3.5mm
	D-1208-08	NI75TFH	F	Thermistor 3.5mm
	D-1197-14	NI75TCBH	B	Thermocouple 3.5mm
	D-1197-15	NI75TCCH	C	Thermocouple 3.5mm
	D-1197-16	NI75TCDH	D	Thermocouple 3.5mm
	D-1197-17	NI75TCFH	F	Thermocouple 3.5mm
	D-1197-18	NI75TCJH	J	Thermocouple 3.5mm

Family Name	Mfg. Part Number	Catalog Number	Curve	Temperature Sensor
EZ Steer ThermoCool NAV Catheters	D-1292-01	BN175TCDDH	D-D	Thermocouple 3.5mm
	D-1292-02	BN175TCFFH	F-F	Thermocouple 3.5mm
	D-1292-03	BN175TCJJH	J-J	Thermocouple 3.5mm
	D-1292-04	BN175TCFJH	F-J	Thermocouple 3.5mm
	D-1292-05	BN175TCDFH	D-F	Thermocouple 3.5mm
Stockert 70 RF Generator	S7001			
CoolFlow Pump	M-5491-02			
Cool Flow Pump Irrigation Tubing Set	D-1233-01-S			
CARTO Navigation System CARTO XP Navigation System CARTO 3 Navigation System	CARTO M-4700-01 M-4800-01			
Catheter interface cables	D-1195:	C5-MHNAVMH-S C6-MRMSTKDTC-S		
	D-1170:	C6-MR10MSTK-S C10-MR10MSTK-S		

The original PMA (P030031) was approved on November 5, 2004, and is indicated for the treatment of Type I atrial flutter in patients age 18 or older. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the device.

II. Indications for Use

The Navistar ThermoCool Catheter and EZ Steer ThermoCool NAV Catheter are indicated for catheter-based cardiac electrophysiological mapping (stimulating and recording), and when used with the Stockert 70 generator, for the treatment of

a) Type I atrial flutter in patients age 18 or older.
b) Recurrent drug/device refractory sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction (MI) in adults.
c) Drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three-dimensional electroanatomic mapping systems.

III. Contraindications

The device should not be used:

- if the patient has had a ventriculotomy or atriotomy within the preceding eight weeks because the recent surgery may increase the risk of perforation;
- in patients with prosthetic valves as the catheter may damage the prosthesis;
- in the coronary vasculature due to risk of damage to the coronary arteries;
- in patients with an active systemic infection because this may increase the risk of cardiac infection;

- in the patient with a myxoma or an intracardiac thrombus as the catheter could precipitate an embolus;
- via the transseptal approach in a patient with an interatrial baffle or patch because the opening could persist and produce an iatrogenic atrial shunt;
- via the retrograde trans-aortic approach in patients who have had aortic valve replacement.

IV. Warnings and Precautions

The warnings and precautions can be found in the instructions for use for each of the catheters, the Carto EP Navigation System, Stockert 70 Radiofrequency Generator User Manual and the CoolFlow Pump User Manual.

V. Device Description

With reference to the model numbers indicated in Table 1 for Device and Accessory Model Numbers, the devices that are the subject of this PMA Supplement are the NaviStar ThermoCool Catheter and EZ Steer ThermoCool NAV Catheter.

These devices are used in conjunction with the Stockert 70 RF generator, the CoolFlow Pump and Tubing Set, and catheter interface cables.

A brief device description of each of the catheters subject of this PMA Supplement and the ancillary devices is provided below. For catheter ablation procedures, the device components require the use of the grounding pad (indifferent patch electrode) previously approved for use with the Stockert 70 RF generator under P990071. Consult the instruction manual for the Stockert 70 RF for more information. For cooling, all ThermoCool Catheters are used in conjunction with the CoolFlow Irrigation Pump and Tubing Set.

For additional aid in navigation, the NaviStar ThermoCool Catheter and the EZ Steer ThermoCool NAV Catheter may be used with the following legally marketed devices:

- RefStar reference devices – originally cleared under K954390; and
- Carto EP Navigation System – originally cleared under K954395.

The NaviStar ThermoCool Catheter and the EZ Steer ThermoCool NAV catheter provide location information when used with Carto, Carto XP, and Carto 3 EP Navigation Systems. Compatibility with these systems has been demonstrated via bench testing to confirm that the device is capable of providing accurate location information when used in accordance with the instructions for use.

A. NaviStar ThermoCool Catheter

The NaviStar ThermoCool catheter is a family of steerable, multi-electrode catheters with a deflectable tip. The NaviStar ThermoCool catheter is a luminal, electrophysiology electrode

catheter with a 3.5 mm tip electrode, three ring electrodes, a location sensor, and a temperature sensor (thermocouple or thermistor) incorporated into the deflectable tip. All of the electrodes may be used for recording and stimulation purposes. The tip electrode serves to deliver RF current from the RF generator to the desired ablation site, and incorporates several small holes through which normal saline is passed for irrigation and cooling. A temperature sensor embedded in the tip electrode is used to verify adequate irrigation flow rate. The magnetic location sensor embedded in the tip electrode transmits location information to the Carto XP EP Navigation System.

The tip electrode and ring electrodes are platinum-iridium with 2-5-2 spacing of the ring electrodes. The deflectable tip is extruded from biocompatible polyurethane and is made up of three lumens. One lumen (0.022") contains a coil spring and a puller-wire, the second lumen (0.033") is used for irrigation, and the third lumen (0.036") contains the location sensor and the lead wires.

The catheter body is single lumen high-torque 7.5F shaft extruded from biocompatible PEBAX with a handpiece at the proximal end. A puller wire is anchored in the tip electrode and runs though the catheter shaft to a piston in the handpiece. A saline tube also extends from the tip through the shaft to an irrigation port on the handpiece. The irrigation port terminates in a standard luer fitting to permit the injection of normal saline to irrigate the tip electrode. During ablation, normal heparinized saline is passed through the .027" diameter lumen of the catheter and through the tip electrode, to irrigate and cool the ablation site.

