Summary of Safety and Effectiveness Data

I. General Information

Device Generic Name: Irrigated Diagnostic/Ablation Catheter and accessories

Device Trade Names: NAVISTAR THERMOCOOL Deflectable Diagnostic/Ablation Catheter

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

Date of Panel Recommendation:

Pre-market Approval Application (PMA) Number: P040036

Date of Notice of Approval to Applicant: AUG 11 2006

Device and Accessory Model Numbers

Family Name	Model Number	Curve	Temperature Sensor
NAVISTAR THERMOCOOL	NI75TBH	B	Thermistor 3.5mm
	NI75TCH	C	Thermistor 3.5mm
	NI75TDH	D	Thermistor 3.5mm
	NI75TFH	F	Thermistor 3.5mm
	NI75TCBH	B	Thermocouple 3.5mm
	NI75TCCH	C	Thermocouple 3.5mm
	NI75TCDH	D	Thermocouple 3.5mm
	NI75TCFH	F	Thermocouple 3.5mm
	NI75TCJH	J	Thermocouple 3.5mm
Stockert 70 RF Generator	S7001		
CARTO Navigation System	M-5385-59		
Catheter interface cables	D-1195: C5-MH/NAVMH-S D-1170: C6-MR10/MSTK-S C10-MR10/MSTK-S		

Explanation of Model Numbers

The NAVISTAR THERMOCOOL /Ablation Deflectable Tip catheters are available in the B, C, D, F and J curves, each being determined by the angle between the tip and shaft of the catheter, and by the radius of the curve. The catheter line is available with either a thermistor or thermocouple for sensing the tip temperature during an ablation procedure. The "J" curve type is only available with the thermocouple and not with the thermistor temperature sensor. Both thermistor and thermocouple versions of the catheter work equally well with the Stockert 70 Generator.

For the NAVISTAR THERMOCOOL /Ablation Deflectable Tip catheter, NI75T signifies the thermistor, and NI75TC signifies the thermocouple. Furthermore, the letter located after the "NI75T(C)X-" in the model number signifies the type of curve for the catheter. For example, the NI75TCFH model has curve type F.

The catheter interface cables that connect the NAVISTAR THERMOCOOL /Ablation Deflectable Tip catheter to the patient interface unit were previously approved under P990025.

Related Pre-market Applications

Under P030031, the NAVISTAR THERMOCOOL catheter was approved for the treatment of Type I atrial flutter. The catheter that is the subject of this current PMA application is identical in design, materials, and technological characteristics to the catheter approved under P030031.

The NAVISTAR THERMOCOOL catheter is derived from the NAVISTAR catheter approved under P990025 and the NAVISTAR DS catheter approved under P010068. The major differences are the length of the tip electrode in the present NAVISTAR THERMOCOOL catheters (3.5 compared to 4 and 8 mm in the previous devices) and the use of an additional lumen for irrigation in the NAVISTAR THERMOCOOL catheter. Additionally, the NAVISTAR catheter is approved with indications for treatment of supraventricular tachycardias (AV nodal reentrant tachycardia, interruption of AV conduction pathways, creation of complete AV block), and the NAVISTAR DS catheter is approved for the treatment of type I atrial flutter. Furthermore, a prior version of the Stockert 70 RF generator was approved under P990071. Relevant design specifications were maximum power output of 50 W and use for single temperature sensor only except for the dual temperature sensor DS catheters, which are indicated for use of up to 70 W. These data are incorporated by reference in the present PMA. For more information on the data that supported each application, please refer to the summaries of safety and effectiveness data available on the FDA CDRH Internet Home Page located at http://www.fda.gov/cdrh/pmapage.html. Written request for this information can also be made to the Dockets Management Branch (HFA-305), FDA, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

II. Indications for Use

The NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter and related accessory devices, when used with the STOCKERT 70 Radiofrequency (RF) Generator, are indicated for the treatment of recurrent drug/device refractory sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction (MI) in adults.

The NAVISTAR THERMOCOOL catheter provides location information when used with the CARTO EP / XP Navigation System, and can be used for catheter-based cardiac electrophysiological mapping (stimulation and recording).

III. Contraindications

Do not use the NAVISTAR THERMOCOOL catheter:

- 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

IV. Warnings and Precautions

The warnings and precautions can be found in the NAVISTAR THERMOCOOL Diagnostic/Ablation Catheter instructions for use, and the STOCKERT 70 Radiofrequency Generator User Manual.

V. Device Description

With reference to the model numbers indicated in the above table on Device and Accessory Model Numbers, the device components that are the subject of the PMA are the NAVISTAR THERMOCOOL Diagnostic/Ablation Catheters;

For catheter ablation procedures, the device components require the use of the STOCKERT 70 RF generator and grounding pad (indifferent patch electrode) previously approved for use with the STOCKERT 70 RF generator under P990071. Consult instruction manual for the STOCKERT 70 RF for more information.

The device also requires the use of catheter interface cables approved for use with the NAVISTAR catheters under P990025.

For additional aid in navigation, the NAVISTAR THERMOCOOL catheter may be used with the following legally marketed devices:

- REFSTAR reference catheters – originally cleared under K954390; and
- CARTO EP/XP Navigation System – originally cleared under K954395 and other pre-market notifications.

