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PMA # P030031/S11

BIOSENSE WEBSTER
NAVISTAR® THERMOCOOL® Catheter
for the Radiofrequency Ablation of Symptomatic Paroxysmal Atrial Fibrillation

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Sponsor Executive Summary

THERMOCOOL® Catheters for the Treatment of Drug Refractory Symptomatic Paroxysmal Atrial Fibrillation (P030031/S11)

EXECUTIVE SUMMARY

REGULATORY CONTEXT

Biosense Webster has conducted a prospective clinical study of the NAVISTAR® THERMOCOOL® Diagnostic/Ablation Deflectable Tip Catheter for the treatment of drug refractory symptomatic paroxysmal atrial fibrillation. The basic questions for the Panel are whether the study results support revised indications for use, to include the treatment of drug refractory symptomatic paroxysmal atrial fibrillation, and consequently, whether the clinical study results should be added to the catheter labeling.

BACKGROUND

- The approval under consideration by the Circulatory System Devices Advisory Panel is a PMA Supplement for a new indication for use, drug refractory symptomatic paroxysmal atrial fibrillation.
- The THERMOCOOL Catheters are open-irrigated radiofrequency (RF) ablation catheters, used in conjunction with the STOCKERT™ 70 RF generator, the COOLFLOW™ Irrigation Pump and Tubing Set, and catheter interface cables. THERMOCOOL catheters are currently marketed for the following FDA-approved indications: Type 1 atrial flutter (NAVISTAR and CELSIUS catheters) and ventricular tachycardia (NAVISTAR catheters).
- The tip electrode which delivers RF current to the ablation site incorporates several small holes through which normal saline is passed for irrigation and cooling purposes. This unique design feature allows for the creation of larger lesions, as well as a reduced risk of charring and coagulation on the tip electrode.
- The design, materials, and technological characteristics of the catheters subject to this PMA supplement are identical to the catheters previously approved under P030031 and P040036.
- THERMOCOOL Catheters are used worldwide to treat arrhythmias. They have been available outside the US since 1998, are marketed in 39 countries, and have an excellent safety profile. Approximately 250,000 catheters have been distributed worldwide, including about 70,000 in the US since commercialization in 2005.
- FDA has granted this PMA Supplement expedited review based upon the belief that "ablation catheters may provide a novel approach for the treatment of atrial fibrillation, which present a risk of serious morbidity."[1]

PUBLIC HEALTH NEED

- It is estimated that 2.3 – 5.6 million US adults suffer from chronic permanent or paroxysmal atrial fibrillation (AF),[2] representing anywhere from 0.4% to 1.0% of the general population.[3]

- AF is a debilitating disease, increasing the risk of ischemic stroke from 2 to 7 times that of individuals without AF. Symptomatic AF is associated with higher medical costs and increased morbidity and risk of death,[4] and it has been shown to reduce quality of life.[5]
- Pharmacological treatment is considered the primary therapeutic option, despite evidence of variable efficacy of antiarrhythmic drug (AAD) therapy, which has a likelihood of AF recurrence (within 6-12 months) of at least 50% for most drugs.[6]
- Surgical interventions also have their limitations, including the associated risk of death (>1%), permanent pacing (with right side lesions), recurrent bleeding requiring additional surgery, impaired atrial transport functions, and scar-related atrial arrhythmias (atrial flutter). Implantable atrial defibrillators have been shown to treat AF, but the required energy for this purpose is not well-tolerated by most patients.
- There is no catheter currently approved by FDA to treat atrial fibrillation. Increased off-label use of catheters for this indication has grown substantially during the course of the NAVISTAR THERMOCOOL catheter study.

CURRENT PMA-APPROVED INDICATIONS FOR USE

- The Biosense Webster THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter and related accessory devices are indicated for catheter-based cardiac electrophysiological mapping (stimulating and recording) and, when used with the STOCKERT 70 RF Generator, for the treatment of:

  a) Type I atrial flutter in patients age 18 or older (NAVISTAR and CELSIUS; P030031)
  b) Recurrent drug/device refractory sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction (MI) in adults (NAVISTAR; P040036)

  The NAVISTAR THERMOCOOL Diagnostic/Ablation Deflectable Tip Catheter provides location information when used with the CARTO® EP Navigation System.

PROPOSED ADDITION TO CURRENT INDICATIONS FOR USE

c) Drug refractory symptomatic paroxysmal atrial fibrillation (NAVISTAR and CELSIUS)

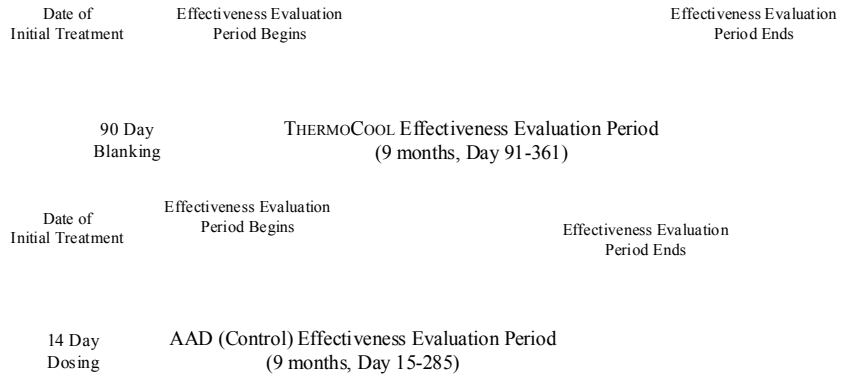
RELEVANT REGULATORY AND STUDY MILESTONES

PIVOTAL TRIAL DESIGN

Study Design

- The study was a prospective, randomized (2:1), active control, unblinded, multicenter pivotal clinical investigation conducted at 19 sites.
- The study was designed to test the hypothesis that AF ablation with the NAVISTAR THERMOCOOL Catheter has superior effectiveness compared to optimal medical management with anti-arrhythmic drugs (AAD), with acceptable safety. Subjects with symptomatic paroxysmal atrial fibrillation (PAF), refractory or intolerant to antiarrhythmic drug therapy, were randomized to THERMOCOOL ablation or AAD therapy and evaluated for recurrence over a nine-month evaluation period.

Figure ES1 - Illustration of Treatment and Effectiveness Periods



- This trial constitutes valid scientific evidence regarding the safety and effectiveness of the THERMOCOOL Catheter for the treatment of atrial fibrillation.

- The protocol closely followed the recommendations in the FDA Guidance document, "Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation (January 2004)".[7]
- ACC 2001 "Guidelines for Management of Subjects with Atrial Fibrillation" was utilized for recommending the appropriate dosing for the AAD (Control) group, as they were the operative guidelines at the time of design and initiation of the trial.[8]

- The study was the subject of successful FDA Bioresearch Monitoring Office of Compliance (BiMo) audits at the two highest enrolling sites, as well as of the Sponsor. No Form 483 inspectional observations were cited in any of these three inspections. All sites were frequently monitored by Sponsor representatives for quality control and to provide rigorous oversight of the investigation.

Primary Effectiveness Endpoint

- The primary effectiveness endpoint was the chronic success rate, defined as freedom from symptomatic AF based on electrocardiographic data and no changes in AAD regimen during the nine month effectiveness evaluation period, which was defined as day 91-361 for the THERMOCOOL group (following a three-month blanking period) and day 15-285 for the AAD (control) group (following a 14 day dosing period), as shown in Figure ES1.

- Symptomatic AF recurrence was assessed via transtelephonic monitoring (TTM). TTMs were collected, analyzed and adjudicated using a 3-step review process that helped to ensure the highest possible rigor for detection of AF recurrence. TTM compliance was excellent in the study (88.8% ±16.0).

Primary Safety Endpoint

- The protocol-specified primary safety endpoint was the incidence of specific early-onset (within 7 days of ablation procedure) adverse events (referred to as 'primary AEs') for subjects undergoing an ablation procedure with the THERMOCOOL catheter. The pre-determined safety endpoint of 7% (upper confidence bound of 16.0%) was based on a comprehensive literature review of complication rates associated with left- and right-sided radiofrequency ablation of atrial arrhythmias.

Challenges to Enrollment

- Biosense Webster encountered unprecedented challenges to timely enrollment for completion of this study, enrolling only 2.5% of screened subjects over 2 years. These extreme enrollment challenges were discussed in detail during the *FDA Circulatory System Device Panel: Clinical Trial Designs for Atrial Fibrillation Treatment Devices* held in September 2007.

- Enrollment challenges were resolved through the following actions, developed in collaboration with FDA:
  - The inclusion criteria were modified to include patients in whom calcium channel blocking or beta receptor blocking agents failed to control AF.
  - Four high-volume AF ablation sites outside of the US were added to the trial. All non-US sites complied with the study protocol, Biosense Webster applicable SOPs and with 21CFR 812 and 21CFR 814.15 regulations.
  - Approximately 5,500 patients were screened and 167 subjects enrolled prior to meeting the early stopping criteria.
  - A Bayesian statistical analysis plan was implemented to reduce the total number of patients needed to achieve a valid test of the study hypothesis.

Interim Statistical Analysis

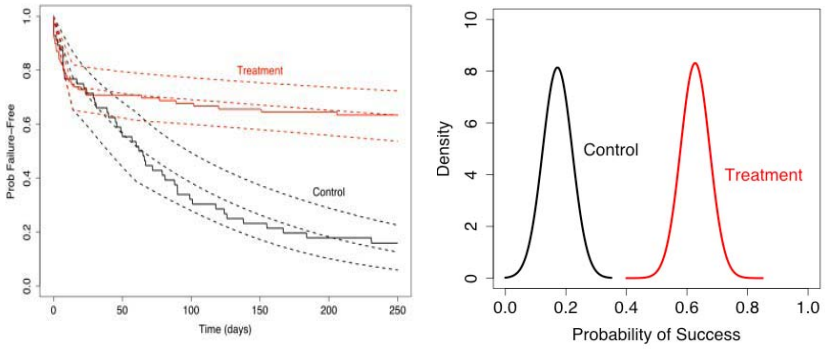
- An interim analysis was conducted in accordance with the approved IDE protocol (Version 12.2). This analysis was performed by an independent consulting group at the request of FDA. The interim analysis determined that there was sufficient statistical evidence for meeting the safety and effectiveness endpoints to stop enrollment at the current sample size and declare the trial an early success.
- Results from the interim analysis (October 2007) were comparable to the updated PMA supplement dataset analysis (June 2008).

NAVISTAR THERMOCOOL CLINICAL STUDY: EFFECTIVENESS RESULTS

Primary Effectiveness Endpoint

- The study met its primary effectiveness endpoint, namely superior effectiveness of AF ablation with the THERMOCOOL catheter compared to AAD treatment, with a 95% probability that the treatment difference is 31% - 58% in favor of THERMOCOOL catheter ablation. Using Bayesian methodology, the posterior mean probability of success is 0.627 ± 0.048 for the THERMOCOOL group and 0.172 ± 0.049 for the AAD (Control) group. The 95% credible interval for the difference between the THERMOCOOL and AAD (Control) probabilities of success is 0.313 to 0.584, with a median difference of 0.457.

Figure ES-2 EFFECTIVENESS OF TREATMENT GROUPS



- **Figure ES-2** shows the Bayesian analysis of the probability of freedom from chronic effectiveness failure (left) and the posterior distributions of the probabilities of nine-month failure-free treatment success (right) for each treatment group.
- The effectiveness evaluation in this study utilized a conservative definition for the chronic effectiveness endpoint, in which more than freedom from documented symptomatic AF recurrence was required to be adjudicated a chronic success.
  - For the THERMOCOOL group, any of the following resulted in the subject being adjudicated as a chronic effectiveness failure, irrespective of symptomatic AF recurrence: AAD failure (the

addition/increased dose of AADs, including Class I and Class III antiarrhythmic drugs, beta blockers, and ACE inhibitors), repeat ablation after day 80, or acute procedural failure.

- It is important to note that AV nodal blocking agents were formally considered AADs when prescribed for AF, even though recent ACC/AHA/ESC guidelines have clarified that their principal role in the treatment of atrial fibrillation is to achieve ventricular rate control, and not for AF prevention. This adjudication rule was added at the time the protocol was amended to permit enrollment of subjects who had only failed AV nodal agents as Class II/IV agents may affect symptoms (e.g., palpitations). In fact, 9% (9/103) of the THERMOCOOL subjects were adjudicated as chronic failures solely due to use of an AV nodal blocking agent/ACE inhibitor, or late repeat ablation in the blanking period, in the absence of symptomatic AF recurrence.

Additional Effectiveness Analyses

- While not a pre-specified analysis, THERMOCOOL catheter ablation subjects had a 72% likelihood of freedom from any observed AF recurrence, symptomatic or asymptomatic, after 9 months of effectiveness evaluation vs. 21% for the AAD (Control) group. While the monitoring regimen for recurrence was not continuous, this nonetheless demonstrates that THERMOCOOL catheter ablation reduced AF recurrence and did not simply render subsequent episodes asymptomatic.

- As was allowed by the study protocol, 16% (26/167) of patients in the trial were enrolled due to failure of a rate control drug (AV nodal blocking agent), rather than a Class I or III drug. There was no substantial difference observed between those failing Class I or III vs. those failing only Class II or IV at baseline in chronic success results within either treatment arm.