Tip deflection is controlled at the proximal end by a handpiece in which a piston slides; a thumbknob on the piston controls piston travel. When the thumbknob is pushed forward, the tip is deflected (curved). When the thumbknob is pulled back, the tip straightens. The shape of the curve depends on the deflectable tip length (2-3"). Five curve types designated "B", "C", "D", "F" and "J" are available. The "J" curve type is only available with the thermocouple and not with the thermistor temperature sensor. The high torque shaft also allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site.

The usable length of the NaviStar ThermoCool catheter is 115 centimeters and is provided sterile and for single patient use only. The NaviStar ThermoCool catheter interfaces with standard recording equipment and the Stockert 70 RF Generator via accessory extension cables with the appropriate connectors.

B. EZ Steer ThermoCool NAV Catheters

The EZ Steer ThermoCool NAV Catheter is a multi-electrode luminal catheter with a bi-directional deflectable tip designed to facilitate electrophysiological mapping of the heart and to transmit radiofrequency (RF) current to the catheter tip electrode for ablation purposes. The catheter shafts measures 7.5 F with 8 F ring electrodes. For ablation, the catheters are used in conjunction with an RF generator and a dispersive pad (indifferent electrode).

The catheter has a high-torque shaft with a bi-directional deflectable tip section containing an array of 4 platinum-iridium electrodes, which includes a 3.5 mm tip dome. All of the electrodes may be used for recording and stimulation purposes. The tip electrode serves to deliver RF current from the RF generator to the desired ablation site. The tip electrode and ring electrodes are made from platinum-iridium. The EZ Steer ThermoCool NAV Catheter incorporates a thermocouple temperature sensor, which is embedded in the 3.5mm tip electrode. A Rocker Lever on the handle is used to deflect the tip. The high-torque shaft also allows the plane of the curved tip to be rotated to facilitate accurate positioning of the catheter tip at the desired site. Additionally, a variety of curve types are available in symmetric or asymmetric combinations, providing two 180° opposed, single planed curves. Currently, the available curves for the EZ Steer ThermoCool NAV Catheters include DD, FF, JJ, DF, and FJ.

At the proximal end of the catheter, a saline input port with a standard luer fitting terminates from the open lumen. This saline port permits injection of normal saline to irrigate the tip electrode. During ablation, heparinized normal saline is passed through the internal lumen of the catheter and through the tip electrode to irrigate and cool the ablation site as well as the electrode tip. The CoolFlow Irrigation Pump is approved for use to control the saline irrigation. The catheter interfaces with standard recording equipment and the Stockert 70 RF Generator via accessory extension cables with the appropriate connectors.

The EZ Steer ThermoCool NAV Catheter features a magnetic location sensor embedded in the tip section that transmits location information to the Carto EP Navigation System. An appropriate reference device is required for location reference position purposes.

The handle of the Catheter is laser etched for easy identification of catheter and direction of curve deflection.

C. Stockert 70 RF Generator

A prior version of the Stockert 70 RF generator was approved under P990071 for delivering up to 50 W of RF power. In the NaviStar DS PMA (P010068), the Stockert 70 generator was modified (a) to deliver up to 70 W of RF power and (b) to read two thermocouples simultaneously, while choosing the higher of the two temperature readings.

The Stockert 70 RF Generator can detect the specific catheter to which it is connected. It will deliver up to 70 W of power only if the catheter selection is part of the NaviStar DS catheter families. Otherwise, it will deliver only up to 50 W.

D. CoolFlow Pump and CoolFlow Pump Tubing Set

The CoolFlow Irrigation Pump and Tubing Set is a peristaltic irrigation pump designed for the delivery of saline solution when used in conjunction with the Stockert 70 RF Generator and the ThermoCool Irrigation Catheter.

The pump has a dual rate feature for one-touch irrigation rate change between a low flow rate (1-5 ml/min) and a high flow rate (5-30 ml/min). A large LED display indicates the flow rate selected. An optional foot pedal can be used to initiate high flow irrigation.

The CoolFlow Pump utilizes a disposable Tubing Set which consists of a drip chamber with IV spike for connection to an IV bag; a pump head section with custom features for mounting to the CoolFlow Irrigation Pump, and a patient and that terminates in a standard luer lock connector. A 3-way stopcock is included. The Tubing Set is intended for single use only.

The CoolFlow Pump and Tubing Set were approved as an "accessory" to the Stockert 70 Generator under PMA P990071, Supplements 5 and 8 approved on June 6, 2005 and April 19, 2006, respectively.

E. Catheter Interface Cables

The Catheter Interface Cables (models D-1195 and D-1170) for the NaviStar ThermoCool catheters are marketed cables that carry thermocouple signals, in addition to other signals, from the NaviStar ThermoCool catheter to the Stockert 70 RF generator. The D-1195 cable connects the NaviStar ThermoCool catheter to the patient interface unit (PIU) in the Carto EP Navigation System, and the D-1170 cable connects the Carto System Patient Interface Unit to the STOCKERT 70 generator. These reusable cables were approved under P030031 and are supplied sterile.

VI. Alternative Practices and Procedures

Alternative therapy for symptomatic paroxysmal atrial fibrillation includes the following:

- Pharmacological therapy for rate and/or rhythm control and cardioversion
- Surgical intervention to create atrial lesions
- Implantable devices to control heart rates

VII. Marketing History

The NaviStar ThermoCool catheter is marketed in the following countries: European Union, Canada, Australia, New Zealand, China, Hong Kong, Korea, Taiwan, Singapore, Croatia, Indonesia, Romania, Ukraine, Philippines, Nicaragua, Honduras, Dominican Republic, Costa Rica, Trinidad, Pakistan, India, Malaysia, Sri Lanka, Argentina, Brazil, Mexico, Colombia, Bulgaria, Egypt, Kazakhstan, Russia, Peru, South Africa, Panama, Jamaica, El Salvador, Chile, and Tobago.

The EZ Steer ThermoCool NAV catheter is approved in the United States and European Union.