Irrigation for the NAVISTAR THERMOCOOL catheters must be provided via use of a commercially available irrigation pump that provides irrigation at rates indicated in the catheter instructions for use.

NAVISTAR THERMOCOOL Diagnostic/Ablation Catheter

The NAVISTAR THERMOCOOL Diagnostic/Ablation catheter is a family of steerable, multi-electrode catheters with a deflectable tip.

The NAVISTAR THERMOCOOL catheter is a lumenal, electrophysiology electrode catheter with a 3.5 mm tip electrode, three ring electrodes, a location sensor, and a temperature sensor incorporated into the deflectable tip. 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 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.

The usable length of the NAVISTAR THERMOCOOL catheter is 115 centimeters. The catheter is provided sterile and for single patient use only.

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. The STOCKERT 70 generator currently is capable of delivering up to 70 W of RF power and to reading 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.

Catheter Interface Cables

The Catheter Interface Cables (models D-1195 and D-1170) for the NAVISTAR THERMOCOOL catheters are marketed cables under P990025 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 system, and the D-1170 cable connects the CARTO System Patient Interface Unit to the STOCKERT 70 generator. These reusable cables are supplied sterile.

VI. Alternative Practices or Procedures

Alternative therapy for recurrent drug/device refractory sustained monomorphic VT due to prior MI includes direct surgical ablation or removal of myocardial tissue, use of drugs for arrhythmia control, intracardiac defibrillator therapy, antiarrhythmia pacing, and catheter ablation with the approved NAVISTAR catheter.

VII. Marketing History

The NAVISTAR THERMOCOOL Diagnostic/Ablation Catheters and accessories have been marketed in the following countries/jurisdictions:

- European Union
- Canada
- Australia
- New Zealand
- China
- Hong Kong
- Korea
- Taiwan
- Singapore
- Pakistan
- India
- Malaysia
- Sri Lanka
- Argentina
- Brazil
- Mexico
- Colombia

There are no countries from which the NAVISTAR THERMOCOOL catheter, or the related accessory devices have been withdrawn from marketing for any reason related to safety or effectiveness.

VIII. Potential Adverse Effects (AEs) of the Device on Health

Potential AEs associated with cardiac ablation for treatment of recurrent drug/device refractory sustained monomorphic VT due to prior MI include the following:

- Acute Respiratory Distress Syndrome (ARDS)
- Air embolism
- Anemia
- Anesthesia reaction
- Arrhythmias
- Atypical flutter
- AV fistula
- Cardiac perforation/tamponade
- Cardiac thromboembolism
- Cerebrovascular accident (CVA)
- Chest pain/discomfort
- Complete heart block
- Component damage to ICD or implantable pacemaker
- Congestive heart failure
- Coronary artery spasm
- Local hematomas/ecchymosis
- Mobile strands in the inferior vena cava
- MI
- Nerve Palsy
- Obstruction or perforation or damage to the vascular system
- Pericardial effusion/tamponade
- Pericarditis
- Phrenic nerve damage
- Pleural effusion
- Pneumonia
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary embolism
- Pump failure
- Respiratory depression/failure

- Coronary artery thrombosis
- Coronary artery dissection
- Distal aortic / coronary artery dissection
- Death
- Dislodgement of implantable cardioverter defibrillator or permanent pacing leads
- Endocarditis
- Exacerbation of pre-existing atrial fibrillation
- Expressive aphasia
- Heart Failure
- Hemothorax
- Increased phosphokinase level
- Infection
- Laceration
- Leakage of air or blood into the lungs or other organs due to perforation
- Seizure
- Skin burns
- Tamponade
- Temperature elevation
- Temporary complete heart block
- Thrombi
- Thromboembolism
- Transient ischemic attack (TIA)
- Unintended (in)complete AV, sinus node or other heart block or damage
- Valvular damage/insufficiency
- Vascular bleeding
- Vasovagal reactions
- Ventricular Tachyarrhythmia
- Visual Blurring
- Volume overload
- Worsening chronic obstructive pulmonary disease

For actual AEs observed during the clinical study (within 7 days post-ablation), please refer to Table 8.

IX. Summary of Pre-Clinical Studies

Biosense Webster conducted preclinical and animal studies on the NAVISTAR THERMOCOOL catheter, STOCKERT 70 RF generator, catheter and generator interface cables, and the CARTO 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 clinical testing described below was performed with the NAVISTAR THERMOCOOL catheter.

A. Objective

The objective of the study was to evaluate the safety and effectiveness of the NAVISTAR THERMOCOOL catheter used in conjunction with CARTO EP/XP Navigation System and the STOCKERT 70 RF Generator and related accessories for ablation of recurrent drug/device refractory sustained monomorphic VT due to prior MI in adults.

B. Study Design

The study was a single-arm, prospective, non-randomized, unblinded, multi-center study conducted at 18 investigational sites located in the United States.

Inclusion Criteria: (Patients must fulfill *all* of the following criteria to be included.)