- Eleven (11) subjects in the AAD (Control) group were enrolled and placed on the same or higher dose of a previously failed drug, rather than the per protocol new antiarrhythmic drug, due to regional limitations in availability of protocol-specified AADs. Although these subjects had a comparable failure rate as the remaining 45 control subjects prescribed a new AAD, a sensitivity analysis was performed removing these 11 subjects. In addition, 4 control subjects received less than the protocol-specified AAD dosage (including 1 of the aforementioned 11). Bayesian multiple imputation analysis was conducted for these 14 subjects. The results of these analyses confirmed the superiority of the THERMOCOOL group vs. control with respect to the primary effectiveness endpoint.

- The analysis of the primary effectiveness endpoint revealed site variations in outcomes, modes of failure, and medical management. In particular, the highest enrolling site was examined carefully, due to an unusually high chronic success rate (100%) for the THERMOCOOL group.
  - Poolability across investigational sites is justified by the design of the study, based on the uniform study protocol, monitoring of study compliance at all sites, and identical data collection methods and instruments.
  - To explore the site differences, three stratifications of the effectiveness results, in addition to randomization group, are provided (US vs. non-US, high vs. low-to-medium enrolling sites, highest enrolling vs. remaining sites) for the primary chronic effectiveness endpoint, for freedom from symptomatic AF recurrence and for freedom from any AF recurrence. Throughout these many analyses, the direction of the treatment effect, though varying in magnitude, remains consistently in favor of the THERMOCOOL catheter vs. AAD therapy.
  - Additional Bayesian statistical analyses were conducted to evaluate the robustness of the US-site results. The overall conclusion was that even if one heavily discounts the non-US sites, the result is still compellingly in favor of the THERMOCOOL Group.
  - Therefore, Biosense Webster is confident that any site differences observed do not undermine the overall conclusions of the study.

- Information in the published literature, including other randomized clinical trials,[9,10] as well as a comprehensive, systematic literature review and 2 resulting meta-analyses[11] corroborate the effectiveness results observed in this clinical trial, namely that RF has superior effectiveness to AADs in the treatment of AF. In addition, the 62.7% (Bayesian) posterior mean success rate for the THERMOCOOL group achieved in this study, using a conservative definition, is consistent with the ranges of success reported in the literature.

Secondary Endpoint – Quality of Life

- THERMOCOOL subjects demonstrated approximately 50% improvement (on average) in quality of life from baseline in terms of symptom frequency and severity. This contrasts with the absence of improvement in the AAD (Control) group at the 3-month and 6-month visits, though some improvement was observed at the 9-month visit in the few remaining control subjects that had not undergone catheter ablation, as permitted by the protocol following AAD effectiveness failure. Clinically meaningful improvements were also measured with the SF-36 instrument for the THERMOCOOL subjects. These results together further substantiate the clinical benefit of THERMOCOOL catheter ablation for treatment of AF.

NAVISTAR THERMOCOOL CLINICAL STUDY: SAFETY RESULTS

- The results for the primary safety endpoint are presented in the table below.

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
% of Subjects with Primary AEs	7.0	10.8
One-sided 95% Confidence Bound*	16.0	16.1

* Exact binomial using a commercially available software package.

- All 15 subjects observed with a primary AE experienced either improvement or complete resolution of the adverse event. One subject with pericarditis was improved at the time of hospital discharge. No primary AE was adjudicated as device-related.

- Additional safety analyses were performed to characterize the early-onset (≤ 90 days) adverse events by severity, comparing the AAD (Control) group and THERMOCOOL group subjects. It is often challenging to compare adverse events between such different treatment modalities, and the types of adverse events were different between groups, as would be expected. Nevertheless, an analysis of the number of early onset serious adverse events (SAEs) showed that the rate was significantly lower in the THERMOCOOL (18.4%; 19/103) vs. AAD (Control) group (35.1%; 20/57; p= 0.022; unpowered secondary endpoint without multiplicity adjustment).

- No severe adverse events such as death, atrio-esophageal fistula, stroke, cerebrovascular accident, atrial perforation, myocardial infarction, thromboembolism, TIA, diaphragmatic paralysis,

pneumothorax, heart block or severe pulmonary vein stenosis occurred within 7 days of the ablation procedure.

- No pulmonary vein (PV) stenosis, defined in the study protocol as ≥70% reduction in the diameter of the pulmonary vein from baseline, has been reported to date in this study. The PV stenosis rates observed in this clinical trial compare favorably to the results found in the literature, in which the overall incidence of symptomatic or asymptomatic PV stenosis (≥70% reduction in PV diameter) was 1.6%.
- Overall, the primary and secondary safety analyses performed to date represent an excellent safety profile for THERMOCOOL catheter ablation in this AF population, with THERMOCOOL group subjects experiencing approximately one-half the serious adverse events of their AAD (Control) arm counterparts. The study safety results are further corroborated by the published literature. [11]

ADDITIONAL DATA

- A post-approval study has been proposed by Biosense Webster to provide long-term safety and effectiveness data for the NAVISTAR THERMOCOOL catheter for the treatment of paroxysmal atrial fibrillation in a post-market setting. This study will gather 5 year data prospectively at selected centers in the US and will be used to confirm that the study results may be generalized to actual clinical practice, as well as collect additional safety information on the procedure.

CONCLUSIONS

- The clinical trial data presented in this PMA represent the most rigorously conducted and thoroughly vetted randomized, controlled multicenter trial of catheter ablation for treatment of AF completed to date.
- The collaboration between FDA and Biosense Webster achieved a rigorous but feasible randomized, controlled study that provides the valid scientific evidence needed for a determination of safety and effectiveness.
- The results of the prospectively planned analyses demonstrate superiority for the primary chronic effectiveness endpoint with an acceptable safety profile.
  - Subjects randomized to THERMOCOOL catheter ablation had a superior chronic effectiveness outcome compared to conventional AAD therapy throughout a nine-month evaluation period. The THERMOCOOL group demonstrated a (Bayesian) posterior mean success rate of 62.7 ± 4.8% compared with 17.2 ± 4.9% for the AAD (control) group.
  - Clinically meaningful improvement in Quality of Life was shown in the THERMOCOOL group compared to the control group.
  - The THERMOCOOL group experienced only half the incidence of serious adverse events of the control group.
- Additionally, THERMOCOOL catheter ablation subjects were more likely to be free from any documented AF recurrence, symptomatic or asymptomatic, at the end of the evaluation period than the control group.
- While the study was conducted with the NAVISTAR version of the THERMOCOOL catheter, the results may be extrapolated to the CELSIUS version. The AF ablation procedure used in the study is

anatomically based, beginning with pulmonary vein isolation and adding linear lesions as needed. This technique does not rely solely on the CARTO maps enabled by the NAVISTAR sensor, the only difference between the NAVISTAR and CELSIUS versions. The precedent for approving the CELSIUS version based on a NAVISTAR study for an anatomically based procedure was established by the THERMOCOOL approval for atrial flutter (P030031) and the NAVISTAR DS catheter as well (P010068).

- Effective treatment of AF represents a significant unmet clinical need. Use of radiofrequency ablation of atrial fibrillation has grown so dramatically that it is now recognized as second line therapy by the major electrophysiology professional societies and a standard of care in treatment guidelines.[12] However, no ablation catheter has been market-approved for treatment of AF in the US.
- Public interest is best served by communicating the results of the NAVISTAR THERMOCOOL AF study, and AF ablation risks and benefits, in FDA-approved device labeling. Furthermore, adding symptomatic atrial fibrillation to the approved indications for use will permit company-sponsored training specific to AF treatment parameters and help assure that physicians use the commercially-available THERMOCOOL ablation catheters to treat AF in the most safe and effective manner.
- Therefore, we conclude that the probable therapeutic benefits associated with the use of the THERMOCOOL catheters for ablation therapy of paroxysmal AF outweigh the probable risks, when used in accordance with the proposed instructions for use.

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Tab 5

Draft SSED

2 Summary of Safety and Effectiveness Data

2.1 General Information

Device Generic Name:

Irrigated Diagnostic/Ablation Catheter and Accessories

Device Trade Names:

NaviStar ThermoCool Deflectable Diagnostic/Ablation Catheter
Celsius ThermoCool Deflectable Diagnostic/Ablation Catheter
NaviStar RMT ThermoCool Diagnostic/Ablation Steerable Tip Catheter
EZ Steer ThermoCool Nav Bi-directional Catheter
EZ Steer ThermoCool Bi-directional 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:

P030031 / S_

Date of Notice of Approval to Applicant:

Table 5 provides device and accessory model numbers.

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Table 5: Device and Accessory Model Numbers

Family Name	Mfg. Part Number	Catalog Number	Curve	Temperature Sensor
NaviStar ThermoCool Catheters	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
Celsius ThermoCool Catheters	D-1189-01	D17TCBLRT	B	Thermocouple 3.5mm
	D-1189-02	D17TCDLRT	D	Thermocouple 3.5mm
	D-1189-03	D17TCFLRT	F	Thermocouple 3.5mm
	D-1189-04	D17TCJLRT	J	Thermocouple 3.5mm
	D-1192-01	D17T-BL-RT	B	Thermistor 3.5mm
	D-1192-02	D17T-DL-RT	D	Thermistor 3.5mm
	D-1192-03	D17T-FL-RT	F	Thermistor 3.5mm
NaviStar RMT ThermoCool Catheters	D-1266-02	NR7TCSIYU	NA	Thermocouple 3.5mm
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
EZ Steer ThermoCool Catheter	D-1294-01	BD175TCDDRT	D-D	Thermocouple 3.5mm
	D-1294-02	BD175TCFFRT	F-F	Thermocouple 3.5mm
	D-1294-03	BD175TCJJRT	J-J	Thermocouple 3.5mm
	D-1294-04	BD175TCFJRT	F-J	Thermocouple 3.5mm
	D-1294-05	BD175TCDFRT	D-F	Thermocouple 3.5mm
	D-1295-01	BD175TDDRT	D-D	Thermistor 3.5mm
	D-1295-02	BD175TFFRT	F-F	Thermistor 3.5mm
	D-1295-03	BD175TJJRT	J-J	Thermistor 3.5mm
	D-1295-04	BD175TFJRT	F-J	Thermistor 3.5mm
	D-1295-05	BD175TDFRT	D-F	Thermistor 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	M-5385-59			
Catheter interface cables	D-1195:	C5-MHNAVMH-S		
	D-1170:	C6-MRMSTKDTC-S C6-MR10MSTK-S C10-MR10MSTK-S		

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2.2 Indications for Use

NaviStar ThermoCool Catheters

The Biosense Webster NaviStar ThermoCool Diagnostic/Ablation Deflectable Tip Catheters and related accessory devices 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 symptomatic paroxysmal atrial fibrillation.

The NaviStar ThermoCool Catheter provides location information when used with the Carto EP Navigation System.

Celsius ThermoCool Catheters

The Biosense Webster Celsius ThermoCool Diagnostic/Ablation Deflectable Tip Catheters and related accessory devices 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) Drug refractory symptomatic paroxysmal atrial fibrillation.

NaviStar RMT ThermoCool Catheters

The Biosense Webster NaviStar RMT ThermoCool Diagnostic/Ablation Steerable Tip Catheters and related accessory devices 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 symptomatic paroxysmal atrial fibrillation.

The NaviStar RMT ThermoCool Catheter provides location information when used with the Carto RMT EP Navigation System. NaviStar RMT ThermoCool Catheter is for use only with the Stereotaxis Magnetic Navigation System (MNS).

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NOTE: Compatibility with the Sterotaxis Cardiodrive has not been determined.

EZ Steer ThermoCool Catheter

The Biosense Webster EZ Steer ThermoCool Diagnostic/Ablation Deflectable Tip Catheters and related accessories are indicated for use in catheter-based cardiac electrophysiological mapping (stimulating and recording) and, when used with the Stockert 70 RF Generator, for the treatment of:

a) Type I atrial flutter in patients age 18 or older.
b) Drug refractory symptomatic paroxysmal atrial fibrillation.

EZ Steer ThermoCool NAV Catheters

The Biosense Webster EZ Steer ThermoCool NAV Diagnostic/Ablation Deflectable Tip Catheter and related accessory devices are indicated for catheter-based cardiac electrophysiological mapping (stimulating and recording) and, when used with the Stockert 70 RF 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 symptomatic paroxysmal atrial fibrillation.

The EZ Steer ThermoCool NAV Diagnostic/Ablation Deflectable Tip Catheter provides location information when used with the Carto EP Navigation System.

2.3 Contraindications

The contraindications 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.

2.4 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.

2.5 Device Description

With reference to the model numbers indicated in Table 1 for Device and Accessory Model Numbers, the device components that are the subject of this PMA Supplement are the following:

A. NaviStar ThermoCool Catheters;
B. Celsius ThermoCool Catheters;
C. NaviStar RMT ThermoCool Catheters;
D. EZ Steer ThermoCool Catheters;
E. EZ Steer ThermoCool NAV Catheters

These devices are used in conjunction with the following devices:

F. Stockert 70 RF generator;
G. CoolFlow Pump and Tubing Set; and
H. 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 other pre-market notifications.
- Carto EP Navigation System – originally cleared under K954395 and other pre-market notifications.

For additional aid in navigation, the NaviStar RMT ThermoCool Catheter may be used with the following legally marketed device:
- Carto RMT EP Navigation System– originally cleared under K042681 and other pre-market notifications.
- RefStar RMT Reference Devices – originally cleared under K042998.

A. 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 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. Celsius ThermoCool Catheters

The Biosense Webster Celsius ThermoCool Catheter is a 7 F multi-electrode luminal catheter with a deflectable tip designed to transmit radiofrequency (RF) current to the catheter tip electrode for ablation purposes. It is used in conjunction with a radiofrequency generator and a dispersive pad (indifferent electrode).