There are no countries from which the NaviStar ThermoCool catheter or EZ Steer ThermoCool NAV Catheter have been withdrawn from marketing for any reason related to safety or effectiveness.

VIII. Potential Adverse Effects of the Device on Health

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device:

- Cardiac thromboembolism
- Air embolism
- Arrhythmias, bradycardia, tachycardia
- Valvular damage/insufficiency
- Pericardial effusion
- Pulmonary edema
- Pulmonary embolism
- Respiratory depression
- Pleural effusion
- Transient ischemic attack
- Cerebrovascular accident
- Cardiac perforation/tamponade
- Pericarditis
- Myocardial Infarction
- Heart Failure
- Pump failure
- High creatinine phosphokinase (CPK)
- Dislodgement of implantable cardioverter defibrillator or permanent pacing leads
- Obstruction or perforation or damage to the vascular system
- Pulmonary vein stenosis
- Bleeding complications
- Pulmonary vein dissection
- Pulmonary vein thrombus
- Pulmonary hypertension
- Left atrium/esophageal fistula
- Local hematomas/ecchymosis
- AV fistula
- Pseudoaneurysm
- Thromboembolism
- Vasovagal reactions
- Laceration
- Pneumonia
- Pneumothorax
- Hemothorax
- Infections
- Endocarditis
- Chest pain/discomfort
- Complete heart block
- Coronary artery spasm
- Coronary artery occlusion
- Coronary artery dissection
- Temperature elevation
- Anesthesia reaction
- Volume overload
- Skin burns
- Phrenic nerve damage
- Leakage of air or blood into the lungs or other organs due to perforation
- Unintended complete or incomplete AV, Sinus node, or other heart block or damage
- Pulmonary hypertension

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. Summary of Pre-Clinical Studies

The applicant conducted preclinical and animal studies on the NaviStar ThermoCool catheter, Stockert 70 RF generator, CoolFlow Pump and Tubing Set, catheter and generator interface cables, and the Carto EP Navigation System. These tests were submitted as a part of a prior PMA, P030031, for this device. The details of the preclinical testing can be found

in the Summary of Safety and Effectiveness for this file at:
http://www.fda.gov/cdrh/pdf3/p030031b.pdf.

There have been no changes to the design or materials for this application.

The NaviStar ThermoCool Catheter is validated for a three-year shelf life.

X. Summary of Clinical Studies

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of radiofrequency cardiac ablation in the treatment of patients with drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three-dimensional electroanatomic mapping systems, in the United States, Brazil, Canada, Italy, and Czech Republic, under IDE # G030236. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Objective:
The primary objective of this trial was to demonstrate the safety and efficacy of the NAVISTAR® THERMOCOOL® catheter for the radiofrequency ablation treatment of subjects with symptomatic paroxysmal Atrial Fibrillation (PAF) who were refractory or intolerant to antiarrhythmic drug therapy.

B. Study Design:
The study was a prospective, randomized, unblinded, multicenter pivotal clinical investigation conducted at 19 investigational sites (15 in the US and 4 outside of the US).

B.1. – Study Endpoints:
The endpoints for the study were as follows:

The ***primary effectiveness endpoint*** was the chronic success rate of the NAVISTAR® THERMOCOOL® catheter for the treatment of symptomatic PAF.

Acute success was defined as confirmation of entrance block in all targeted pulmonary veins.

Chronic success was defined as freedom of symptomatic atrial fibrillation (AF) based on electrocardiographic data and no changes in antiarrhythmic drug AAD regimen during comparable evaluation periods for the THERMOCOOL and AAD (Control) groups through 12 months of follow-up. AF status was evaluated by periodic transtelephonic monitoring and 24-hour Holter recordings.

Quality of life was evaluated using the AF frequency/severity checklist and SF-36 questionnaire

The ***primary safety endpoint*** was the incidence of early onset (within 7 days of the ablation procedure) primary adverse events. This included the following adverse events:

- Death
- Myocardial Infarction (MI)

- Pulmonary Vein (PV) stenosis
- Diaphragmatic paralysis
- Atrio-esophageal fistula
- Transient Ischemic Attack (TIA)
- Stroke
- Cerebrovascular accident (CVA)
- Thromboembolism
- Pericarditis
- Cardiac Tamponade
- Pericardial effusion
- Pneumothorax
- Atrial perforation
- Vascular access complications
- Pulmonary edema
- Hospitalization (initial and prolonged)
- Heart block

Secondary safety endpoints included comparisons between the THERMOCOOL and AAD (Control) groups on the following:

- Early onset (≤ 90 days post treatment) of serious adverse events.
- Late Onset (>90 days post treatment) of serious adverse events

B.2. – Subject Accountability:

Table 2 – Subject Accountability and Disposition

Subject Disposition	
Total Number of Subjects Enrolled	167
Subjects randomized to THERMOCOOL	**106**
Excluded Subjects	3
Subjects who underwent ablation with the study catheter	103
Discontinued Subjects	0
Subjects randomized to AAD (Control)	**61**
Excluded Subjects	4
Subjects administered AAD therapy	57
Discontinued Subjects	1
AAD (Control) subjects undergoing RF ablation	36

The following definitions were used to classify subjects:

Effectiveness Analysis Cohort (n = 159) was comprised of subjects that received the treatment that they were randomized to and also did not meet the definitions of being excluded or discontinued.

Primary Safety Analysis Cohort (n = 139) was comprised of subjects that underwent insertion of the THERMOCOOL catheter, including subjects that were randomized to AAD (Control) group and became eligible for RF ablation with the THERMOCOOL catheter.

Secondary Safety Analysis Cohort (n = 160) was comprised of subjects that received the treatment that they were randomized to, including subjects classified as discontinued.

B.3. – Subject Demographics:
The table below summarizes the demographic information. Subjects were randomized 2:1 upon signing informed consent.