- Four or more documented spontaneous episodes of sustained symptomatic ventricular tachycardia, OR incessant VT (present 50% of the time with intervention for a period >12 hr) refractory to medication and cardioversion due to prior myocardial infarction that have occurred in the last six months.
  - For patients with an ICD: Documented episodes must be four or greater for entry into the study.
  - For patients without an ICD: Documented episodes must be two or greater within two months and the assessment will be performed by a review of ECGs and hospitalization records
- Failed therapy with an antiarrhythmic drug or ICD due to spontaneous recurrence of symptomatic ventricular tachycardia.
- Left ventricular ejection fraction > 10% as estimated by echocardiography, contrast ventriculography or radionuclide imaging within the previous 30 days.
- Informed consent

Exclusion Criteria: (Patients meeting *any* of the following criteria will be excluded.)

- Age < 18 years.
- Definite protruding left ventricular thrombus on pre-ablation echocardiogram.
- Myocardial infarction within the preceding 2 months. Patients with incessant VT (present 50% of the time with intervention for a period >12 h) may be enrolled if their MI is at least 3 weeks old.
- Patients with idiopathic VT.
- Other disease process likely to limit survival to less than 12 months.
- Class IV heart failure.
- Serum creatinine of > 2.5 mg/dl.
- Thrombocytopenia or coagulopathy.
- Contraindication to heparin.
- Women who are pregnant.
- Cardiac surgery (i.e. ventriculotomy, atriotomy) within the past 2 months. Patients with incessant VT (present 50% of the time with intervention for a period >12 h) may be enrolled if their surgery is at least 3 weeks old.
- Acute illness or active systemic infection.
- Unstable angina.
- Severe aortic stenosis or flailed mitral valve.
- Uncontrolled heart failure.
- Significant congenital anomaly or medical problem that in the opinion of the principal Investigator would preclude enrollment in the study.
- Enrolled in an investigational study evaluating another device or drug.
- Unwilling to participate in the study or unavailable for follow up visits.

B.1 Study Endpoints

The endpoints for the study were as follows:

Acute procedural success for VT was defined as the termination and non-inducibility of all clinically relevant VTs upon hospital discharge. A clinically relevant VT was defined as any spontaneous VT or any induced VT, with cycle lengths equal to (± 20 msec) or greater than that of the spontaneous clinical VT.

Chronic success for VT was defined at 6 months following the RF ablation procedure as no recurrence of clinically relevant monomorphic VT(s) that were targeted at ablation. In order to qualify for chronic success, a patient must have already met the acute procedural success endpoint. Chronic success was the primary effectiveness endpoint for the study. VT recurrences were to be documented by ICD telemetry for subjects who had an implanted defibrillator, or by transtelephonic monitoring (TTM), ECG recordings from paramedics or emergency room visits in the event of recurrence of sustained VT in subjects who did not have an ICD implant. Chronic success for incessant VTs was also defined as no recurrence of incessant VTs during the 6-month follow-up period.

Note: Acute procedural success and chronic success were determined from the last study ablation procedure prior to hospital discharge. Subjects who underwent an ablation procedure during the 6-month follow-up period (after hospital discharge) were deemed chronic failures.

Procedural safety was determined by the number of subjects who experienced acute or sub-chronic major complications associated with the use of the investigational device within seven days of the ablation procedure.

B.2 Protocol Endpoints

The protocol endpoints were prospectively established. The protocol endpoint for the safety endpoint was based on selected medical literature. The success criteria are defined below:

- **Safety**: major adverse events (AEs) within 7 days of the procedure occur at a rate of **22%** or less with a **30%** one-sided 95% upper confidence bound;
- **Acute procedural success**: **75%** with a **65%** one-sided 95% lower confidence bound.
- **Chronic success**: **50%** with a **40%** one-sided 95% lower confidence bound.

The trial design and endpoints of this study were based on historical controls. Limitations of the historical controls used for this study included the following:

- Incomplete recording of safety results were available in the scientific literature.

- Literature patient populations were not necessarily comparable to current study population in disease severity, treatment of ischemic heart disease, duration of follow up, type of ablation treatment, ablation treatment not standardized, percent of patients with implanted defibrillators, and percent of patients treated with amiodarone.

- Available literature included some non-randomized descriptions of patient care.

B.3 Patient Accountability

Table 1 documents the accountability and disposition of enrolled subjects.

TABLE 1. Subject Enrollment and Accountability

Subject Disposition	
Total Number of Subjects Enrolled	**240**
Subjects Excluded (prior to ablation)	7
Safety Analysis Cohort	**233**
Discontinued Subjects (prior to ablation)	7
Effectiveness Analysis Cohort	**226**
Subjects who underwent ablation with **only** NAVISTAR THERMOCOOL catheter	205
Subjects who underwent ablation with NAVISTAR THERMOCOOL catheter **and** non-investigational catheter*	21

* This category involved enrolled subjects that were treated with the investigational catheter at the beginning of the procedure and the investigator then switched to a non-protocol catheter to complete the treatment of VT. Furthermore, subjects who could not be treated due to investigational device failure are included in this category. These subjects were considered acute procedural and chronic failures.

The following definitions were used to classify subjects:

Enrolled Subjects (n = 240) are subjects who signed informed consent.

Excluded Subjects (n = 7) are subjects that were enrolled but never underwent insertion of the investigational catheter.

Discontinued Subjects (n = 7) are subjects that had the investigational catheter inserted but did not undergo an ablation procedure with the investigational device, (ie, no RF energy was applied).