The catheter has a high-torque shaft with a 3.5 mm deflectable tip and incorporates either a thermocouple or thermistor temperature sensor that is embedded in the tip electrode. This catheter does not have a magnetic location sensor embedded in the tip electrode, and, therefore, is not intended for use with the Carto EP Navigation System. It is, however, otherwise similar to the NaviStar ThermoCool Catheter.

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 (2-4.4”). Four curve types designated “B”, “D”, “F”, and “J” are available. 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.

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, normal saline is passed through the 0.030” diameter lumen of the catheter and through the tip electrode to irrigate and cool the ablation site. 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.

C. NaviStar RMT ThermoCool Catheters

The Biosense Webster NaviStar RMT ThermoCool Diagnostic/Ablation Steerable Tip Catheter is a luminal catheter with a steerable 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 measures 8F. For electrophysiology mapping, the catheter is used with the Carto RMT EP Navigation System (a magnetic field location technology), the Stereotaxis Magnetic Navigation System (MNS), and a RefStar RMT with QwikPatch External Reference Patch. For ablation, the catheter is used in conjunction with a RF generator and a dispersive pad (indifferent electrode).

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The catheter has a nylon shaft with a steerable tip section containing an array of platinum electrodes. 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 catheter incorporates a thermocouple temperature sensor that is embedded in the 3.5mm tip electrode. Tip deflection is controlled by the interaction of magnets placed in the catheter tip and shaft, and the magnetic field created by the external Stereotaxis MNS.

At the proximal end of the catheter, a saline input port with a standard luer fitting terminates from the open lumen. This saline port serves to permit the injection of normal saline to irrigate the tip electrode. During ablation, heparinized normal saline is passed through the irrigation 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.

This catheter features a magnetic location sensor embedded in the tip electrode that transmits location information to the Carto RMT EP Navigation System.

The catheter interfaces with standard recording equipment and the Stockert 70 RF Generator via accessory extension cables with the appropriate connectors.

D. EZ Steer ThermoCool NAV Catheters

The Biosense Webster EZ Steer ThermoCool NAV Catheters are multi-electrode luminal catheters 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 catheters have 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.

E. EZ Steer ThermoCool Catheters

The EZ Steer ThermoCool Catheter is identical to the EZ Steer ThermoCool NAV Catheter with the following two exceptions:

- The EZ Steer ThermoCool Catheter does not have a magnetic location sensor and related electronics and connector. Therefore it is not intended for use with the Carto EP Navigation System.
- The EZ Steer ThermoCool Catheter is available with either a thermocouple or thermistor temperature sensor while the EZ Steer ThermoCool NAV Catheter is only available with a thermocouple temperature sensor.

F. 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.

G. 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 in 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.

H. 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.

2.6 Alternative Practices or 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

2.7 Marketing History

Below is a listing of countries followed by a superscript of the numbers 1, 2 and 3. Each number represents a catheter name as follows:

1 = NaviStar ThermoCool Catheter
2 = Celsius ThermoCool Catheter
3 = NaviStar RMT ThermoCool Catheter

Each country name is followed by a superscript, which indicates that the corresponding catheter is marketed in that country.

- European Union[1,2,3]
- Canada[1,2,3]
- Australia[1,2]
- New Zealand[1,2]
- China[1,2]
- Hong Kong[1,2,3]
- Korea[1,2]
- Taiwan[1,2]
- Singapore[1]
- Croatia[1,2]
- Indonesia[1,2]
- Romania [1,2]
- Ukraine[1,2]
- Philppines [1,2]
- Nicaragua[12,]
- Honduras[1,2,]
- Dominican Republic[1,2]
- Costa Rica[1,2]
- Trinidad[1,2]
- Pakistan[1,2]
- Pakistan[1,2]
- India[1,2]
- Malaysia[1,2]
- Sri Lanka[1]
- Argentina[1,2]
- Brazil[1,2]
- Mexico[1,2]
- Colombia[1,2]
- Bulgaria[1,2]
- Egypt[1,2]
- Kazakhstan[1,2]
- Russia[1,2]
- Peru[1,2]
- S. Africa[1,2]
- Panama[1,2]
- Jamaica[1,2]
- El Salvador[1,2]
- Chile[1,2]
- Tobago[1,2]

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The EZ Steer ThermoCool and EZ Steer ThermoCool NAV Catheters have not yet been marketed anywhere in the world as the development of these catheters has just been completed. Regulatory approvals and world-wide launch of these catheters are pending.

There are no countries from which the NaviStar ThermoCool catheter, Celsius ThermoCool Catheter, EZ Steer ThermoCool Catheter or EZ Steer ThermoCool NAV Catheter have been withdrawn from marketing for any reason related to safety or effectiveness. The NaviStar RMT ThermoCool catheter was recalled February 28, 2008; PMA Supplement P030031/S10 was submitted on July 11, 2008 for a design change to resolve the issues.

2.8 Potential Adverse Effects of the Device on Health

Potential adverse events (AEs) associated with cardiac ablation for treatment of symptomatic paroxysmal atrial fibrillation include the following:

- 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 actual AEs observed during the clinical study (within 7 days post-ablation), please refer to Tables 3.6.5.1.1 and 3.6.5.1.2 of the clinical report.

2.9 Summary of Pre-Clinical Studies

Biosense Webster 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.

2.10 Summary of Clinical Studies

The clinical testing described below was performed with the NaviStar ThermoCool catheter.

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 AF based on electrocardiographic data and no changes in AAD regimen during comparable evaluation periods for the THERMOCOOL and AAD (Control) groups. 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 1 – Subject Accountability and Disposition

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

	THERMOCOOL n/N (%)	**AAD (Control)** n/N (%)	**Total** n/N (%)	**p-value**
	N = 106	**N = 61**	**N =167**	
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	

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.

C. Results

C.1 - Procedural Data

Tables 3 and 4 present the procedural data.

Table 3: 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 4: 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 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. Table 5

summarizes the lesion sets applied to THERMOCOOL group subjects during the index ablation procedures.

Table 5: 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)

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

C.2 - Acute Procedural Success

Acute procedural success results are presented in Table 6.

Table 6: 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 ---- tual certainty that the final posterior probability would have been larger than ---- (protocol specified level needed for success).

Chronic success results are described in Table 7.

Table 7: 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 survival curves for each of the treatment groups.

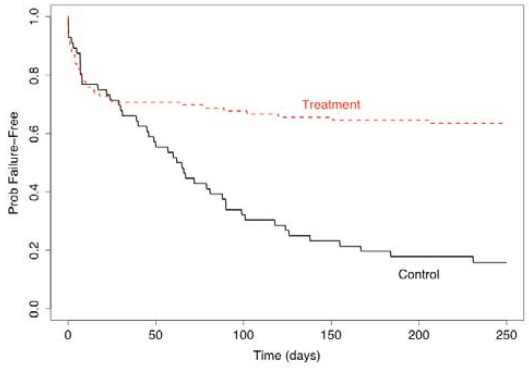

FIGURE 1 Kaplan-Meier Analysis – Probability of Freedom from Chronic Effectiveness Failure For Each Treatment Group*

The June 2008 dataset status of each of the 159 subjects is reported in Table 8. 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 8: 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

Figure R 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.

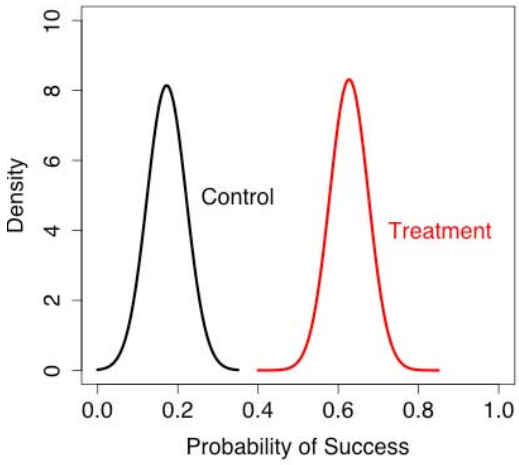

FIGURE R 2: The Posterior Distributions of the Probabilities of 9-month Failure-Free Treatment Success for Each Treatment Group

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 9 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

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 slightly 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 9: 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 10 summarizes the primary AEs.

Table 10: 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 11 compares the incidence of early onset serious adverse events between the two treatment groups occurring within the first 90 days of initial therapy.

TABLE 11 Percentage of Early Onset 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 the NAVISTAR THERMOCOOL catheter met the protocol specified effectiveness endpoint with an acceptable safety profile.

2.11 Conclusions Drawn from the 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.

The IDE study ---- subject of this PMA Supplement, demonstrated that use of the NaviStar ThermoCool catheter for the treatment of drug refractory symptomatic paroxysmal atrial fibrillation is superior when compared to the AAD (Control) group. 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.

2.12 Gender Variances with Atrial Fibrillation

Both genders were well represented in the study conducted under IDE ---- (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 (LVEF 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 Afib is equal or greater than that of men[28]. 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[29]. It is likely this this is an explanation for the enrollment ratio for study IDE ---- being slightly less than population based prevalence estimates have indicated.

BWI 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

[28] 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.
[29] 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.

therapy were male.[30] The number of patients included in the 16 reports ranged from 20-2374 patients with a total of 3907. Female patients represented 27.6% weighted average (1027/3907) of the patient population. Factors that affect the precentage of females represented in published literature include the following:

- The prevalence of AF in men is somewhat greater[31]
- Women are referred for AF ablation later with a more complex clinical pre-operative presentation[32]

Table 6 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 ---- As demonstrated from the data in the table, the percentage of female subjects enrolled in IDE study ---- 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 conclusion, the IDE study ---- 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.

[30] 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.
[31] 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.
[32] 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.

Table 6: Data from Pubished 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 on the following page.

Biosense Webster, Inc.
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2.13 Pediatric Medical Device Safety and Improvement

2.13.1 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.

2.13.2 The 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.

2.14 Panel Recommendation

2.15 CDRH Decision

2.16 Approval Specifications

Tab 6

Draft IFU

*Note: Each of the ThermoCool variants has a separate IFU. For the purposes of the Panel Pack, only the NaviStar ThermoCool IFU is included.

BiosenseWebster
a Johnson & Johnson company

NAVISTAR® THERMOCOOL® Diagnostic/Ablation Catheter
INSTRUCTIONS FOR USE

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STERILE	EO

Sterilized with ethylene oxide gas.

REF
Catalog No.

Use by.

LOT

Lot No.

For one use only.

NAVISTAR® THERMOCOOL® Diagnostic/Ablation Catheter

INSTRUCTIONS FOR USE

Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.

SINGLE USE ONLY. DO NOT RESTERILIZE.

1. DEVICE DESCRIPTION

The Biosense Webster NAVISTAR® THERMOCOOL® Diagnostic/Ablation Deflectable Tip Catheter is a luminal catheter with a 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 shaft measures 7.5 F with 8.0 F ring electrodes. For ablation, the catheter is used in conjunction with a RF generator and a dispersive pad (indifferent electrode).

The catheter has a high-torque shaft with a deflectable tip section containing an array of platinum electrodes. 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 catheter incorporates either a thermocouple or thermistor temperature sensor that is embedded in the 3.5mm tip electrode. 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" – 4.3" or 51 mm – 109 mm"). 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.

At the proximal end of the catheter, a saline input port with a standard luer fitting terminates from the open lumen. This saline port serves to permit the injection of normal saline to irrigate the tip electrode. During ablation, heparinized normal saline is passed through the 0.027" (0.69 mm) diameter 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.
This catheter features a magnetic location sensor embedded in the tip electrode that transmits location information to the CARTO® EP Navigation System.

The catheter interfaces with standard recording equipment and the Stockert 70 RF Generator via accessory extension cables with the appropriate connectors.

For further description of the operation of the CARTO® EP Navigation System and Stockert 70 RF Generator, refer to the operating instructions for these instruments.

2. INDICATIONS AND USAGE

The Biosense Webster NAVISTAR® THERMOCOOL® Diagnostic/Ablation Deflectable Tip Catheters and related accessory devices 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 symptomatic paroxysmal atrial fibrillation.

The NAVISTAR® THERMOCOOL® Catheter provides location information when used with the CARTO® EP Navigation System.

3. CONTRAINDICATIONS

Do not use this device:

- 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

4. WARNINGS AND PRECAUTIONS

1. Do not use the temperature sensor to monitor tissue temperature. The temperature sensor located within the tip electrode of the catheter does not reflect either electrode-tissue interface or tissue temperature due to the cooling effects of the saline irrigation of the electrode. The temperature displayed on the RF generator is the temperature of the cooled electrode, not tissue temperature. The temperature sensor is used to verify that the irrigation flow rate is adequate. Before initiating the application of RF current, a decrease in electrode temperature confirms the onset of saline irrigation of the ablation electrode. Monitoring the temperature from the electrode during the application of RF current ensures that the irrigation flow rate is being maintained.
2. It is important to carefully follow the power titration procedure as specified in the instructions for use. Too rapid an increase in power during ablation may lead to perforation caused by steam pop.
3. This catheter may damage the prosthetic tricuspid valve of a patient if the catheter is accidentally advanced through the valve.
4. The patient who has had a prior atrial flutter ablation procedure may be at greater risk for perforation and/or pericardial effusion with the use of this catheter system.