Table 3 – Subject Demographics

	THERMOCOOL n/N (%) **N = 106**	**AAD (Control)** n/N (%) **N = 61**	**Total** n/N (%) **N =167**	**p-value**
Gender				0.3997
Female	33 / 106 (31.1)	23 / 61 (37.7)	56 / 167 (33.5)	
Male	73 / 106 (68.9)	38 / 61 (62.3)	111 / 167 (66.5)	
Ethnicity				0.7031
Hispanic	1 / 106 (0.9)	0 / 61 (0.0)	1 / 167 (0.6)	
Other	2 / 106 (1.9)	0 / 61 (0.0)	2 / 167 (1.2)	
White	103 / 106 (97.2)	61 / 61 (100.0)	164 / 167 (98.2)	
Age (years)				0.3009
Mean	55.5 ± 9.34	56.1 ± 12.84	55.7 ± 10.72	
Median	56	58	57	
Min / Max	32 / 76	19 / 77	19 / 77	
LA Dimension (mm)**				0.7118
Mean	40.0 ± 5.5	40.3 ± 5.3	40.1 ± 5.4	
Median	40	41	40	
Min / Max	27.0 / 50.0	26.5 / 49.0	26.5 / 50.0	
LV Ejection Fraction (%)***				0.4670
Mean	62.3 ± 9.8	63.1 ± 7.4	62.6 ± 9.0	
Median	62	63	63	
Min / Max	30.0 / 86.0	44.0 / 80.0	30.0 / 86.0	

** Data are not available for 15 subjects (6 in ThermoCool group and 9 in AAD group).
*** Data are not available for 14 subjects (7 in ThermoCool group and 7 in AAD group).

The age in the above table was when the subject signed the informed consent. The p-value listed compares the randomized groups. There was one subject of Arab ethnicity and one subject that was Native American.

Subjects enrolled in the study reported a mean of 63.2 ± 92.4 AF episodes in the six months prior to baseline. Patients classified as NYHA Class III and IV were excluded from the study. Approximately half of the enrolled subjects had a history of hypertension at baseline; 48.6% (51/105) in the ThermoCool group and 50.0% (30/60) in the AAD (Control) group. Less than a third of the enrolled subjects (27.7%; 44/159) had a history of atrial flutter at

baseline. The overall mean number of AADs failed at baseline was 2.2 ± 1.2, with 27 of the 167 enrolled subjects having previously failed only a Class II/IV AAD.

C. Results

C.1 - Procedural Data:
Tables 4 and 5 present the procedural data.

Table 4: Summary of RF Applications, Saline Infused, Power, Temperature and Impedance Data (THERMOCOOL Effectivenss Cohort, n =103 [1])

Description	Mean ± Standard Deviation
Number of RF Applications (n = 125 procedures)	53.2 ± 36.6
Mean Saline Infused (ml) by NAVISTAR THERMOCOOL Catheter (n = 123 procedures)	1591.0 ± 752.7
Maximum Power (W)/procedure (n = 125 procedures)	41.5 ± 7.1
Maximum Temperature (°C)/procedure (n = 126 RF procedures)	43.9 ± 4.1
Maximum Impedance (ohms)/procedure (n = 125 RF procedures)	135.4 ± 25.4

[1] Complete procedural data were not reported for all subjects.

Table 5: Summary of Ablation Procedure Parameters – All Ablation Procedures (THERMOCOOL Effectiveness Cohort, n = 103*)

Procedure Parameters	THERMOCOOL Group Mean ± SD (n)
Total Procedure Time (min)	211.3 ± 86.1 (126)
Ablation Procedure Time (min)	111.0 ± 62.6 (127)
Total Fluoroscopy Duration (min)	47.9 ± 40.2 (127)
Total Fluid Input (mL)	2877.5 ± 1914.0 (125)
Total Fluid Output (mL)	783.8 ± 884.4 (126)
Balance (input-output) (mL)	2193.0 ± 1348.2 (121)

*Data parameters not available for all ablation procedures.

Note: Tables 3 and 4 include all ablation procedures for subjects randomized to the THERMOCOOL group, including 24 repeat ablation procedures (average of 1.2 ablation procedures per subject).

The overall fluoroscopy and procedure times reported include both the investigational (NAVISTAR THERMOCOOL) procedure time and all other procedures performed during the subject's stay in the electrophysiology (EP) lab. Therefore, the data do not solely reflect the actual use of the NAVISTAR THERMOCOOL catheter.

All AF ablation procedures began with circumferential lesions targeting all pulmonary veins, with additional atrial ablation lines created as clinically required. Additional RF lesion sets placed in the left atrium (LA) included the LA roofline, LA posterior wall line, and left inferior PV-mitral isthmus line. Additional lesion sets in the right atrium included cavo-tricuspid isthmus lines and circumferential lesions around the superior vena cava (SVC). Table 6 summarizes the lesion sets applied to THERMOCOOL group subjects during the index ablation procedures.

Table 6: Outcomes by Ablation Targets per Subject – 1st Ablation Procedure (THERMOCOOL Group Subjects, n=103)*

Ablation Targets	THERMOCOOL Group (n =103)		
	Success n (%)	**Fail n (%)**	**Total n (100%)**
PV Only	**18 (41.9)**	**25 (58.1)**	**43 (100.0)**
>= 4 PV	17	24	
< 4 PV	1	1	
PV + Atrial Lines	**28 (84.8)**	**5 (15.2)**	**33 (100.0)**
+ Right Atrial Lines	11	3	
+ Left atrial Lines	2	2	
+ Combination Left and Right	15	0	
PV + Foci	**3 (42.9)**	**4 (57.1)**	**7 (100.0)**
PV + Atrial Lines + Foci	**4 (66.6)**	**2 (33.4)**	**6 (100.0)**
Total	53 (59.6)	36 (40.4)	89 (100.0)

* 14 Subjects were still within the effectiveness evaluation period and therefore not included in this analysis.

C.2 - Acute Procedural Success:
Acute procedural success results are presented in Table 7.

Table 7: Acute Effectiveness Outcome for THERMOCOOL Group (n=103)*

	THERMOCOOL n
Underwent RF Study procedure	103
Entrance Block Confirmed	102**
Ablation Procedure >80 days	2
Non-study Catheter Utilized for AF Targets	0
>2 Repeat Ablation Procedures	0
Acute Effectiveness Success	100

* Includes all THERMOCOOL group subjects undergoing ablation with the study catheter.