Effectiveness Analysis Cohort (n = 226) included the 226 subjects that underwent an ablation procedure with the investigational device.

Safety Analysis Cohort (n = 233) included the 226 subjects in the Effectiveness Analysis Cohort plus the 7 discontinued subjects.

The Safety Analysis Cohort (n = 233) and Effectiveness Analysis Cohort (n = 226) include 205 subjects who underwent ablation with the investigational device and 21 subjects who underwent ablation with the investigational device and a non-investigational device due to investigator preference, procedural complications, suspected catheter malfunction, perceived lack of effectiveness, subject anatomy, fluid management, or non-

investigational device malfunction (and were deemed an effectiveness failure under the protocol).

The results of this study were evaluated as point estimates and qualitatively compared to existing literature and the current state of clinical practice for this patient group and indication.

B.4 Subject Demographics

Table 2 summarizes the demographic information of all enrolled subjects in the study.

TABLE 2. Summary Demographics (Enrolled Subjects with Data, n = 240)

Description	Enrolled	
	n	%
Gender		
Female	25	10.4
Male	215	89.6
Total	240	100.0
Age (years)		
Mean	65.1	
Standard Deviation	10.8	
Minimum	31	
Maximum	87	

Of the 240 enrolled subjects, 232 (96.7%) had a preexisting history of myocardial infarction (MI). Additionally, 225 (93.8%) subjects were confirmed to have an ICD implanted prior to study enrollment. Spontaneous monomorphic VT characteristics were reported in 199 of the 240 subjects with data enrolled in the study. Three hundred and ten (310) spontaneous VTs were reported in 199 subjects. The predominant VT QRS morphology of those reported was right bundle branch block superior axis (24.2%, 75/310), followed by left bundle branch block superior axis (9.4%, 29/310) and right bundle branch block inferior axis (8.1%, 25/310). The average cycle length of the VTs was 397.4 ms, with a median at 400 ms.

A total of 889 VTs were induced in 224 subjects, an average of approximately 3.97 VTs per subject. The majority of the subjects (171/226; 75.7%) had induction of at least one unmappable VT during the procedure. Thirty point five percent of subjects (30.5%; 69/226) exhibited only unmappable induced VTs.

C. Results

C.1 Intraprocedural Data

Tables 3 and 4 present the procedural data.

TABLE 3. Summary of RF Applications, Saline Infused, Power, Temperature and Impedance Data (Effectiveness Analysis Cohort, n = 226[1])

Description	Mean ± Standard Deviation
Number of RF Applications (n = 256 procedures)	26.4 ± 16.5
Total Saline Infused (ml) by NAVISTAR THERMOCOOL Catheter (n = 233 procedures)	1483.8 ± 838.4
Maximum Power (W)/application (n = 6509 RF applications)	42.5 ± 13.1
Maximum Temperature (°C)/application (n = 6506 RF applications)	39.3 ± 7.8
Maximum Impedance (ohms)/application (n = 6531 RF applications)	103.0 ± 58.2

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

Note: Above table includes all ablation procedures including repeat procedures.

TABLE 4. Summary of Overall Fluoroscopy and Procedure Time (Effectiveness Analysis Cohort, n = 226)

Description	Mean ± Standard Deviation
Total fluoroscopy time (hrs)/procedure (n = 244 procedures)	1.0 ± 1.8
Total procedure time (hrs)/procedure[1] (n = 258 procedures)	5.6 ± 2.2

[1] Time from first cannula placed into vein/artery of subject to time when all catheters were removed from subject.

Note: Above table includes all ablation procedures including repeat procedures.

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 EP lab. Therefore, the data do not solely reflect the actual use of the NAVISTAR THERMOCOOL catheter.

C.2 Acute Procedural Success

The procedure was considered an acute failure if clinically relevant VT(s) were present at the end of the procedure and/or recurred spontaneously prior to hospital discharge. In addition, the procedure was considered an acute failure if a non-protocol ablation catheter was utilized. Table 5 describes the acute ablation outcomes.

Acute procedural success in subjects with incessant VT was defined as termination of the incessant VT and no recurrence prior to hospital discharge. Incessant VT was defined as those VTs which continue despite attempted electrical or pharmacological cardioversion such that the VT is present more than 50% of the time for a period of > 12 hours. Subjects with incessant VT were considered acute failures if incessant VT recurred prior to hospital discharge.

TABLE 5. Summary of Acute Procedural Success (Effectiveness Analysis Cohort, n = 226)

Subset Description	n	Acute Success	Percent (%)	95% C.I.[1]
Effectiveness Analysis Cohort[2,3]	226	171	75.7	71
Protocol Endpoint			75	65

[1] Exact binomial confidence bound.

[2] Data includes non-protocol catheter procedures considered *a priori* acute failures.

[3] Data includes subjects with incessant VT.

The results from the acute outcome analysis based on termination of all clinical relevant VT upon hospital discharge demonstrate that the percentage of subjects achieving acute success (75.7%; 95% lower confidence bound of 71%) met the protocol endpoint for acute procedural success.

C.3 Chronic Success - Freedom from VT Recurrence at Six-Month Follow-Up

Chronic success results are described in Table 6.