5. In accordance with your hospital's protocol, monitor the patient's fluid balance throughout the procedure to avoid fluid volume overload. Some patients may have factors that reduce their ability to handle the volume overload, making them susceptible to developing pulmonary edema or heart failure during or after the procedure. Patients with congestive heart failure or renal insufficiency, and the elderly are particularly susceptible. Prior to procedure, always identify the patient's risk of volume overload.
6. The device has not been shown to be safe at electrode temperatures above 50° C; verify that the CATHETER SELECTION KNOB on the Stockert 70 RF Generator is on the "ThermoCool" option to ensure that the maximum temperature is set at 50° C. If the Stockert 70 generator does not have a "Thermocool" option, contact Biosense Webster Technical Support immediately.
7. Implantable pacemakers and implantable cardioverter/defibrillators (ICDs) may be adversely affected by RF current. It is important to have temporary external sources of pacing and defibrillation available during ablation, and to temporarily reprogram the pacing system to minimum output or OFF mode to minimize the risk of inappropriate pacing. Exercise extreme caution during ablation when in close proximity to atrial or ventricular permanent leads; program the ICD to the OFF mode during the ablation procedure; and, perform complete implantable device analysis on all patients after ablation.
8. Patients undergoing septal accessory pathway ablation are at risk for complete AV block which requires the implantation of a permanent pacemaker. Patients who experience inadvertent complete AV block as a result of RF ablation may also require permanent pacing.
9. During the trans-aortic approach, adequate fluoroscopic visualization is necessary to avoid placement of the catheter in the coronary vasculature. Intracoronary placement of the ablation catheter, RF energy application, or both have been associated with myocardial infarction.
10. If phrenic nerve location is a concern, precautionary measures are recommended to evaluate the proximity of the nerve to the ablation electrode, such as pacing maneuvers.
11. To minimize risk of atrio-esophageal fistula, precautionary measures should be taken when ablating on posterior wall of the left atrium in proximity to the esophagus
12. Minimize X-ray exposure during the procedure. Catheter ablation procedures present the potential for significant X-ray exposure, which can result in acute radiation injury as well as increased risk for somatic and genetic effects to both patients and laboratory staff due to the X-ray beam intensity and duration of the fluoroscopic imaging. Catheter ablation should only be performed after adequate attention has been given to the potential radiation exposure associated with the procedure, and steps have been taken to minimize this exposure. Careful consideration must therefore be given to the use of the device in pregnant women.
13. Do not expose the catheter to organic solvents such as alcohol.
14. Do not autoclave the catheter.
15. Do not immerse proximal handle or cable connector in fluids; electrical performance could be affected.
16. Do not scrub or twist the distal tip electrode during cleaning.
17. Inspect irrigation saline for air bubbles prior to its use in the procedure. Air bubbles in the irrigation saline may cause emboli.
18. Purge catheter and irrigation tubing with heparinized normal saline.
19. Electrophysiology catheters and systems are intended for use only in X-ray shielded rooms due to electromagnetic compatibility requirements and other hospital safety guidelines.
20. Do not attempt to operate the Biosense Webster NaviStar® ThermoCool® Diagnostic/Ablation Deflectable Tip Catheter or the Stockert 70 RF generator prior to completely reading and understanding the applicable instructions for use.
21. Cardiac ablation procedures should be performed by appropriately trained personnel in a fully-equipped electrophysiology laboratory. Appropriate clinical instruction in use of the ThermoCool® Irrigated Catheters should also be completed.
22. The long-term risks of protracted fluoroscopy and creation of RF induced lesions have not been established. Furthermore the risk/benefit in asymptomatic patients has not been studied.
23. To avoid thromboemboli, intravenous heparin should be used when entering the heart during ablation, and many physicians prescribe aspirin, less often warfarin, for about 3 months afterward. No consensus yet exists about the need for short-term anticoagulation after ablation.
24. When using the Biosense Webster NaviStar® ThermoCool® Diagnostic/Ablation Deflectable Tip Catheter with conventional systems (using fluoroscopy to determine catheter tip location), or with the Carto® EP Navigation System, careful catheter manipulation must be performed in order to avoid cardiac damage, perforation, or tamponade. Catheter advancement should be done under fluoroscopic guidance. Do not use excessive force to advance or withdraw the catheter when resistance is encountered. The firmness of the braided tip dictates that care must be taken to prevent perforation of the heart.
25. Always pull the thumbknob back to straighten the catheter tip before insertion or withdrawal of the catheter.
26. Always maintain a constant heparinized normal saline infusion to prevent coagulation within the lumen of the catheter.
27. When RF current is interrupted for either a temperature or an impedance rise (the set limit is exceeded), the catheter should be removed, and the tip cleaned of coagulum, if present. When cleaning the tip electrode, be careful not to twist the tip electrode with respect to the catheter shaft, as twisting may damage the tip electrode bond and loosen the tip electrode. Make sure the irrigation holes are not plugged prior to re-insertion.
28. Apparent low power output, high impedance reading, or failure of the equipment to function correctly at normal settings may indicate faulty application of the indifferent electrode(s) or failure of an electrical lead. Do not increase power before checking for obvious defects or misapplication of the indifferent electrode or other electrical leads.
29. Read and follow the indifferent electrode manufacturer's instructions for use; the use of indifferent electrodes that meet or exceed ANSI/AAMI requirements (HF18) is recommended, eg, the 3M Model 1149F or Valley Lab Model 7505.
30. The Biosense Webster NaviStar® ThermoCool® Diagnostic/Ablation Deflectable Tip Catheter is indicated for use only with the Stockert 70 RF Generator, Carto EP Navigation System, Biosense Webster cables, and other appropriate interface cables and connectors. Use of the CoolFlow® Pump is recommended to assure proper irrigation flow rate. In addition, the Stockert-CoolFlow® interface automates the switching of the CoolFlow® Pump between its high and low flow rate settings to assure accurate pump control.
31. The Biosense Webster NaviStar® ThermoCool® Diagnostic/Ablation Deflectable Tip Catheter has been shown to create larger lesions than standard RF ablation catheters. Care should be taken when ablating near structures such as the sino-atrial and atrioventricular nodes.
32. The sterile packaging and catheter should be inspected prior to use. Do not use if the packaging or catheter appears damaged.
33. The catheters are sterilized with ethylene oxide gas and should be used by the "Use By" date on the device package. Do not use the device if past the "Use By" date.
34. The Biosense Webster NaviStar® ThermoCool® Diagnostic/Ablation Deflectable Tip Catheter is intended for single patient use only.
35. Do not resterilize and reuse.
36. Do not use near MRI equipment since movement or heating of the catheter may occur and the image on the display may become distorted.

37. Use both fluoroscopy and electrogram data to monitor catheter advancement and reduce risk of tissue injury.
38. The Biosense Webster NAVISTAR® THERMOCOOL® Diagnostic/Ablation Deflectable Tip Catheter used in conjunction with the Stockert 70 Generator is capable of delivering significant electrical power. Patient or operator injury can result from improper handling of the catheter and indifferent electrode, particularly when operating the device. During energy delivery, the patient should not be allowed to come in contact with grounded metal surfaces. If during ablation, temperature does not rise, discontinue delivery of energy and check set-up.
39. The risk of igniting flammable gases or other materials is inherent in electrosurgery. Precautions must be taken to restrict flammable materials from the electrosurgical suite.
40. Electromagnetic interference (EMI) produced by the Biosense Webster NAVISTAR® THERMOCOOL® Diagnostic/Ablation Deflectable Tip Catheter, when used in conjunction with the Stockert 70 RF during normal operation, may adversely affect the performance of other equipment.
41. Electrodes and probes used for monitoring and stimulating devices can provide paths for high frequency current. The risk of burns can be reduced but not eliminated by placing the electrodes and probes as far away as possible from the ablation site and the indifferent electrode. Protective impedance may reduce the risk of burns and permit continuous monitoring of the electrocardiogram during energy delivery.
42. The temperature sensor measures electrode tip temperature, not tissue temperature. The temperature displayed on the RF generator is for the cooled electrode only and does not represent tissue temperature. If the RF generator does not display temperature, verify that the appropriate cable is plugged into the RF generator. If temperature is still not displayed, there may be a malfunction in the temperature sensing system that must be corrected prior to applying RF power.
43. The temperature measurement accuracy of the Biosense Webster NAVISTAR® THERMOCOOL® Diagnostic/Ablation Deflectable Tip Catheter, as with any temperature measurement electrophysiology catheters, is largely determined by the temperature accuracy specification of the Stockert RF generator used. Please consult the user manual of the RF generator to be used for the temperature accuracy specification. If no temperature accuracy specification is provided in the Stockert RF generator user manual, assume an accuracy of +/- 5° C for this catheter.
44. Before use, check irrigation ports are patent by infusion of heparinized normal saline through the catheter and tubing.
45. Regularly inspect and test reuseable cables and accessories.

5. ADVERSE EVENTS

Clinical trial for atrial flutter indication
Of the 190 subjects in the Safety Population, 33 major adverse events were reported in 30 subjects. See Section 6, "Summary of Clinical Studies Conducted for Atrial Flutter Indication", below for a complete description of the adverse events encountered during the study.

Clinical trial for ventricular tachycardia indication
Of the 233 subjects in the Safety Analysis Cohort, 53 major adverse events (AEs) were reported in 42 subjects. See Section 7, "Summary of Clinical Studies Conducted for Ventricular Tachycardia Indication", below for a complete description of the AEs encountered during the study.

Clinical trial for atrial fibrillation indication
Of the 139 subjects in the Primary Safety Analysis Cohort, 16 serious primary adverse events were reported in 15 subjects. See Section 8, "Summary of Clinical Studies Conducted for Atrial Fibrillation Indication", below for a complete description of the AEs encountered during the study.

6. SUMMARY OF CLINICAL STUDIES CONDUCTED FOR ATRIAL FLUTTER INDICATION

A. Objective
The objective of the study was to determine if the NAVISTAR® THERMOCOOL® Catheter, when used in conjunction with CARTO® EP/XP Navigation System, Stockert 70 RF Generator and related accessories, is safe and effective for the treatment of Type I atrial flutter in patients age 18 or older.

B. Study Design
The study was a prospective, non-randomized, unblinded, multi-center study conducted at 22 investigational sites (21 sites in US; 1 in Canada).

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

- **procedural safety** – defined by the absence of serious complication associated with the use of the investigational device within seven days of the ablation procedure; and

- **acute procedural success** – defined as complete bi-directional conduction block (BDB) across the isthmus, and the inability to induce Type I atrial flutter post-procedure.

Long-term freedom from atrial flutter recurrence was not specifically identified as a study endpoint. Instead, acute procedural success was used as a surrogate endpoint for this parameter. Long-term (defined as 6 months post-treatment) freedom from atrial flutter recurrence information was also collected, in order to enable FDA to assess whether the surrogate endpoint was reasonable

B.2. - Objective Performance Criteria (OPC):
Objective performance criteria (OPC) were prospectively established. The OPC for the safety endpoint used for this study was derived from the FDA guidance document "Cardiac Ablation Catheters Generic Arrhythmia Indications for Use; Guidance for Industry, July 2002 1998 NASPE Registry." The OPC for the effectiveness endpoint was based on an extensive literature search involving acute success rates associated with radiofrequency ablation of atrial flutter. The OPCs are defined below:

- **Safety**: major adverse events within 7 days of the procedure occur at a rate of **2.7%** or less with a **7%** one-sided 95% upper confidence bound;
- **Acute success**: **88%** with an **80%** one-sided 95% lower confidence bound.

B.3. - Subject Accountability

Table 1 - Subject Accountability and Disposition

Subjects enrolled in study	198
Subjects not ablated with the NAVISTAR® THERMOCOOL® Catheter	8
Excluded Subjects - enrolled but in whom the investigational catheter was not inserted	3
Discontinued Subjects - either (1) in whom the investigational catheter was inserted but did not receive RF energy because of non-investigational equipment failure, or (2) for whom the arrhythmia was determined to be non-study arrhythmia at the time of electrophysiologic study (e.g., atypical atrial flutter)	5
Subjects ablated with NAVISTAR® THERMOCOOL® Catheter	190
Subjects ablated with NAVISTAR® THERMOCOOL® Catheter and non-investigational catheter*	19
Subjects ablated **only** with NAVISTAR® THERMOCOOL® Catheter	171
Subjects in whom BDB was not assessable	4

The table above documents the accountability and disposition of enrolled subjects.

* This category includes enrolled subjects who received ablation therapy with the investigational catheter at the start of the procedure and for whom the investigator then switched to a non-protocol catheter to complete the procedure. Further subjects who could not receive ablation due to investigational device failure are included in this category. These subjects were considered acute effectiveness failures.

Effectiveness Analysis Population (n=190) was defined as all subjects who received ablation therapy with the investigational catheter and for whom a valid assessment of BDB at the acute endpoint could be made OR if 6 month follow-up data were available.

Safety Analysis Population (n=190) was defined as all enrolled subjects in whom the investigational catheter was inserted and received ablation therapy. Additionally, the rate of major adverse events is also reported for subjects in whom the investigational catheter was inserted and used for either mapping and/or ablation and for discontinued subjects. This additional category is referred to as the Inserted Patient Cohort (n=195).

B.4. - Subject Demographics

The table below summarizes the demographic information of all study subjects who received ablation therapy

Table 2 – Subject Demographics
(All Subjects who Received Ablation Therapy - n=190)

Gender	N	%
Female	43	22.6
Male	147	77.4
Age (years)		
Mean ± standard deviation	59.8 ± 12.6	
Range	18-90	

Additionally, for the Inserted Patient Cohort of 195 subjects, 72 subjects (36.9%) did not have a concomitant arrhythmia reported in addition to Type I atrial flutter. One-hundred and sixty-five (165) concomitant arrhythmias were reported for 123 subjects. The most common concomitant arrhythmias were atrial fibrillation (n=104) and atypical atrial flutter (n=27).