**End of procedure information for one subject was not available.

C.3 - Chronic Success - Freedom from Chronic Effectiveness Failure:

Primary Effectiveness Analysis

A pre-specified interim analysis was performed per the clinical trial protocol, and the results demonstrated sufficient statistical evidence of the study meeting the effectiveness endpoint. As a result, enrollment was stopped and the trial was declared an early success.

The critical results of the Bayesian analysis are the predictive probability of success for 230 patients and the posterior probability of superiority for the THERMOCOOL group. The posterior probability that the THERMOCOOL group is superior to the AAD (Control) group is essentially 1 (> 0.9999). The model estimates the probability of success for a subject in the THERMOCOOL group is 0.627 with a standard deviation of 0.048. For a subject in the AAD (Control) group, the posterior mean probability of success is 0.172 with a posterior standard deviation of 0.049. The predictive probability of success for the original maximum sample size of 230 subjects is also essentially 1 (>0.9999). That is, if the full sample size of 230 had been enrolled, it is a virtual certainty that the final posterior probability would have been larger than 0.98 (protocol specified level needed for success).

Chronic success results are described in Table 8.

Table 8: Summary of Data Available*- June 2008 Dataset

Group	$0 < t \leq 0.5$			$0.5 < t \leq 2$			$2 < t \leq 9$		
	Expos	**Fail**	**Rate**	**Expos**	**Fail**	**Rate**	**Expos**	**Fail**	**Rate**
THERMOCOOL	40.21	26	0.647	104.17	3	0.029	413.09	7	0.017
AAD (Control)	23.27	13	0.559	54.21	14	0.258	90.46	20	0.221

* The exposure (Expos) time in months and number of failures (Fail) are reported for each of the three intervals in the time to event model.

Figure 1 shows the Kaplan-Meier curves for each of the treatment groups for freedom from chronic effectiveness failure (n=159) and shows superiority of the ThermoCool group (64%) compared to the AAD group (16%) for the primary effectiveness endpoint.

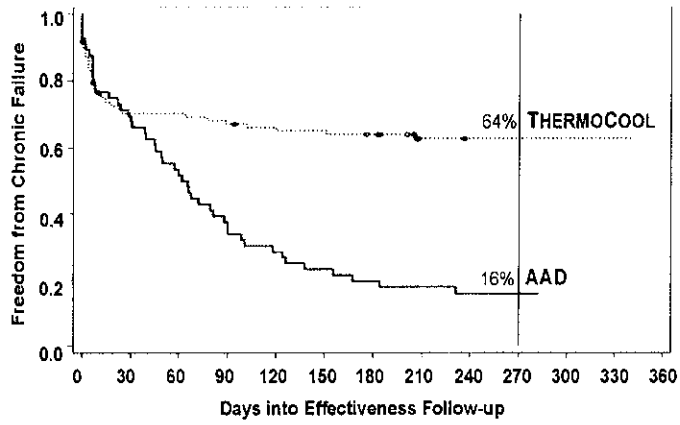

FIGURE 1 Kaplan-Meier Analysis – Probability of Freedom from Chronic Effectiveness Failure For Each Treatment Group*

The June 2008 dataset status of each of the 159 subjects is reported in Table 9. At the time of this analysis, subjects were classified as "Success", "Failure", or "Censored", (i.e. those subjects that had not failed, but did not have complete 9-month follow-up).

TABLE 9: Summary of the Status for Each of the Enrolled Subjects

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

Site variation in primary effectiveness outcome was observed in this study. In particular, one investigational site located outside of the United States had a higher success rate than the remainder of the investigational sites. Various sensitivity analyses were performed which demonstrated that the study conclusions were robust to this site variation.

Figure 2 shows that the 9-month failure-free rate in the THERMOCOOL group is superior to that of the AAD (Control) group. The 95% credible interval for the difference between the treatment and control probability of success is (0.313, 0.584) with a median difference of 0.457.

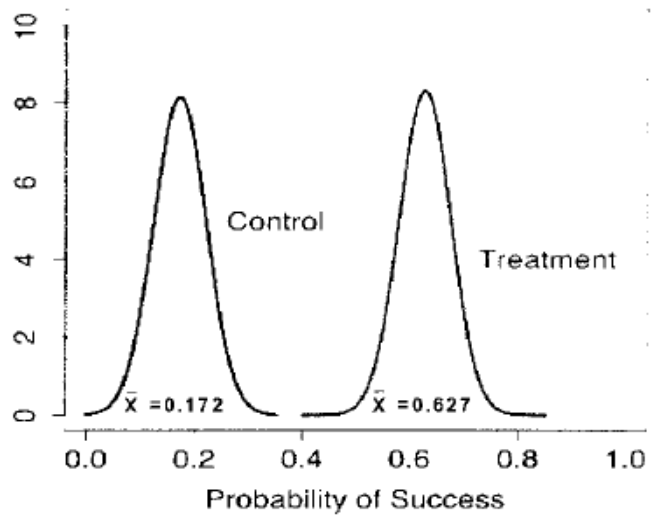

FIGURE 2: The Posterior Distributions of the Probabilities of 9-month Failure-Free Treatment Success for Each Treatment Group

Figure 3 demonstrates that the ThermoCool group had a higher probability of freedom from any documented symptomatic or asymptomatic AF recurrence, subject to the monitoring provisions of the protocol, than the AAD (Control) subjects.. The difference in likelihood of AF recurrence after 9 months of effectiveness evaluation was 51% (72% vs. 21%) in favor of the ThermoCool catheter treatment group.