TABLE 6. Summary of Chronic Success (Effectiveness Analysis Cohort, n = 226)

Subset Description	n	Chronic Success	Percent (%)	95% C.I.[1]
Effectiveness Analysis Cohort[2,3]	226	107	47.3	41.7
Protocol Endpoint			50	40

[1] Exact binomial confidence bound.

[2] Data includes non-protocol catheter procedures considered a priori acute failures.

[3] Data includes subjects with incessant VT.

The results demonstrate that the percentage of subjects achieving chronic success (47.3%, 95% lower confidence bound of 41.7%) met the protocol endpoint for chronic success. This is due to the fact that although the point estimate for chronic success was lower than the protocol endpoint, the 95% lower confidence bound of the estimate was higher than the protocol endpoint.

Kaplan-Meier Analysis

A Kaplan-Meier analysis was performed to estimate the time to VT recurrence. Standard errors were computed by the Peto method. The one hundred and seventy-one (171) subjects who achieved acute success were included in this analysis. Table 7 provides the number of subjects at risk (number of subjects entering the follow-up interval with acute success), number of subjects censored (number of subjects for whom the last follow-up exhibited freedom from recurrence of VT, at the time-point), number of events (subjects who experienced recurrence of VT), and the point and one-sided 95% C.I. estimation of VT recurrence-free probability. These numbers are defined at the exact time-point indicated, and do not necessarily correspond to the number of subjects followed with the follow-up windows. **Figure 1** provides the freedom from VT recurrence curve.

Freedom from VT recurrence following acute success was 67.5% at 6 months.

TABLE 7 Kaplan-Meier Data Including the Nominal Interval, Number of Subjects at Risk, Number of Subjects Censored, and Number of Events, Point and One-sided 95% Confidence Interval Estimation of Recurrence-Free Probability Using Peto Method (Acute Success Subjects, n = 171)

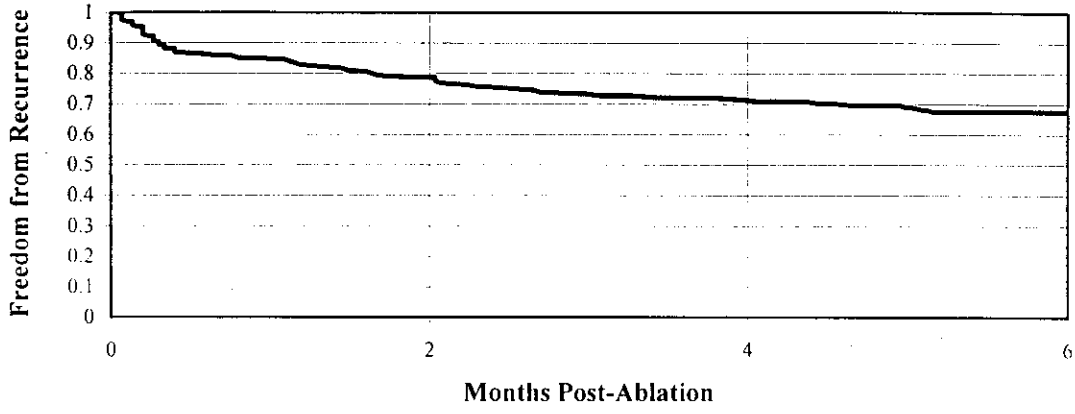
Nominal Interval	No. of Subjects at Risk[1]	Cumulative		Recurrence-Free Probability		
		No. of Subjects Censored	No. of Subjects with Events	Point Estimate	Peto Standard Error	One-sided 95% Lower Confidence Limit (Peto)
Day 0	171	0	0	1.0000	0.0000	1.0000
Discharge[2]	164	0	8	0.9529	0.0162	0.9262
3-weeks[3]	145	2	24	0.8586	0.0268	0.8145
1-month	143	3	25	0.8526	0.0274	0.8076
2-months	132	3	36	0.7870	0.0316	0.7350
3-months	124	3	45	0.7332	0.0343	0.6768
4-months	115	8	48	0.7148	0.0356	0.6563
5-months	107	14	52	0.6890	0.0379	0.6267
6-months	54	64	54	0.6754	0.0534	0.5876

[1] The number of subjects at risk is the number who did not have events or censoring before the time-point. If there are no events at a time-point, the total number of subjects in the analysis (171) equals the number at risk + the cumulative number censored + the cumulative number of events. This equation holds except at discharge, 3-months, 5-months, and 6-months. There are an event exactly at discharge, an event at 3-months, an event and a censoring at 5-months, and a censoring at 6-months.

[2] Subjects were discharged within 5 days from ablation. For the purpose of computation, discharge was defined as 5 days.

[3] For purposes of this table, 3 weeks = 21 days, 1 month = 30 days, 2 months = 61 days, 3 months = 91 days, 4 months = 122 days, 5 months = 152 days, and 6 months = 183 days.