C. Results

C.1. - Intraprocedural Data

Tables 3 and 4 describe the procedural data.

Twenty-eight (28) subjects received ablation therapy for an arrhythmia other than Type I atrial flutter during the same index ablation procedure. The additional arrhythmias ablated were: 14 atrial fibrillation, 9 atrial tachycardia, 3 AVNRT, 1 intra-atrial tachycardia, 1 non-isthmus atrial flutter and 1 macro-reentry around the SVC eustachian ridge. One subject had more than one concomitant arrhythmia ablated.

Table 3 - Power, Temperature and Impedance Data

Description	Mean ± Standard Deviation	Range
# RF applications/procedure[1] (n=188 procedures)	19 ± 16	1-86
Total saline infused by THERMOCOOL® Catheter (ml)[2] (n=169 procedures)	999.7 ± 605.5	60-3750
Maximum power (Watts)/application[3] (n=3502 RF applications)	35.0 ± 9.5	2-59
Maximum temperature (°C)/application[3] (n=3476 RF applications)	39.6 ± 5.1	14-87
Maximum impedance (Ohms)/application[3] (n=3431 RF applications)	112.1 ± 21.0	13-251

[1] One subject had missing RF information; one subject did not undergo ablation with the NAVISTAR® THERMOCOOL® Catheter.
[2] Some procedural data are missing.
[3] Power, temperature, and impedance not documented for several RF applications.

Table 4 – Overall Fluoroscopy/Procedure Time (minutes)

Description	Mean ± Standard Deviation	Range
Total fluoroscopy time/procedure[1] (n=189 procedures)	50.2 ± 32.4	8-174
Total procedure time[1] (n=190 procedures)	341.6 ± 166.9 (5.7±2.8 hours)	96-925
Total fluoroscopy time/procedure for subjects with additional rhythms ablated during index procedure (n= 28 procedures)	58.8 ± 24.7	18-115
Total fluoroscopy time/procedure for subjects without concomitant ablation (n=161 procedures)	48.7 ± 33.4	8-174
Total procedure time for subjects with additional rhythms ablated during index procedure (n= 28 procedures)	503.8±193.0 (8.4±3.2 hours)	158-804
Total procedure time for subjects without concomitant ablation (n= 162 procedures)	313.5±145.2 (5.1±2.4 hours)	96-925

[1] Incomplete fluoroscopy time was reported for one (1) subject and incomplete procedure time was reported for one (1) subject.

C.2. - Acute Procedural Success

Acute success, defined as complete bi-directional conduction block across the isthmus at a minimum of 60 minutes following application of the last RF application, was analyzed. Acute success evaluation was based on the Efficacy Population, which was defined as all subjects who received ablation therapy with the investigational catheter and in whom a valid assessment of BDB could be made (n = 190 - 4 = 186).

Table 5 describes the acute ablation outcomes.

Table 5 - Acute Ablation Outcomes (n=186)

	# Success / # Subjects Ablated	Percentage (one-sided 95% confidence bound)
Acute Study Results	158/186	85% (80%)
OPC		88% (80%)

C.3. – Composite Assessment of Atrial Flutter Ablation Success

As noted in the above section, 158 subjects had BDB confirmed acutely after the ablation procedure.

In addition, of the four subjects in whom BDB was not measured acutely after the ablation procedure, 3 subjects were free of recurrence of atrial flutter at 6 months follow-up and one could not be validated. For the composite assessment, the 3 subjects were considered a success and the 1 subject a failure. Table 6 summarizes the composite results.

Table 6 – Composite Assessment of Atrial Flutter Success

	# Success / # Subjects Ablated	Percentage (one-sided 95% confidence bound)
Study Results	161/190	85% (80%)
OPC		88% (80%)

C.4. - Freedom from Type I Atrial Flutter Recurrence at Six-Month Follow-Up
As indicated in section B.1 above, long-term freedom from atrial flutter recurrence was not a study endpoint. The long-term results are presented here in order to assess the suitability of the surrogate endpoint BDB.

Freedom from Type I atrial flutter recurrence was evaluated in subjects in whom BDB was achieved (as measured acutely) and for whom 6-month post-ablation information was available. Based on these criteria, information was available on a total of 147 subjects. Results are described in the table below.

Table 7 - Freedom from Type I atrial flutter at 6 months (Results based on 147 subjects)

Description	N	Percent
Subjects in whom BDB was achieved acutely and for whom 6-month information was available	147	100%
Subjects free from recurrence	136	93%
Subjects free from recurrence and anti-arrhythmic drug change	118	80%
Subjects with recurrence of atrial flutter	11	
Subjects with AAD changes to treat atrial fibrillation	15	
Subjects with AAD changes to treat atrial or supraventricular tachycardias	3	

These results provide reasonable evidence that acute procedural success serves as an appropriate surrogate for long-term freedom from atrial flutter recurrence.

C.5. - Adverse Events

A major adverse event was defined as any clinical event that occurred within seven days post-ablation and which resulted in (1) death, (2) a life-threatening complication, or (3) a persistent or significant disability/incapacity that required inpatient hospitalization or prolonged hospitalization or required intervention to prevent a permanent impairment of a body function or damage to a body structure. A minor adverse event was defined as any adverse event resulting in minimal transient impairment of a body function or damage to a body structure, or which did not require any intervention other than monitoring or events occurring more than 7 days post-ablation.

Major Adverse Events
Of the 190 subjects who received ablation therapy with the investigational catheter, 33 major adverse events were reported in 30 subjects. The overall percentage of subjects who experienced a major adverse event was 15.8%. The one-sided 95% confidence bound rate was 20.9%. For subjects who had the investigational catheter inserted and used for mapping and/or ablation (n = 195), the major adverse event rate was 15.4%, and the one-sided 95% confidence bound rate was 20.4%.

Table 8 summarizes the major adverse events.

Table 8 - Major Adverse Events observed within 7 days post-ablation

Total Number Subjects with a Major AE n=30	
Cardiovascular	total = 15 subjects
Arrhythmia complications = 5 subjects complete atrioventricular block during procedure bradycardia requiring pacemaker implant ventricular tachycardia atrial fibrillation atrial fibrillation & atypical atrial flutter	
Pericardial effusion/tamponade = 4 subjects pericardial tamponade pericardial tamponade after mapping only pericarditis with effusion RA thrombus, LV thrombus and pericardial effusion	
Intracardiac thrombus = 2 subjects RAA thrombus RA thrombus, LV thrombus and pericardial effusion	
myocardial infarction = 1 subject	
congestive heart failure = 4 subjects pedal edema dyspnea, rales requiring furosemide dyspnea treated with one dose furosemide pulmonary edema by PE treated with one dose furosemide	
Pulmonary	total = 8 subjects
acute respiratory distress syndrome = 2 subjects	
aspiration pneumonia = 2 subjects	
pneumonia = 3 subjects	
asthma = 1 subject	
Anesthesia related	total = 2 subjects
sedation induced apnea (intubation not required) sedation induced CO_2 retention with lethargy (intubation not required)	
Vascular	total = 2 subjects
arteriovenous fistula/femoral artery-saphenous vein pseudoaneurysm/right femoral artery	
Urologic	total = 2 subjects
urinary tract infection urinary retention	
Cholecystitis	1 subject
Neurologic	2 subjects
parkinson's disease transient extremity numbness/possible tia	

* Note: Some subjects are listed more than once in the above table.

Three subjects died during the course of the study. One subject died due to cardiac arrest caused by cardiomyopathy and chronic obstructive pulmonary disease (COPD) complications 11 days post-ablation, one subject died following pulmonary valve replacement surgery 2 months post-ablation, and the third death was due to lung cancer more than 2 years following the ablation procedure. All deaths were determined to be unrelated to the procedure and device.

An overall risk benefit evaluation of these adverse events was performed and a detailed review of each adverse event was completed. The adverse event rate described above was assessed to be specifically correlated to (1) the concomitant ablation procedures performed during the index procedure and (2) the increased number of co-morbid conditions present in the subject population enrolled relative to patient population from which the OPCs were derived. See section C.1 for a list of concomitant ablation procedures.

C.6. - Statistical Analysis

Table 9 summarizes the safety and effectiveness of the device when compared to the control group OPC established for safety and acute success.

Table 9 - Comparison of Endpoints between NAVISTAR® THERMOCOOL®I® Study and OPC

Endpoint	OPC		NAVISTAR® THERMOCOOL® Study	
	%	One-sided 95% Confidence Bound	% (N)	One-sided 95% Confidence Bound
Acute Success	88%	80%	85% (161/190)	80% (Lower bound)
Major Complications	2.7%	7%	15.8% (30/190)	20.9% (upper bound)

With comparison of the lower bounds of the acute success endpoints (80% vs. 80%), the results demonstrate that the NAVISTAR® THERMOCOOL® Catheter met the OPC for acute success. As previously explained in section C.5, although the device exceeded the upper bound of major complications, review of the specific events showed that they were related to the concomitant ablation procedures performed in addition to atrial flutter ablation and the subject population co-morbid conditions. Accordingly, study results demonstrate a reasonable assurance of the safety profile of the device.

7. SUMMARY OF CLINICAL STUDIES CONDUCTED FOR VENTRICULAR TACHYCARDIA INDICATION

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.

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.

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.

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:

- Available literature included incomplete recording of safety results.
- 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 - Subject Accountability

Table 10 documents the accountability and disposition of enrolled subjects.

Table 10. 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 11 summarizes the demographic information of all enrolled subjects in the study.

Table 11. 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. (VTs were not induced in two subjects who underwent ablation with the investigational device). 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 12 and 13 present the procedural data.

Table 12. 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 13. 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

Acute procedural success results are presented in Table 14.

Table 14. 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 15.

Table 15. 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.

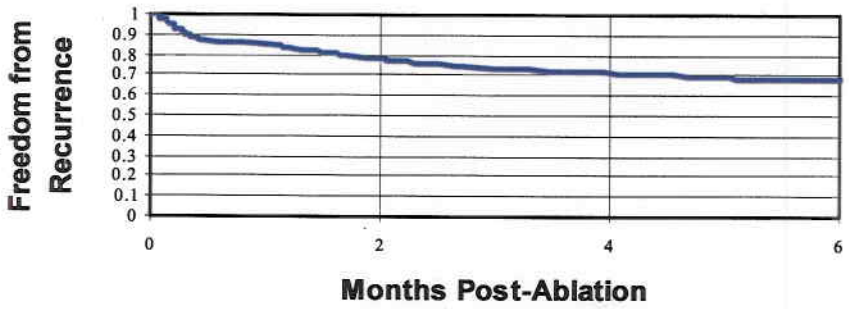
Freedom from VT recurrence following acute success was 67.5% at 6 months.

Table 16. 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 (AE)
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 Adverse Events

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 17 summarizes the major AEs.

Table 17. 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%
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 18 lists the LVEF measurements stratified by the presence or absence of major AEs. Survival status stratified by LVEF (%) is presented in Table 19.

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 18. 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 19. 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 20).

Table 20. Comparison of Safety Endpoint between NAVISTAR THERMOCOOL Study and Protocol Endpoint (Safety Analysis Cohort, n = 233)

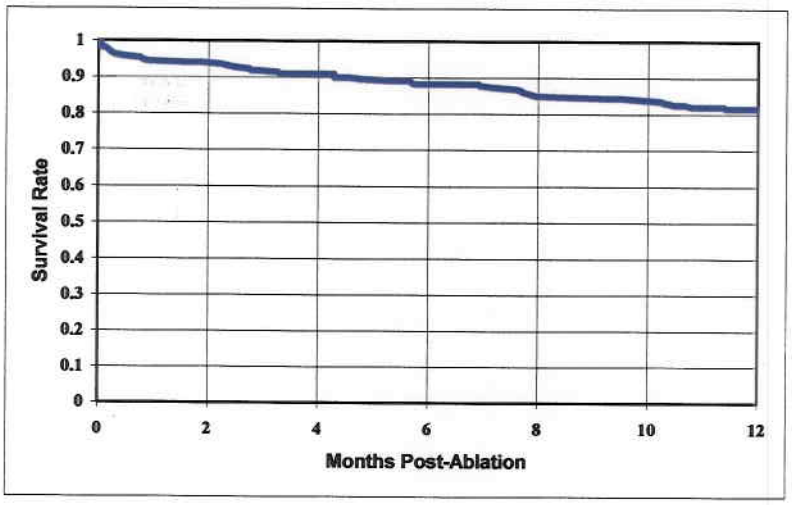
Endpoint	Protocol Established Endpoints[1]		NAVISTAR THERMOCOOL Study	
	%	One-sided 95% Confidence Bound[2]	% (n)	One-sided 95% Confidence Bound[2]
Major Complications	22	30	18.0 (42/233)	23 (Upper Bound)

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

Table 21. 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 all the protocol endpoints for safety and effectiveness.

8. SUMMARY OF CLINICAL STUDIES CONDUCTED FOR ATRIAL FIBRILLATION INDICATION

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 AF based on electrocardiographic data and no changes in AAD regimen during comparable evaluation periods for the THERMOCOOL and AAD (Control) groups. 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 1 – Subject Accountability and Disposition

Subject Disposition	
Total Number of Subjects Enrolled	167
Subjects randomized to THERMOCOOL	**106**
Subjects who underwent ablation with the study catheter	103
Excluded Subjects	3
Discontinued Subjects	0
Subjects randomized to AAD (Control)	**61**
Subjects administered AAD therapy	57
Excluded Subjects	4
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 2 – 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	

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.