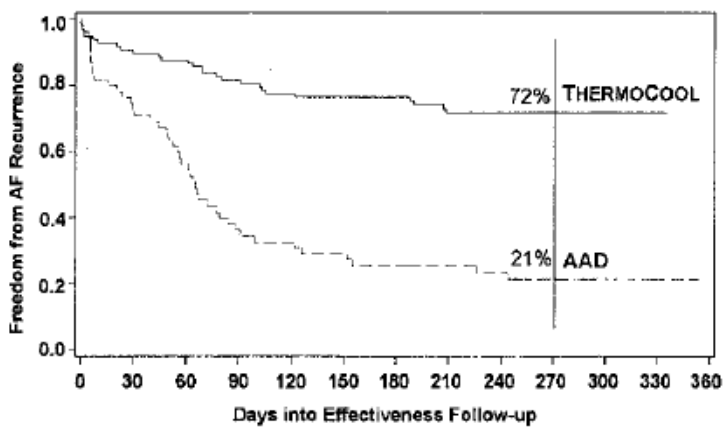

FIGURE 3 Kaplan-Meier Analysis – Probability of Freedom from Any Observed AF Recurrence For Each Treatment Group (n=159)

C.4 - Adverse Events (AE):

The primary safety endpoint for this study was defined as the incidence of early-onset (within 7 days of ablation procedure) primary adverse events for subjects undergoing a study ablation procedure. The Primary Safety Cohort (n=139) was comprised of THERMOCOOL

group subjects (n=103) and AAD (Control) group subjects undergoing an ablation procedure (n=36).

Primary Safety Endpoint – Primary AEs

Table 10 presents the protocol-established endpoint and safety results based on the June 2008 dataset. There were 16 primary AEs reported for 15 subjects. The overall percentage of subjects who experienced a serious primary AE was 10.8 % (15/139) and the upper confidence bounds based on the Primary Safety Cohort was 16.1 %. The safety endpoint specified in the protocol was 7.0% (upper confidence bound of 16.0%). While the primary safety results exceeded the protocol-established primary safety endpoint for this study, the nature and types of adverse events experienced in this trial nonetheless represent and acceptable risk profile.

TABLE 10: Primary Safety Endpoint Outcome – Primary Adverse Events (Primary Safety Cohort, n=139)

	Protocol Established Endpoint	**n**
Number of Subjects in Safety Cohort		139
Number of Subjects with Primary AEs		15
% Primary AEs	7.0	10.8
One-sided 95% Confidence Bound*	16.0	16.1

* Exact binomial using a commercially available software package.

Table 11 summarizes the primary AEs.

Table 11: Primary Safety Endpoint – Early-Onset (Within (≤) 7 Days) Primary Adverse Events (Primary Safety Cohort, n=139)

Description	Number of Subjects with Primary AEs n/139 (%)
Total Serious Primary AEs	**15 (10.8 %)**
Death	0
Atrio-Esophageal Fistula	0
Atrial Perforation	0
Cardiac Tamponade	0
Myocardial Infarction	0
Stroke	0
Cerebrovascular Accident	0
Thromboembolism	0
Transient Ischemic Attack	0
Diaphragmatic Paralysis	0
Pneumothorax	0
Heart Block	0
Pulmonary Vein Stenosis	0
Pulmonary Edema	1 (0.7 %)
Pericarditis	1 (0.7 %)
Hospitalization (initial and prolonged)	7(5.0%)
Pericardial Effusion	1 (0.7 %)
Vascular Access Complication	5 (3.6 %)

Table 12 compares the incidence of early onset serious adverse events between the two treatment groups occurring within the first 90 days of initial therapy.

TABLE 12 Percentage of Early Onset Serious Adverse Events (SAE) by Randomization Group (Overall Safety Cohort, n=160)

Randomization Group	Percent % of SAEs (n/N)	p-value
THERMOCOOL Group	18.4 (19/103)	0.022
AAD (Control) Group*	35.1 (20/57)	

* For AAD subjects undergoing an ablation procedure, only SAE prior an ablation procedure were considered in this analysis.

One subject in the THERMOCOOL group expired during the effectiveness evaluation period. This event occurred 284 days after the ablation procedure.

C.5 – Study Conclusion:
In conclusion, the results demonstrate that there is a reasonable assurance of safety and effectiveness to support the use of the NaviStar ThermoCool ablation catheter to treat patients with drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with advanced three-dimensional electroanatomic mapping systems.

D – Subgroup Analyses

D.1 – Subgroup Analysis: Gender Variances with Atrial Fibrillation
Both genders were well represented in the study conducted under IDE G030236 (66.5% male and 33.5% female). Gender was assessed as a potential predictor of chronic success outcome by multivariate logistic regression (refer to clinical report section 3.8). Results of the final model showed that after accounting for the significant predictors in the final model (LV ejection fraction and sites), gender effect was not significant (refer to clinical report Table 3.8.1B).

A similar analysis was conducted to assess if gender is a predictor for primary AE; the data showed that gender was not a significant predictor of primary AE. Therefore, it is concluded from this study that the product is equally safe and effective when used in males and females.

Further, the proportion of women enrolled in the IDE study is equivalent to the proportion enrolled in other RF ablation and AAD studies. The prevalence of AF is higher at all ages for men than for women however, given the larger population of women versus men over the age of 75, the absolute number of females with AF is equal or greater than that of men[1]. In a separate study that evaluated the enrollment of females in heart failure studies, women were found to be underrepresented as compared to the population estimates for a variety of reasons[2]. It is likely this is an explanation for the enrollment ratio for study IDE G030236 being slightly less than population based prevalence estimates have indicated.

The applicant performed a literature search of recent published AF ablation therapy articles to compare gender enrollment. The search criteria included the following:

- AF ablation therapy
- A reasonable number of patients treated (≥20)
- Gender identification of treated patients

No distinction was made for AF disease classification. Sixteen (16) peer-reviewed articles were identified that met the criteria between 2002 and 2008. Prior to 2005 the majority of patients referred for AF ablation therapy were male.[3] The number of patients included in the 16 reports ranged from 20-2374 patients with a total of 3907. Female patients represented

---

[1] Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution and gender in patients with atrial fibrillation; analysis and implications. *Arch Intern Med* 1995;155:469–473.
[2] Heiat A, Gross CP, Krumholz HM. Representation of the Elderly, Women, and Minorities in Heart Failure Clinical Trials. *Arch Intern Med.* 2002;162:1682-1688.
[3] Gerstenfeld EP, Callans D, Dixit S, Lin D, Cooper J, Russo AM, Verdino R, Weiner M, Zado E, Marchlinski FE. (2007) Characteristics of patients undergoing atrial fibrillation ablation: trends over a seven-year period 1999-2005. J Cardiovasc Electrophysiol. 18:23-28.