FIGURE 1 Freedom from VT Recurrence
(Acute Procedural Success Subjects, n = 171)



Post hoc analysis of the treatment of Unmappable VT

Acute procedural success in subjects with only mappable induced VTs and in subjects with only unmappable induced VTs was 73.6% and 75.4%, respectively. Acute outcome for subjects with both mappable and unmappable VTs induced during the ablation procedure was 77.5%. Additionally, 67.3% of the 205 subjects who underwent an electrical stimulation protocol at the end of the procedure had no inducible VTs.
In addition, chronic success rates did not significantly differ among subjects with only mappable, only unmappable, or both mappable and unmappable VTs. Chronic success in subjects with only induced mappable VTs was 52.8% while in subjects with induced unmappable VT only, the success rate was 52.2%. Chronic success outcome for subjects with both mappable and unmappable VTs induced during the ablation procedure was 41.2%. Although the success rate was slightly lower for the combined mappable and unmappable group, this is not unexpected considering that multiple different VTs in a single subject have previously been associated with lower success outcomes.

Reduction in Post-ablation ICD therapies analyzed in selected subset of the study population

Data were available to calculate the reduction in ICD therapies after the ablation procedure for 130 subjects in the effectiveness analysis cohort. While not an endpoint for the study, a reduction in the number of VT therapies is also considered clinically relevant and has been used in literature to define "clinical success". The significant proportion of subjects with ICDs allowed for a comparison of the frequency of VT episodes before and after ablation (utilizing subjects as their own control). Of the effectiveness analysis cohort, 130 subjects were available for analysis through 6 months follow-up. There were

a total of 79.2% (103/130) subjects with evidence of reduction in the rate of VT episodes post-ablation, while in 20.8% (27/130), there was an increase in the rate of VT episodes post-ablation. In this study, all sustained VTs detected by ICD were considered, not just VTs that met the predefined endpoint as significant, thus representing a conservative evaluation of the endpoint. The absolute magnitude of the reduction in rate of ICD therapies was substantial for more than two thirds of this group. Approximately 70% (70.0%; 91/130) of the subjects had a documented reduction of more than 75% in ICD therapies during the follow-up period. For chronic failure subjects with available data, 55.4% (31/56) demonstrated a reduction in ICD therapies during the follow-up period.

C.4 Adverse Events

The protocol defined a major AE as any clinical event within seven days of the procedure that resulted in death, a life-threatening complication, or a persistent or significant disability/incapacity that requires inpatient hospitalization or prolongs hospitalization or requires intervention to prevent a permanent impairment of a body function or damage to a body structure. A minor AE was defined as any AE resulting in minimal transient impairment of a body function or damage to a body structure, or which does not require any intervention other than monitoring or events occurring more than 7 days after the procedure.

The study was not designed nor statistically powered to measure the long-term impact of ablation with the NaviStar ThermoCool catheter on cardiac function and mortality.

Major AEs

Of the 233 subjects in the safety analysis cohort, 53 major AEs were reported for 42 subjects. The overall percentage of subjects who experienced a major AE was 18%. Table 8 summarizes the major AEs.

Table 8. Major AEs observed within 7 Days Post-Ablation (Safety Analysis Cohort, n = 233)

Description	No. of Subjects	
Cardiovascular	**21**	**9.01%**
Incessant VT – Death	4	1.72%
Hypotension	2	< 1%
VT Storm – Death	2	< 1%
Recurrent VT	1	< 1%
Acute MI – Death	1	< 1%
Congestive Heart Failure	1	< 1%
Cardiogenic Shock - Death	1	< 1%
Atrial ICD Lead Malfunction	1	< 1%
VF Refractory to Monophasic Defibrillation	1	< 1%
Mitral Valve Regurgitation	1	< 1%
Mild Pericarditis	1	< 1%
Recurrent Atrial Flutter	1	< 1%
Mild Congestive Heart Failure	1	< 1%
Cardiac Ischemia	1	< 1%
Incessant VT	1	< 1%
Multiple VT	1	< 1%
Recurrent ICD Shocks	1	< 1%
Pulmonary	**8**	**3.43%**
Pulmonary Edema	4	1.72%
Transient Respiratory Insufficiency (no intubation required)	1	< 1%
Hypoxia - Volume Overload	1	< 1%
Respiratory Distress (required intubation)	1	< 1%
Pleural Effusion	1	< 1%
Peripheral Vascular	**13**	**5.58%**
Hematoma	4	1.72%
Pseudoaneurysm	3	1.29%
Groin Bleeding	2	< 1%
Hematoma/Hypotension	1	< 1%
Hematoma and Pseudoaneurysm	1	< 1%
Hematoma Post-cardiac Catheterization	1	< 1%
Bilateral Cephalic Vein Thrombosis	1	< 1%
Genitourinary	**3**	**1.29%**
Bleeding - Traumatic Foley Insertion	1	< 1%
Hematuria, Urinary Retention	1	< 1%
Hypergastric Pain Related to Urinary Retention	1	< 1%

Table 8. Major AEs observed within 7 Days Post-Ablation (Safety Analysis Cohort, n = 233)

Hematologic	**3**	**1.29%**
Anemia	1	< 1%
Heparin-Induced Thrombocytopenia and Disseminated Intravascular Coagulation	1	< 1%
Epistaxis secondary to over anticoagulation	1	< 1%
Systemic Infection	**1**	**< 1%**
Methicillin Resistant *S. aureus* Infection	1	< 1%
Neurovascular	**1**	**< 1%**
CVA	1	< 1%
Gastrointestinal	**1**	**< 1%**
Diverticulosis	1	< 1%
Musculoskeletal	**1**	**< 1%**
Atypical chest pain	1	< 1%

Note: 1. Fifty-three major AEs were reported for 42 subjects. 2. Some subjects are listed more than once in above table.