C. Results

C.1 - Procedural Data

Tables 3 and 4 present the procedural data.

Table 3: 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 4: 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 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. Table 5 summarizes the lesion sets applied to THERMOCOOL group subjects during the index ablation procedures.

Table 5: 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)

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

C.2 - Acute Procedural Success

Acute procedural success results are presented in Table 6.

Table 6: 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 7.

Table 7: 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 survival curves for each of the treatment groups.

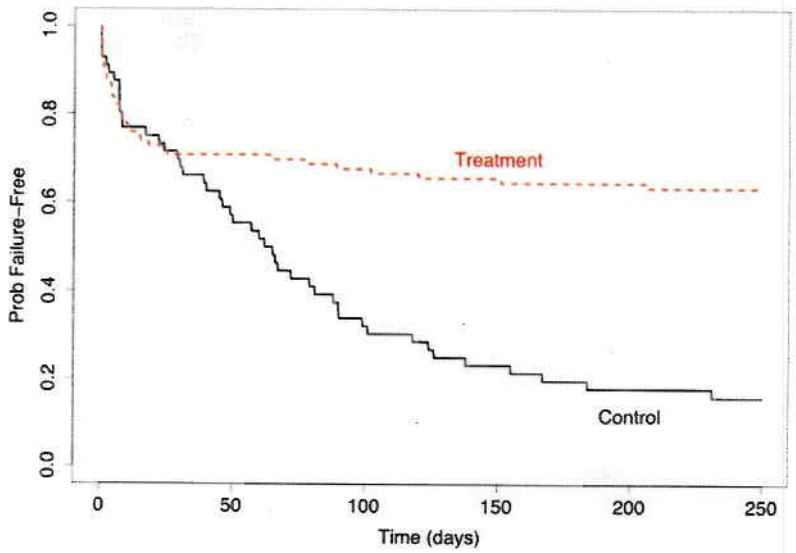


FIGURE 1 Kaplan-Meier Analysis – Probability of Freedom from Chronic Effectiveness Failure For Each Treatment Group*

The June 2008 dataset status of each of the 159 subjects is reported in Table 8. 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 8: 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

Figure R 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.

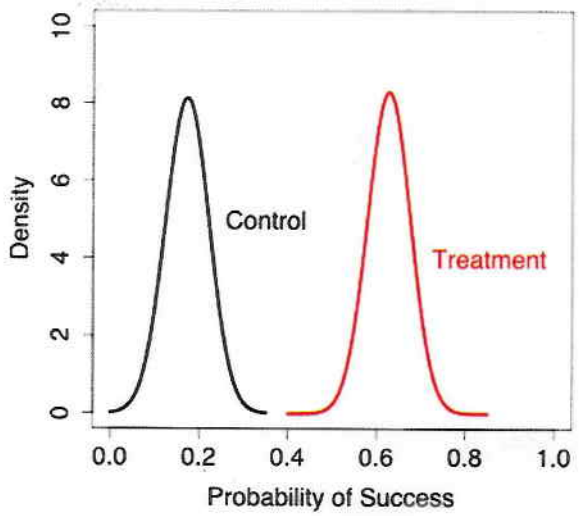


FIGURE R 2: The Posterior Distributions of the Probabilities of 9-month Failure-Free Treatment Success for Each Treatment Group

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 AEs 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 Adverse Events

Table 9 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 % (14/139) 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 slightly 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 9: 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 10 summarizes the major CRAEs.

Table 10: 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 11 compares the incidence of early onset serious adverse events between the two treatment groups occurring within the first 90 days of initial therapy.

TABLE 11 Percentage of Early Onset 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 the NAVISTAR THERMOCOOL catheter met all the protocol endpoints for safety and effectiveness.

9. HOW SUPPLIED

- The NAVISTAR® THERMOCOOL® Diagnostic/Ablation Catheter is supplied STERILE.
- The catheter is supplied with a choice of of five curve types: B, C, D, F, and J.
- The Stockert 70 RF Generator with appropriate interface cables is supplied separately.
- A grounding pad (indifferent electrode) is supplied separately.
- The CARTO® EP Navigation System is supplied separately.
- The appropriate Reference Patch is provided separately.

9.1 Packaging

The NAVISTAR® THERMOCOOL® Diagnostic/Ablation Catheter is provided in sterile packaging. The catheter is secured to a mounting card placed in a sealed film/Tyvek pouch and packaged inside a cardboard box. Both the pouch and the shipping container are labeled sterile.

9.2 Storage

The NAVISTAR® THERMOCOOL® Diagnostic/Ablation Catheter must be stored in a cool, dry place. Storage temperature should be between 5 and 25° C (41 and 77° F).

9.3 Shelf-Life

The NAVISTAR® THERMOCOOL® Diagnostic/Ablation Catheter has a shelf life of three (3) years.

10. DIRECTIONS FOR USE

Please refer to the User Manuals for the CARTO® EP Navigation System, COOLFLOW® Pump, Stockert 70 RF Generator, and the Instructions for Use for the COOLFLOW® Irrigation Tubing Set for instructions on connecting and operating these systems in conjunction with the NAVISTAR® THERMOCOOL® Diagnostic/Ablation Catheter.

1. Remove catheter from package and place in a sterile work area.
2. Create a vascular access in a large central vessel using aseptic techniques.
3. To verify compatibility between sheath and catheter, advance catheter through sheath prior to insertion
4. Connect the catheter to the Patient Interface Unit (PIU) via the appropriate Biosense Webster cable with 25-pin Hypertronics interlocking connectors on both ends. Connect the PIU to the Stockert 70 RF Generator via the Biosense Webster cable with 10-pin Redel connectors on both ends. Connect the PIU to appropriate recording and mapping systems, including the CARTO® EP Navigation System, with appropriate interface cables. Use only Biosense Webster interface cables. If electrogram recording equipment is used, the catheter tip electrode must be switched from the electrogram equipment (via the generator controls or an external switch) to the RF generator power output for ablation. To complete the electrical circuit, connect an indifferent electrode to the indifferent electrode input on the generator.
5. Connect the COOLFLOW® Irrigation Tubing Set to a room temperature, heparinized (1 u heparin/ml) normal saline bag using standard safe hospital practices. Open the stopcock on the end of the tubing set and fill the tubing set as slowly as possible. Remove any trapped air and then close the stopcock.
6. Load the COOLFLOW® Irrigation Tubing Set in the pump. Open the stopcock and press and hold the Flush button on the COOLFLOW® Pump until the air is expelled through the open end of the tubing.
7. Connect the stopcock on the end of the COOLFLOW® Irrigation Tubing Set to the luer fitting of the NAVISTAR® THERMOCOOL® Diagnostic/Ablation Catheter.
8. Flush the catheter and tubing to ensure purging of trapped air bubbles and to verify that the irrigation holes are patent.
9. Start continuous irrigation at a flow rate of 2 ml/min by pressing the Low Flow button on the COOLFLOW® pump.
10. Insert the NAVISTAR® THERMOCOOL® Diagnostic/Ablation Catheter via the entrance site, using an appropriately sized introducer sheath and advance the catheter to the area under investigation. Use both fluoroscopy and electrograms to aid in proper positioning.
11. The catheter tip can be deflected to facilitate positioning by using the thumbknob to vary tip curvature. Pushing the thumbknob forward causes the catheter tip to deflect; when the thumbknob is pulled back, the tip straightens.
12. Verify that the CATHETER SELECTION KNOB on the Stockert 70 RF Generator is on the "ThermoCool" option. When this option is chosen, the Stockert 70 RF generator defaults to the safety parameters established for the ThermoCool catheter.
13. Recommendation for irrigation: Increase the irrigation to high flow rate starting up to 5 seconds before the onset of RF energy delivery and maintaining this higher flow rate until 5 seconds after termination of the energy application. For power levels up to 30 watts, a high flow rate of 17ml/min should be used. For power levels between 31-50 watts, a high flow rate of 30ml/min should be used.
14. The application of RF energy must not be initiated until the increase in irrigation flow rate is confirmed by a minimum of 2° C decrease in tip electrode temperature.
15. Monitor the catheter tip temperature throughout the procedure to ensure adequate irrigation. If the temperature increases to 50° C during RF application, power delivery will be interrupted by the temperature cutoff of the Stockert 70 RF Generator. The irrigation system must be rechecked prior to restarting RF application.
16. Recommendation for RF power delivered:

For treatment of atrial flutter: Start a procedure at 15 - 20 Watts. After 15 seconds, power may be increased by 5 - 10 W increments as needed, until a transmural lesion is achieved, defined by > 80% reduction in unipolar atrial electrogram amplitude, or emergence of double potentials of equal and low amplitude. It is recommended that power not exceed 50 W when the catheter is parallel to the tissue and 35 W if the catheter is perpendicular to the tissue. The duration of each RF application should not exceed 120 seconds. Dragging the catheter to the next site is permissible during the 120 second energy application. RF current may be reapplied to the same or alternate sites using the same catheter.

For treatment of ventricular tachycardia: Start a procedure at 31 Watts. If needed, increase power in 5 W increments (to maximum 50 W) until a transmural lesion is achieved. The duration of each RF application should not exceed 120 seconds. Dragging the catheter to the next site is permissible during the 120 second energy application.

For treatment of atrial fibrillation: It is recommended that power not exceed 50 W and 35 W if the catheter is perpendicular to the tissue. Refer to Summary of Clinical Studies above lesion recommendations.

17. In the event of a generator cutoff (impedance or temperature), the catheter must be withdrawn and the tip electrode cleaned of coagulum, if present before RF current is reapplied. A sterile gauze pad dampened with sterile saline may be used to gently wipe the tip section clean; do not scrub or twist the tip electrode as damage to the tip electrode bond may occur and loosen the tip electrode. Prior to reinsertion, ensure that the irrigation holes are not plugged by increasing flow rate and verifying flow from each of the six irrigation holes.

    If irrigation hole occlusion occurs:

    a. Fill a 1 or 2 ml syringe with sterile saline and attach to the stopcock on the end of the tubing set
    b. Carefully inject the saline from the syringe into the catheter. A stream of fluid should be visible from all six (6) holes.
    c. Repeat steps a and b, if necessary until the holes are cleared.
    d. Flush catheter and tubing per standard technique to ensure purging of trapped air bubbles and to verify that the irrigation holes are patent.
    e. The catheter can now be reintroduced into the patient

    WARNING: Do not continue use of the catheter if still occluded or it is not functioning properly.

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Tab 7

Clinical Report

PRE-MARKET APPROVAL APPLICATION
PANEL PACK CLINICAL REPORT
PMA # P030031/S11

BIOSENSE WEBSTER
NAVISTAR® THERMOCOOL® Catheter
for the Radiofrequency Ablation of Symptomatic Paroxysmal Atrial Fibrillation

October 16, 2008

SPONSOR

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Forward

This clinical report is an amendment of the Pre-Market Approval (PMA) Supplement Application Clinical Report dated August 12, 2008 (original clinical report). Please note the following:

- Some tables and figures were intentionally removed for brevity from the original clinical report as presented in the PMA, based on discussion with the FDA. All table and figure numbering is consistent with the original clinical report; an "R" prefix prior to the table or figure number denotes tables revised post PMA supplement submission (e.g., TABLE 3.6.5.1A is now TABLE R 3.6.5.1A).
- Some Appendices are intentionally removed for brevity from the original clinical report as presented in the PMA supplement.