27.6% weighted average (1027/3907) of the patient population. Factors that affect the percentage of females represented in published literature include the following:

- The prevalence of AF in men is somewhat greater[4]
- Women are referred for AF ablation later with a more complex clinical pre-operative presentation[5]

Table 13 on the following page identifies the number of male and female subjects reported in the 16 studies examined as well as a complete reference list of the reviewed articles. The table also contains the data for IDE study G030236. As demonstrated from the data in the table, the percentage of female subjects enrolled in IDE study G030236 was 33.5%. This percentage of female subjects modestly exceeds the weighted average (27.6%) from the analysis of the cited papers and representative of real world current treatment options offered to female patients diagnosed with AF.

In addition, results from a separate systematic literature review and meta-analysis) of RF ablation and AAD studies for the treatment of AF support the proportion of females represented in IDE study G030236. 0f 69 treatment groups analyzed for AF ablation that reported gender, 28% of the patients were female (1,768/6,321 total patients). In 46 treatment arms where the patents received AAD therapy, females represented 35.4% of patients (2,004/5,662 total patients)[6].

In conclusion, the IDE study G030236 enrolled a reasonable percentage of women to detect gender variation. Based on the study findings, disease prevalence and the literature evaluations, it can be concluded that gender issues have been adequately addressed.

---

[4] Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. (1994) Independent risk factors for atrial fibrillation in a population-based cohort. The Framingham Heart Study. JAMA 271:840-844.

[5] Forleo GB, Tondo C, De Luca L, Dello Russo A, Casella M, De Sanctis V, Clementi F, Fagundes RL, Leo R, Romeo F, Mantica M. (2007) Gender-related differences in catheter ablation of atrial fibrillation. Europace. 9:613-20.

[6] Calkins H, Spector P, Reynolds MR, et al. Treatment of Atrial Fibrillation with Anti-arrhythmic Drugs or Radiofrequency Ablation: Two Systematic Literature Reviews and Meta-analyses. JAMA. Submitted manuscript May 28, 2008.

Table 13: Data from Published Literature

Total # of Subjects in the Study	# of Male Subjects	# of Female Subjects	References*	% Male Subjects	% Female Subjects
105	76	29	1	0.72381	0.27619
35	30	5	2	0.857143	0.142857
180	141	39	3	0.783333	0.216667
149	112	37	4	0.751678	0.248322
100	73	27	5	0.73	0.27
68	56	12	6	0.823529	0.176471
20	12	8	7	0.6	0.4
43	40	3	8	0.930233	0.069767
2374	1662	712	9	0.700084	0.299916
56	45	11	10	0.803571	0.196429
221	150	71	11	0.678733	0.321267
200	133	67	12	0.665	0.335
70	57	13	13	0.814286	0.185714
80	62	18	14	0.775	0.225
60	50	10	15	0.833333	0.166667
146	129	17	16	0.883562	0.116438

Comparison of Data from Literature vs. Data from BWI IDE Study

Literature Data		**BWI IDE Data**	
Total Subjects in Cited Studies	3907	Number / Percentage of Men in IDE Study	111 / 66.5%
Total # of Female Patients in Cited Studies	1079	Number / Percentage of Women in IDE Study	56 / 33.5%
Weighted Average of Women in Cited Studies	27.6%		
Minimum # of Women in Cited Studies	3		
Maximum # of Women in Cited Studies	712		

*References are contained in section XV below.

D.2 – Subgroup Analysis: Pediatric Medical Device Safety and Improvement

i. Pediatric Subpopulations that Suffer from the Disease or Condition that the Device is Intended to Treat, Diagnose, or Cure

Atrial fibrillation is rare in children. When observed, the pediatric patient usually presents with a genetic abnormality and/or disease state that causes enlargement of the heart. However, when it presents itself, atrial fibrillation can afflict pediatric patients <21 years of age.

Due to the infrequency of atrial fibrillation in the young, catheter ablation targeting directly to atrial fibrillation is rarely indicated or necessary. Therefore, the ThermoCool catheters are not expected to be widely used in the pediatric population.

ii. Number of Affected Pediatric Patients

According to population studies, the overall prevalence of atrial fibrillation is 0.4% in the United States. Atrial fibrillation prevalence is low in children and young adults, but it becomes progressively more common in older age groups. The prevalence of atrial fibrillation increases significantly, reaching 3% to 5% in people older then 65 years. After age 80, the prevalence of atrial fibrillation increases to almost 9%.

Among children with arrhythmias, atrial fibrillation accounts for approximately 4.6% of the arrhythmias observed.

XI. Panel Meeting Recommendation and FDA'S Post-Panel Action

A. Panel Meeting Recommendation

At an advisory meeting held on November 20, 2008, the Circulatory System Devices Panel recommended that the Biosense Webster PMA supplement for the Navistar ThermoCool Catheter and EZ Steer ThermoCool Catheter be conditionally approved. The vote specifically excluded non-navigational, bidirectional deflected, and magnetically deflected models, because these models were not a part of the premarket study. The panel, however, left a decision to FDA to determine whether any of these models may be included based upon additional preclinical information not contained in the panel briefing materials.

The conditions for approval include the submission and FDA approval of a post-approval study to determine the generalizability of the results and to evaluate the long term safety and clinical effectiveness in the population indicated for the device. The Panel also recommended that the sponsor develop an additional training program for physicians tailored to address atrial fibrillation ablation procedures and make modifications to the device labeling to describe the clinical trial.

XII. Conclusions Drawn from Preclinical and Clinical Studies

The NaviStar ThermoCool catheter was previously approved on November 05, 2004, for the treatment of Type I atrial flutter under P030031 and approved on August 11, 2006 under P040036 for the treatment of recurrent drug/device refractory sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction (MI) in adults.