Preexisting Conditions as a Predictor of Major AEs

So that one may determine if a sub-population of subjects is at differential risk, preexisting cardiac function (LVEF) data were analyzed as a potential predictor of major AEs. Table 9 lists the LVEF measurements stratified by the presence or absence of major AEs. Survival status stratified by LVEF (%) is presented in Table 10.

Data showed that the subjects who had LVEF measurements ≤ 30% had a significantly higher major AE rate than the subjects with LVEF measurements > 30% (22.6% vs 10.0%, p = 0.0258, Fisher's Exact test). Of note, 62.7% (146/233) of the Safety Analysis Cohort had LVEF ≤ 30% and would therefore be considered at higher risk of morbidity than study subjects who had higher LVEF. A cut off of 30% LVEF was used to dichotomize the analysis.

TABLE 9. Major AEs by LVEF (%) (Safety Analysis Cohort, n = 233)

LVEF (%)	Total Number of Subjects	With Major AE* n (%)	Without Major AE n (%)
≤ 30	146	33 (22.6)	113 (77.4)
> 30	70	7 (10.0)	63 (90.0)
Not Reported	17	2 (11.8)	15 (88.2)

* p = 0.0258

The subjects who had LVEF measurements ≤ 30% had a significantly higher death rate than the subjects with LVEF measurements > 30% (24.7% vs 8.6%, p = 0.0055 Fisher's Exact test). This reflects a study population at high risk of mortality at study entrance secondary to their baseline cardiovascular condition. In the Safety Analysis Cohort, a total of 45 (45/233, 19.3%) deaths occurred.

TABLE 10. Survival Status by LVEF (%) (Safety Analysis Cohort, n = 233)

LVEF (%)	Total Number of Subjects	Deceased Subjects* n (%)	Subjects Alive n (%)
≤ 30	146	36 (24.7)	110 (75.3)
> 30	70	6 (8.6)	64 (91.4)
Not Reported	17	3 (17.6)	14 (82.4)

* p = 0.0055

The overall percentage of subjects who experienced a major AE was 18% (42/233) (one-sided upper confidence bound (UCB) of 23%). The safety protocol endpoints specified in the protocol was 22% (UCB of 30%). Therefore, this study population met the protocol safety endpoint for this clinical trial (see Table 11).

TABLE 11. Comparison of Safety Endpoint between NAVISTAR THERMOCOOL Study and Protocol Endpoint (Safety Analysis Cohort, n = 233)

Endpoint	Protocol Established Endpoints[1]		NAVISTAR THERMOCOOL Study	
	%	One-sided 95% Confidence Bound[2]	% (n)	One-sided 95% Confidence Bound[2]
Major Complications	22	30	18.0 (42/233)	23 (Upper Bound)

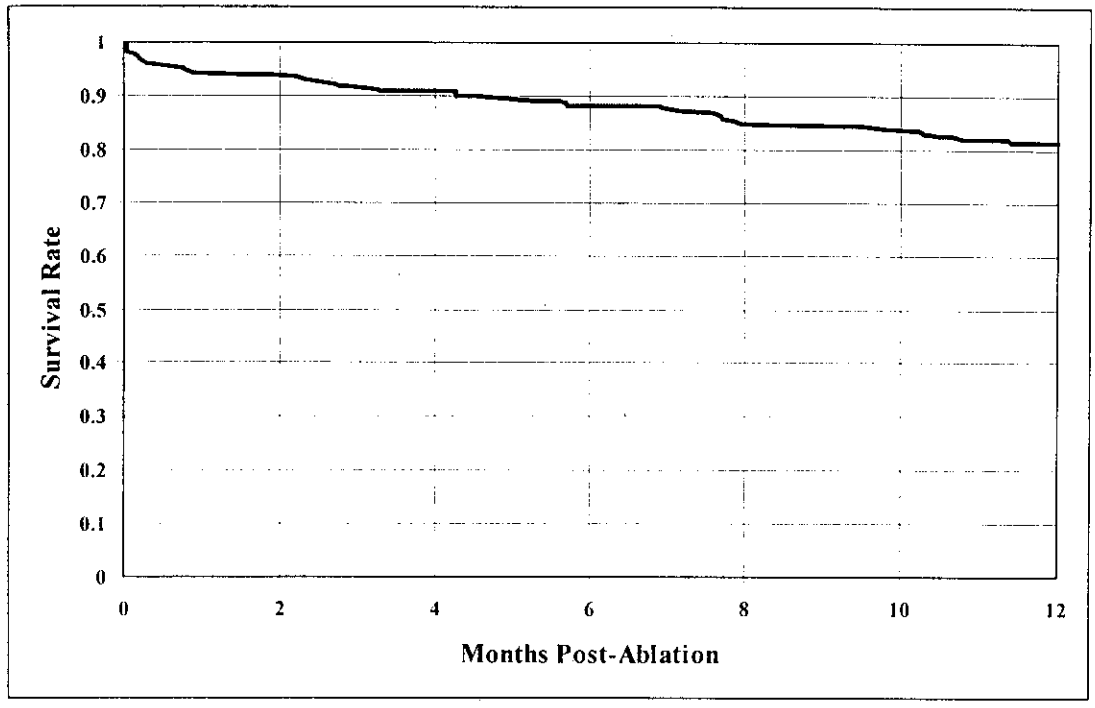
[1] Safety endpoint based on literature search.