1.0 Introduction

1.1 An Overall Perspective

Atrial Fibrillation (AF) is a supraventricular arrhythmia that is characterized by chaotic and uncoordinated contractions of the atria. It is most often diagnosed from an electrocardiogram (ECG) when an irregular ventricular rate is present. Characteristic ECG findings include the absence of P-waves, which are replaced with irregular atrial complexes (fibrillatory waves) that vary in amplitude, shape, and timing. In subjects with intact AV conduction, the R-R interval will almost always vary due to the irregular conduction of impulses from the atria to the ventricles.[1]

AF is the most common sustained arrhythmia in humans. It affects anywhere from 0.4% to 1% of the general population, and increases in prevalence with age, from < 1% in young adults to 8% in patients over 80 years of age.[1,2] The prevalence of AF in men is somewhat greater,[3] and the risk of developing AF in black patients is half that of white patients in age-adjusted populations.[1] Cardiopulmonary co-morbidities, such as heart failure (HF) and hypertension, have been associated with the occurrence of AF.[1] In one study, the 3-year incidence of AF in patients with heart failure was almost 10%.[4]

Patients suffering from episodes of AF describe a considerably impaired quality of life that is independent of the severity of the disease.[5,6] Improvement in their quality of life following their treatment has shown a direct correlation with the restoration and maintenance of a normal sinus rhythm in these patients.[5-8] In addition to life altering symptomatic episodes, individuals with AF have an increased long-term risk of stroke, HF, and all cause mortality.[9] This is especially true among women, where AF is an independent predictor of adverse cardiovascular events such as stroke and heart failure.[9] The ischemic stroke risk of AF patients is anywhere from 2 to 7 times greater than that of individuals without AF,[1] exceeding a rate of 7% per year when pathological changes are detected by brain imaging. AF also has been associated with a 40%-90% increased mortality rate.[10,11]

The treatment of AF and its consequences has made AF a costly public health burden. Approximately one-third of all hospital admissions for cardiac arrhythmias are due to AF, with an observed increase in admissions for AF of 66% over the last 20 years in the US due to the rising prevalence of related co-morbidities. This represents a major US healthcare burden, with annual direct healthcare costs between (US) $4,000 and $5,000 per patient when treated with traditional therapies.[12] Total annual US expenditure for the treatment of AF patients has been estimated at $6.65 billion, and approximately (US) $15.7 billion in the European Union.[1,12]

The medical community has recently adopted a 3-category classification system that attempts to distinguish and standardize the different levels of AF. The 3 definitions are: Paroxysmal (2 or more AF episodes that terminate spontaneously within 7 days), Persistent (AF sustained beyond 7 days or lasting less than 7 days but necessitate termination by intervention), and Longstanding Persistent (AF greater than one-year's duration).[1] The 2007 HRS/EHRA/ ECAS consensus statement on catheter and surgical ablation recommended that, "patients be categorized by their most frequent pattern of AF."[13] However, classification may still be problematic. For example, the range in the paroxysmal AF category includes patients with symptomatic episodes 1-2 times a year as well as patients with multiple episodes a month.[14]

Radiofrequency (RF) catheter ablation has provided excellent results for treating many types of supraventricular arrhythmias.[15,16] Recent reports from 3 small randomized trials in paroxysmal AF patients have de nstrated that catheter ablation is superior to anti-arrhythmic drug therapy in the prevention of recurrent AF.[17] The 2006 ACC/AHA/ESC AF management guidelines now consider catheter ablation to prevent recurrent AF a reasonable alternative to pharmacological therapy, i.e. it is a second treatment option in all categories of its treatment algorithm to maintain sinus rhythm.[1] In fact, catheter ablation techniques targeting the isolation of the pulmonary veins (PVs) are commonly used in the cardiac electrophysiology laboratory today.[1,13]

1.2 Technology of RF Catheter Ablation

RF energy utilizes a high frequency (350 kHz to 1 MHz) alternating current to cause resistive heating of a narrow rim (~1 mm) of tissue that is in direct contact with the electrode tip.[20] Heating beyond this rim is based on transfer of thermal energy to the surrounding tissues, and is the primary mechanism by which RF lesions are formed.[21] Increasing temperature at the electrode-tissue interface increases the lesion size, but if the temperature exceeds 80 to 100°C, coagulum on the electrode tip can form and lead to an abrupt rise in impedance and a marked decrease in tissue heating.[22] The temperature of the electrode-tissue interface, therefore, is a limiting factor to increasing RF lesion size and depth.

The Biosense Webster, Inc. NAVISTAR® THERMOCOOL® catheter, the subject of this pre-market supplement application (PMA), is already approved to treat type I atrial flutter and recurrent drug/device refractory sustained monomorphic ventricular tachycardia due to prior myocardial infarction. This catheter utilizes an open irrigation system that incorporates several small ports on the tip of the catheter that irrigate the tip electrode with saline during the delivery of RF energy. Simultaneous cooling of the tip electrode mitigates the issues of overheating and coagulum formation, thereby allowing applications of higher power to be delivered with a reduced risk. Animal studies of the THERMOCOOL catheter used in this clinical study have demonstrated that, during RF application at high power, saline irrigation maintains a low electrode-tissue interface temperature resulting in deeper and larger lesions.[21] Therefore, this technique may create wider and deeper tissue lesions, possibly resulting in the successful ablation of AF when conventional RF ablation has failed.[23] In addition, this catheter can be used with Biosense Webster Inc.'s CARTO™ EP Navigation System, an electroanatomic mapping system that allows the re-creation of anatomy, activation sequence, and electrogram amplitude (voltage) maps.[24]

1.3 Alternative Practices & Procedures

The 2006 ACC/AHA/ESC management guidelines, lists ventricular rate control, prevention of thromboembolism, and the correction of the altered rhythm state as the three objectives of AF therapy.[1] Until the 1980's, treatment options were limited to cardioversion and pharmacological therapy for rate and/or rhythm control. With the development of surgical ablation techniques, the advent of implantable devices to control heart rates, and the development of intracardiac ablation catheters, AF patients now have more treatment

options available.[1] Of the available options, only surgical intervention and catheter ablation hold the best possibility of permanently restoring sinus rhythm.[13]

1.3.1 Pharmacological Therapy

It is well recognized that the efficacy of antiarrhythmic drug (AAD) therapy of AF is quite variable, with the likelihood of AF recurrence in 6-12 months being at least 50% on most drugs.[25] The First Antiarrhythmic [randomized] Drug Substudy (FADS) of the AFFIRM Trial[26] found no difference at the end of one year in the efficacy of sotalol when compared to all the Class I drugs in the study (quinidine, procainamide, disopyramide, flecainide, propafenone, and moricizine), but found amiodarone (which was not allowed in this study per FDA guidance document for the percutaneous catheter ablation of atrial fibrillation; January 2004) significantly more effective than either sotalol or the Class I drugs in the study.

No single standardized anti-arrhythmic drug treatment protocol has been found to maintain sinus rhythm. Thus, it is recommended that anti-arrhythmic drug therapy be individualized for each patient. The 2006 ACC/AHA/ESC AF management guidelines recommend anti-arrhythmic drug therapy as a first line therapy, despite an anticipated AF recurrence rate at one year of ~50% in treated patients.[1,25] The 2006 ACC/AHA/ESC AF management guidelines consider a successful outcome of antiarrhythmic therapy reasonable if AF recurrence is infrequent and well tolerated, despite the lack of clear long-term efficacy data.[1] Several clinical studies, including the PIAF,[27] RACE,[28] STAF,[29] AFFIRM,[30] and AF-CHF [31] trials, have demonstrated that rate control primarily with drugs (calcium channel blockers and beta-blockers) is a valid primary therapeutic option. In these studies, the symptoms, quality of life, occurrence of systemic emboli, and all-cause mortality were not significantly different between the rate and rhythm control therapy options. That said, a post-hoc analysis of the AFFIRM study has shown that, while restoration of normal sinus rhythm was associated with a 47% reduction in mortality, the use of AAD therapy paradoxically was associated with an increase in mortality of 49%.[32]

Finally, it should be emphasized that Class II and IV AADs, i.e., beta blockers (BBs) and nondihydropyridine calcium channel blockers (CCBs), respectively, although an obvious part of the pharmacologic therapy of AF, are not drugs primarily used or expected to prevent recurrence of AF. They may indirectly affect recurrence of AF by helping to treat some of the associated comorbidities such as hypertension, heart failure, and coronary artery disease. Only in the treatment of the uncommon condition of adrenergically mediated AF are beta blockers (Class II AADs) a primary antiarrhythmic agent for the suppression of AF, and there appears to be no evidence of any primary antiarrhythmic action of calcium channel blockers (Class IV AADs) for this purpose. Nevertheless, these (Class II and IV) drugs are frequently used in the treatment of AF, either as primary drugs to control ventricular rate when pursuing a rate control strategy, or as secondary drugs to control ventricular rate should AF recur when pursuing a rhythm control strategy.

1.3.2 Surgical Intervention

Surgical techniques were based on the hypothesis that AF is the result of a multiple reentrant wavelets mechanism. Numerous atrial lesions (lines of block – mostly connected) are made at locations in the left and right atria. The ensuing scar lesions are designed to prevent sustained AF while attempting to preserve the sinus rhythm and atrial transport function. Because of a high reported rate of success in preventing AF, surgical intervention has become more widely adopted in patients coming to cardiac surgery for reasons other than AF. However, minimally invasive procedures are being developed. The associated risks of the surgical procedure include death (>1%), permanent pacing (with right side lesions), recurrent bleeding requiring additional surgery, impaired atrial transport function, and scar-related atrial arrhythmias (atrial flutter). AF surgical intervention is usually reserved for subjects undergoing surgery for another cause.

1.3.3 Implantable Devices

Treatment of AF with implantable devices makes use of two potential aspects of the device's function, pacing and internal atrial defibrillation. Pacing may be used to permit needed drug therapy which otherwise might

enhance or cause clinically unacceptable bradycardia, especially in the face of sinus node dysfunction, so common in AF patients. Also, some data suggest pacing alone may be helpful in suppressing AF in subjects with bradycardia. This is thought to include suppression of premature beats and/or maintaining atrioventricular (AV) synchrony. In patients with normal heart rates, there is little evidence that pacing reduces the risk of AF. Internal atrial defibrillators have the ability to detect and treat AF, restoring sinus rhythm with a low energy shock. These devices have been shown to effectively convert recurrent AF to sinus rhythm and lengthen the intervals between AF episodes[33]

However, implantable devices are not a widely used option for AF. The amount of energy (usually > 6 J) required to resynchronize the heart rhythm is not well tolerated by most patients.[1,34] The AF patients with normal left ventricular (LV) function who are candidates for these implantable cardioverter defibrillators (ICD) are also typically candidates who are eligible for catheter ablation.

1.3.4 Radiofrequency Catheter Ablation (RFCA)

Prior to the development of left atrial catheter ablation techniques, intracardiac ablation for AF was limited to the ablation of the AV node with a subsequent pacemaker implant to increase or to decrease the AF symptoms. The 2006 ACC/AHA/ESC AF management guidelines still consider this procedure reasonable when ventricular rate cannot be adequately controlled with pharmacologic therapy or is associated with intolerable adverse drug effects. [1] This procedure does improve quality of life and decrease symptoms, but it does not restore sinus rhythm.[35]

Current advances in non-pharmacological therapy by intracardiac catheter ablation techniques have arisen as a result of two recent observations. In 1996, Haïssaguerre and colleagues. [36] observed that paroxysmal AF may arise from the repetitive firing of myocytes in cardiac muscle sleeves that extend from the left atrium into the pulmonary veins (PV). At the same time, a surgical team from Japan noted that an AF surgical procedure that primarily encircled the PVs resulted in the restoration and maintenance of sinus rhythm.[37]

Radiofrequency catheter ablation (RFCA) now appears to provide a promising therapy for AF.[38-40] Several types of RFCA procedures have been proposed [40,48,50,51,56] but the most promising one, which entails RFCA to isolate the initiating source, is supported by "reasonable pathophysiologic principles."[25] More recent reports from three small randomized trials in paroxysmal AF patients have demonstrated that catheter ablation is superior to AAD therapy in the prevention of recurrent AF.[17-19]

The ACC/AHA/ESC AF Management Guidelines now consider catheter ablation to prevent recurrent AF a reasonable alternative to pharmacological therapy (i.e., a second treatment option) in all categories of the treatment algorithm to maintain sinus rhythm.[1] In fact, catheter ablation techniques targeting the isolation of the PVs are commonly used in the electrophysiology laboratory today.[1,13]

Post ablation, restoration of sinus rhythm has been shown to significantly improve LV function, exercise capacity, symptoms, and quality of life in the first 3 to 6 months after the procedure.[41] In addition, catheter ablation has been associated with reduced mortality and morbidity due to heart failure and thromboembolism.[42]

Meta analysis of several published reports[46-58] which utilized the PV isolation approach in larger study populations (range 44-179 subjects), demonstrated an overall chronic success rate adjusted for sample size of 70%. (744/1056). In the earliest reports,[46] the success rate was as low as 33%, but improved to as high as 85% with short-term follow-up.[56] Complication rates followed a similar favorable pattern, with reported complications as high as 23% to a low of 1.6%, with a sample size adjusted average of 9.3%.[46-58] The efficacy and safety results have improved as investigators advanced both their experience and skills with RFCA in or near the PVs.

In this study, we enrolled patients classified as having paroxysmal AF, with the caveat that a subject could be enrolled as long as the confirmed AF episode did not last longer than 30 days and was terminated via cardioversion. At the time the study began, medical literature (reviewed above) demonstrated a higher success rate for patients in the paroxysmal category when the PVs were isolated electrically from the left atrium. Adding support to this approach, Jaïs et. al.[59] demonstrated, in an elegantly constructed series of patient observations, that the effective and functional refractory period of the PV myocyte bundles were significantly shorter than the effective and functional refractory period in left atrial (LA) myocytes for patients with and without AF. His findings provide evidence for how ectopic beats in the PV myocytes can be the driving force for AF and why isolation of these cells from the LA can prevent AF recurrence.

When the study began in 2004, there was a consensus in the medical literature indicating that electrically isolating the PVs from the left atrium was the best method to treat AF in the paroxysmal AF population.[13,49,51,52,56] This belief is still widely held today, and has been said to be "the cornerstone for most AF ablation procedures".[13] When the study first began, several research centers were also investigating the benefits of placing additional RF lesions in the left and right atria[13,51,60,61] (e.g. a line of block between the left inferior PV and the mitral annulus). Today, there is no consensus on the necessity of these extra RF lesions, nor on their number or anatomical placement. Some individuals and research centers extol the virtues of placement of additional RF lesions. However the reason for successful outcomes is not clear.

The recently published consensus statement by HRS, EHRA and the ECAS has provided recommendations on AF catheter ablation and standardizing patient follow-up to address the lack of agreement between previous guidelines and current clinical practice.[13] The primary justifications for catheter ablation as presented in the consensus statement are the improvement in a patient's quality of life and the freedom from symptomatic AF.[13] Improved survival, decreased stroke risk and decreased heart failure may also be the outcome of a successful catheter ablation procedure, but these reasons are as yet unproven, and will require a systematic evaluation in large randomized trials.[13]

AF represents an important public health issue. To date there is no FDA approved catheter based treatment of AF. Increased off label use of catheters for this indication has grown substantially during the exceptionally long duration of the conduct of this IDE study. This multicenter randomized study, conducted under the recommendations established in the FDA guidance document, "Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation (January 2004)"[63] evaluates the safe and effective use of the THERMOCOOL catheter for the treatment of paroxysmal AF.