Bench and animal testing submitted in support of PMA P030031 demonstrated that the NaviStar ThermoCool catheter, Stockert 70 RF Generator, CoolFlow Pump and accessories maintain mechanical and electrical integrity and are biocompatible under the proposed indications for use.

Upon recommendation of the *Circulatory System Devices Panel*, FDA reviewed the preclinical and animal data submitted by the sponsor related to the EZ Steer ThermoCool Nav catheter. The catheter models are largely the same with the one notable difference being that the EZ Steer model has a bidirectional deflection mechanism as opposed to a unidirectional mechanism in the NaviStar model. The EZ Steer model complied with the same engineering parameters associated with stiffness and deflection as applied to the NaviStar model. FDA concluded from these data that this model demonstrated equivalent features and mechanical characteristics such that no additional concerns related to safety or effectiveness of the device were raised. Therefore, FDA's interpretations of the data submitted to support a reasonable assurance of safety and effectiveness for the NaviStar ThermoCool catheters also apply to the EZ Steer ThermoCool Nav model of the device.

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval, as described above. Overall, the 95% upper bound for the primary safety endpoint was 16.1%. The performance goal for this endpoint was 16.0%.

B. Effectiveness Conclusions

With respect to effectiveness, the estimated mean probability of success for a subject in the ThermoCool group is 62.7% with a posterior standard deviation of 4.8 % and for a subject in the AAD (control) group, the posterior mean probability of success is 17.2% with a posterior standard deviation of 4.9%. The 95% credible interval for the difference between the treatment and control probability of success is (0.313, 0.584) with a median difference of 0.457.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIII. CDRH Decision

CDRH issued an approval order on February 06, 2009. Please see the approval order for the final conditions of approval.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System Regulation (Part 820).

XIV. Approval Specifications

Direction for Use: See the labeling (Instructions for Use).

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the labeling.

Post-approval Requirements and Restrictions: See Approval Order.

XV. References

1. Dixit S, Gerstenfeld EP, Ratcliffe SJ, et al. Single Procedure Efficacy of Isolating All Versus Arrhythmogenic Pulmonary Veins on Long-term Control of Atrial Fibrillation: A Prospective Randomized Study. Hearth Rhythm 2008 Feb; 5 (2):182-3
2. Estner HL, Hessling G, Ndrepepa G, et al. Acute Effects and Long-Term Outcome of Pulmonary Vein Isolation in Combination with Electrogram-guided Substrate Ablation for Persistent Atrial Fibrillation. Am J Cardiol. 2008 Feb 1; 101 (3):332-7
3. Moreira W, Timmermans C, Wellens HJ, et al. Long Term Outcome of Cavotricuspid Isthmus Cryoablation for the Treatment of Common Atrial Flutter in 180 Patients: A Wingle Center Experience. J Interv Card Electrophysiol. 2008 Apr; 21(3): 235-40
4. Schietinger BJ, Bozlar U, Hagspiel KD, et al. The Prevalence of Extracardiac Findings by Multidetector Computed Tomography Before Atrial Fibrillation Ablation. Am Heart J. 2008 Feb; 155(2):254-9
5. Chevalier P, Al Ghazzy M, Rivard L, et al. Radiofrequency Ablation of Atrial Fibrillation: The first 100 Cases in Lyon. Int J Cardiol. 2008 Jan 9
6. Shin SH, Park MY, Oh WJ, et al. Left Atrial Volume is Predicator of Atrial Fibrillation Recurrence After Catheter Ablation. J Am Soc Echocardiogr. 2008 Jun; 21 (6):697-702
7. Pratola C, Baldo E, Notarstefano P, et al. Radiofrequency Ablation of Atrial Fibrillation: is the Persistence of all Intraprocedural Targets Necessary for Long-Term Maintenance of Sinus Rhythm? Circulation. 2008 Jan 15; 117(2): 136-43
8. Sacher E, Corcuff JB, Schraub P, et al. Chronic Atrial Fibrillation Ablation Impact on Endocrine and Mechanical Cardiac Functions. Eur Heart J 2008 May; 29(10): 1290-5
9. Fenelon G, Scanavacca M, Atie J, et al. Atrial Fibrillation Ablation in Brazil: Results of the Registry of the Brazilian Society of Cardiac Arrhythmias. Arg Bras Cardiol. 2007 Nov; 89(5):258-62
10. Seow SC, Lim TW, Koay CH, et al. Efficacy and Late Recurrences with Wide Electrical Pulmonary Vein Isolation for Persistent and Permanent Atrial Fibrillation. Europace. 2007 Dec; 9(12):1129-33
11. Forleo GB, Tondo C, De Luca L, et al. Gender-Related Differences in Catheter Ablation of Atrial Fibrillation. Europace. 2007 Aug; 9(8):613-20

12. Cheema A, Vasamreddy CR, Dalal D, et al. Long-term Single Procedure Efficacy of Catheter Ablation of Atrial Fibrillation. J Interv Card Electrophysiol. 2006 Apr; 15(3):145-55
13. Oral H, Knight B, Tada H, et al. Pulmonary Vein Isolation for Paroxysmal and Persistent Atrial Fibrillation. Circulation 2002; 105:1077-81
14. Oral H, Scharf C, Chugh A, et al. Catheter Ablation for Paroxysmal Atrial Fibrillation: Segmental Pulmonary Vein Ostial Ablation Versus left Atrial Ablations. Circulation. 2003; 108:2355-60
15. Lemola K, Oral H, Chugh A, et al. Pulmonary Vein Isolation as an End Point for Left Atrial Circumferential Ablation of Atrial Fibrillation. J Am Coll Cardiol. 2005 Sep 20; 46(6): 1060-66
16. Oral H, Pappone C, Chugh A, et al. Circumferential Pulmonary-Vein Ablation for Chronic Atrial Fibrillation. N Engl J Med. 2006 Mar 2; 354(9):934-41