[2] Exact binomial using a commercially-available software package.

A total of 45 deaths (45/233, 19.3%) occurred during the study. Eight subjects (8/233; 3.4%) expired within seven days of the ablation procedure, while an additional 37 (37/233; 15.9%) subjects expired more than 7 days post-procedure.

A Kaplan-Meier Analysis was performed to estimate survival rate after first ablation procedure. Standard errors were computed by the Peto method. Two hundred and thirty-three subjects were included in this analysis. The survival rate was 82 % at 12-months. **Figure 2** provides the survival curve over 12-months after first ablation procedure.

Figure 2. Survival Rate by Time Post-Ablation (Safety Analysis Cohort, n=233)



C.5 Analysis of study results compared to protocol endpoints

Table 12 summarizes the results of the open label single arm observational trial when compared to the protocol established for safety and effectiveness endpoints.

TABLE 12. Comparison of Endpoints Between NAVISTAR THERMOCOOL Study and Protocol Endpoint

Endpoint	Protocol Established Endpoints[1]		NAVISTAR THERMOCOOL Study	
	%	One-sided 95% Confidence Bound[2]	% (n)	One-sided 95% Confidence Bound[2]
Acute Procedural Success	75	65	75.7	71(Lower bound)
Chronic Success	50	40	47.3	41.7(Lower bound)
Procedural Safety	22	30	18.0 (42/233)	23 (Upper bound)

[1] Effectiveness endpoints established in the protocol are based on protocol endpoint; Safety endpoint based on literature search

[2] Exact binomial using a commercially-available software package.

In conclusion, the results demonstrate that the NAVISTAR THERMOCOOL catheter met the protocol endpoints for all safety and effectiveness endpoints.

XI. Conclusions Drawn from the Studies

This identical device was previously approved on November 05, 2004, for the treatment of Type I atrial flutter under P030031. Bench and animal testing submitted in support of that application demonstrate that the NAVISTAR THERMOCOOL catheter, STOCKERT 70 RF Generator, and accessories will maintain mechanical and electrical integrity and are biocompatible under the proposed indications for use.

The clinical study demonstrated that use of the NAVISTAR THERMOCOOL catheter for the treatment of ventricular tachycardia eliminates recurrent tachycardia in 47.3% of patients for up to six months. This device is associated with an 18% major complication rate within seven days of the procedure.

XII. Panel Recommendation

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation.

However, CDRH obtained feedback in the form of homework assignment from two members of the Circulatory System Devices Panel. These panel members reviewed the clinical study design and results. They were asked to assess whether the device presented a reasonable assurance of safety and effectiveness for the proposed indication. The panelists determined that the study design presented some challenges in that some differences existed between the patient population reported in the clinical study and the patient population described in the literature. However, they concluded that based on their knowledge of the clinical literature and their clinical expertise, that the populations were largely comparable and that the study cited reasonable point estimates for the control. Moreover, the panelists confirmed that the device presented a comparable risk of mortality to the risk understood for the patient population in the ablation of ventricular tachycardia. Finally, the panelists concluded that additional clinical data were needed to more fully characterize the acute and long-term safety and effectiveness of the device.

Both panelists recommended that the device be approved because they concluded that the data presented a reasonable assurance of safety and effectiveness for the treatment of VT with the NAVISTAR THERMOCOOL /Ablation Deflectable Tip catheter. This approval recommendation was based upon the condition that a postapproval study be conducted to determine the long-term effects of VT ablation.

XIII. CDRH Decision

CDRH evaluated the clinical study results, as documented in Section X. above for the indication of treatment of ventricular tachycardia. As described above, the device met both the safety and effectiveness endpoints of the study. The study showed that the device eliminated recurrent tachycardia in 47.3% of patients for up to six months and was associated with an 18% major complication rate within seven days of the procedure.

The study design presented some challenges in the evaluation of the above study results because of the incorporation of an historical control which complicated the statistical analysis needed for these data. As a result, CDRH primary relied upon a qualitative evaluation of the risk-benefit profile of the device.

Accordingly, based on its own assessment of the safety and effectiveness information and the recommendations made by the panelists from the Circulatory System Devices Panel, CDRH determined that the sponsor demonstrated reasonable assurance of safety and effectiveness for the above device and indications.

CDRH also determined that additional post-market evaluation of the device in the form of a condition of approval (CoA) study was required. Specifically, the objectives of the

CoA study are: (1) to confirm the point estimates of safety and effectiveness at additional centers to more completely characterize the generalizibily of the premarket clinical data to the broadened clinical population; (2) to prospectively measure 12-month mortality and determine whether a patient population with a low left ventricular ejection fraction (LVEF < 30%) is at greater risk of death; and (3) to determine the long-term effect of VT ablation on cardiac function.

CDRH inspection determined the manufacturing facility to be in compliance with the device Quality System Regulation (Par 820). CDRH issued an approval order on AUG 11 2006

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.