2.0 Materials and Methods

2.1 Materials

2.1.1 The NAVISTAR THERMOCOOL Irrigated Catheters

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

The NAVISTAR THERMOCOOL catheter (Figure 2.1.1A) 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.

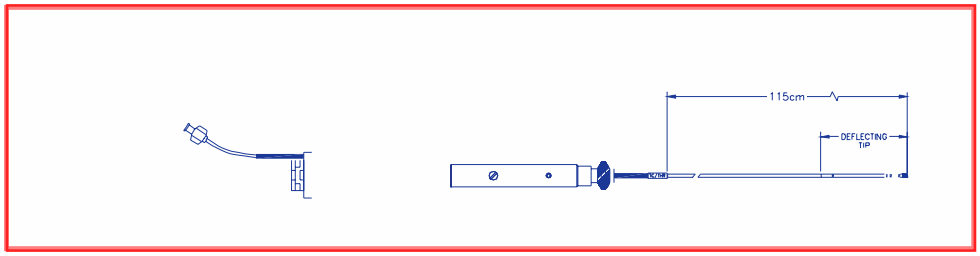
The catheter body is single lumen high-torque 7.5F shaft extruded from biocompatible PEBAX with a handpiece at the proximal end. A puller wire is anchored in the tip electrode and runs though the catheter shaft to a piston in the handpiece. A saline tube also extends from the tip through the shaft to 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 cm 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.

The FDA has approved the commercial distribution of the catheter for the treatment of ventricular tachycardia and atrial flutter.

FIGURE 2.1.1A NAVISTAR THERMOCOOL Catheter



2.1.2 The CARTO Navigation System

The NAVISTAR THERMOCOOL catheter is designed to work with the CARTO to provide the user with real-time anatomical and electrophysiological information. The accuracy of the system has been shown by in vitro studies to be less than or equal to 1 mm. CARTO allows continuous mapping even during RF ablation, and requires the use of only one catheter for mapping and ablating during the procedure.

The CARTO information enables tracking of the tip of the mapping catheter within the heart, enabling navigation of the catheter independent of fluoroscopy. Signals generated within the location sensor are transmitted through a printed circuit board (PCB) in the catheter handpiece, to the main processing unit, via the junction box. The

3D geometry of the chamber is reconstructed in real time, and the color-coded electrophysiological information obtained by the sensing electrode can be superimposed on the anatomical map.

2.1.3 STOCKERT 70 RF Generator and Cables

The STOCKERT™ 70 RF Generator and associated cables were approved for marketing under P990071.

2.1.4 COOLFLOW Irrigation Pump & Tubing (P990071/S005)

The COOLFLOW™ Irrigation Pump is a peristaltic pump designed for the delivery of irrigation solutions when used in conjunction with the COOLFLOW Tubing Set and an irrigation device (eg, the NAVISTAR THERMOCOOL catheter). Additionally, other intravenous access pumps such as MedRad could be used to maintain continuous infusion during the procedure.

2.2 Methods

2.2.1 Study Objective

The primary objective of this trial was to demonstrate the safety and efficacy of the NAVISTAR® THERMOCOOL® catheter for the RF ablation treatment of subjects with symptomatic paroxysmal atrial fibrillation (PAF) who were refractory or intolerant to antiarrhythmic drug (AAD) therapy.

2.2.2 Study Design

The study was a prospective, randomized, unblinded, multi-center pivotal clinical investigation involving up to 230 subjects at up to 30 centers. The guidance document issued on January 9, 2004 entitled, "Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation"[63], was used in the development of this study design.

2.2.2.1 This section intentionally left blank

2.2.3 Safety & Effectiveness Endpoints

2.2.3.1 Effectiveness Parameters

Acute success for the ablation of PAF was defined as the confirmation of entrance block into all targeted PVs.

Chronic success was defined as freedom from symptomatic AF based on electrocardiographic data and no changes in the AAD regimen [class I or III, or AV nodal blocking agents such as beta blockers (BB) and calcium channel blockers (CCB)] during nine months following treatment [Days 91-361 for the THERMOCOOL group and from Days 15-285 for the AAD (Control) group].

FIGURE 2.2.3.1A Effectiveness Evaluation Windows (270 days)

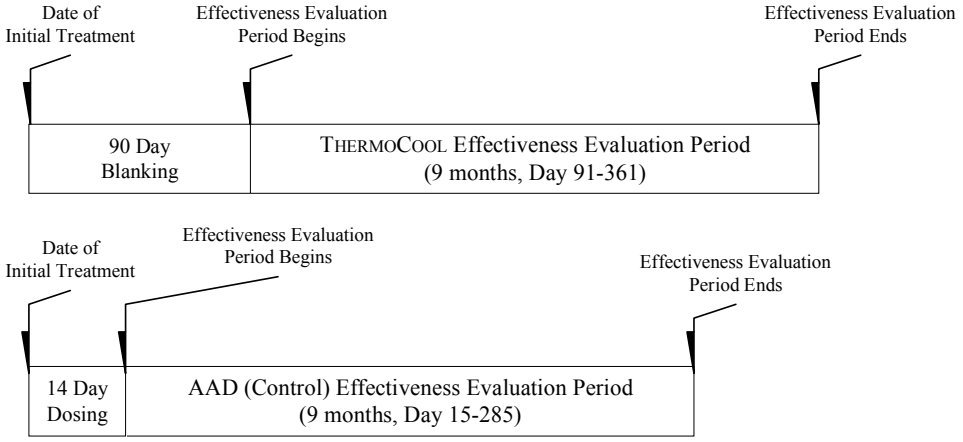


Figure 2.2.3.1A is a visual representation of the nine-month chronic effectiveness evaluation windows. The 9-month effectiveness evaluation window for the THERMOCOOL group was preceded by a 90-day blanking window. The 9-month effectiveness evaluation window for the AAD (Control) group was preceded by a 14-day dosing period wherein the dosing of their study AAD could be adjusted to its most efficacious dose.

Chronic success for the test group was evaluated at 12 months (includes the 3 month blanking period) from the initial ablation procedure. Chronic success for the control group was evaluated 9.5 months after the initiation of the study's AAD therapy.

Acute success was determined at the completion of each study ablation procedure. Subjects undergoing an ablation procedure during the 9-month evaluation period were deemed chronic failures.

The secondary effectiveness endpoints for this study are comparisons between the test and control groups on the following:

- *AF* status will be evaluated for each subject by assessing:
  - 24-hour Holter data
  - Transtelephonic monitor (TTM) data
  - AF frequency/severity checklist
  - Quality of Life (QOL scores)

2.2.3.2 Safety Parameters

Adverse events (AEs) were documented through the course of the study. The primary safety endpoint was single-arm, namely the proportion of subjects undergoing ablation who experienced specific early onset (within 7 days of ablation procedure) adverse events, designated as primary adverse events (primary AEs). Late onset (>90 days post-treatment) and early onset (≤90 days post-treatment) of serious (SAEs) and non-serious AEs were analyzed with descriptive statistics by category and by type of serious event.

The secondary endpoints for this study are comparisons between the test and control groups on the following:

- *Early onset (≤ 90 days post treatment)* of SAEs
- *Early onset (≤90 days post treatment)* of non-serious AEs
- *Late Onset (> 90 days post treatment)* of SAEs

2.2.4 Subject Population

Subjects that were considered for inclusion in the study had to satisfy the criteria specified in sections 2.2.4.1 and 2.2.4.2.

2.2.4.1 Inclusion Criteria

The inclusion criteria underwent a minor amendment during the course of the study. The final inclusion criteria were as follows:

1. Patients with symptomatic PAF who had 3 AF episodes in the 6 months prior to randomization, one of which was documented by electrocardiogram (ECG), transtelephonic monitor (TTM), Holter monitor, or telemetry strip.
2. Failure of at least one AAD for PAF [class I or III, or AV nodal blocking agents such as beta blockers (BB) and calcium channel blockers (CCB)] as evidenced by recurrent symptomatic PAF, or intolerable side effects due to AAD.
3. Signed Patient Informed Consent Form
4. Age 18 years or older
5. Able and willing to comply with all pre-, post-, and follow-up testing and requirements.

2.2.4.2 Exclusion Criteria

1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or non-cardiac cause.
2. Previous ablation for AF.
3. Patients on amiodarone therapy at any time during the previous 6 months.
4. AF episodes that last longer than 30 days and are terminated via cardioversion.
5. Any valvular cardiac surgical procedure.
6. CABG procedure within the last 180 days (six months).
7. Awaiting cardiac transplantation or other cardiac surgery within the next 360 days (12 months).
8. Documented left atrial thrombus on imaging [e.g. Transesophageal echocardiogram (TEE)].
9. History of a documented thromboembolic event within the past one (1) year.
10. Diagnosed atrial myxoma.
11. Presence of implanted ICD.
12. Significant pulmonary disease, (e.g. restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms.
13. Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study.
14. Women who are pregnant (by history of menstrual period or pregnancy test if the history is considered unreliable).
15. Acute illness or active systemic infection or sepsis.
16. Unstable angina.
17. Myocardial infarction within the previous 60 days (two months).
18. Left ventricular ejection fraction (LVEF) <40%.
19. History of blood clotting or bleeding abnormalities.
20. Contraindication to anticoagulation (i.e. heparin or warfarin).
21. Contraindication to computed tomography/magnetic resonance angiography (CT/MRA) procedure.
22. Life expectancy less than 360 days (12 months).
23. Enrollment in an investigational study evaluating another device or drug.
24. Uncontrolled heart failure or NYHA class III or IV heart failure.

25. Presence of intramural thrombus tumor, or other abnormality that precludes catheter introduction or manipulation.
26. Presence of a condition that precludes vascular access.
27. Left atrial size ≥ 50 mm.

2.2.4.3 Definitions

AF episode – an episode of 30 seconds or longer in duration. An episode exhibiting characteristics of both AF and atrial flutter was considered to be an AF episode. An episode of only atrial flutter was not considered to be an episode of AF.

Symptomatic AF – required symptom(s) of AF that were experienced by the subject, made them seek medical attention, and were concurrent with a documented episode by ECG, TTM and/or Holter monitor. Symptoms may have included palpitations, irregular pulse (i.e. rapid, racing, pounding, fluttering, bradycardia), dizziness, weakness, chest discomfort, and breathlessness.

Primary AE – a serious adverse event, from the list below, that occurs within 7 days of a study ablation procedure.

- 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

PV stenosis – greater than or equal to 70% diameter reduction of the PV from the baseline CT/MRA scan.

2.2.5 Study Procedures

2.2.5.1 Screening

Patients who met the inclusion and exclusion criteria, signed the patient informed consent form, and were randomized were considered enrolled into the study.

2.2.5.2 Randomization method

A randomization sequence was generated by a Biosense Webster, Inc. biostatistician prior to the start of the study by allocating treatment groups with use of envelopes. Patients who met study eligibility criteria and signed an informed consent document were randomized in the order of qualification. Randomization was to occur prior to the start of any medical or ablation treatment.

Each patient's study assignment was kept in a sealed confidential envelope. The envelopes were numbered sequentially and the coordinator was instructed to take the lowest number available when each patient was randomized. The envelope was to be opened when the patient was in the outpatient department to ensure that the patient selection was unbiased. Investigators, other study personnel, and the patient were not able to identify the study assignment until the time of randomization.

2.2.5.3 Pre-Procedure Evaluations

Control Group

The following pre-procedure evaluations were performed within 30 days prior to the start of a study drug, unless otherwise indicated:

- Quality of Life Questionnaires (SF36; Atrial Fibrillation Symptom Frequency and Severity Checklist)
- 24-hour Holter Monitor
- ECG (12-lead)
- Transthoracic Echocardiogram (TTE)
- Liver Function tests
- A pregnancy test, for pre-menopausal women only, within 48-hours prior to the start of the study drug.

Test Group and Control Subjects Undergoing Ablation

The following pre-procedure evaluations were performed within 30 days prior to the day of an initial ablation procedure, unless otherwise indicated:

- Quality of Life Questionnaires (SF36; Atrial Fibrillation Symptom Frequency and Severity Checklist)
- 24-hour Holter Monitor. Control subjects undergoing ablation were not required to have a 24-hour Holter Monitor prior to their ablation procedure.
- ECG (12-lead)
- TTE
- CT/MRA scan
- Liver Function tests
- A neurological exam was performed by a medical staff member of the neurology department in the 72 hours prior to the ablation procedure.
- Transesophageal echocardiogram (TEE), within at least 24 hours prior to the ablation procedure to evaluate for the presence of left atrial thrombus.
- A pregnancy test, for pre-menopausal women only, within 48-hours prior to the ablation procedure.
- Anticoagulation therapy was recommended for 30 days prior to the ablation procedure.

2.2.5.4 Dosing Procedures for the Control Group

Subjects randomized to the control arm of the study were eligible to receive the approved medications for treating AF listed in Table 2.2.5.4A. Subjects were to receive trial medications and dosing as determined at the discretion of the investigator. Recommended dosing for each approved AF drug from the "ACC/AHA/ESC 2001 Practice Guidelines for Management of Subjects with Atrial Fibrillation" was included in the protocol and is also cited in Table 2.2.5.4A. The maximum dose was not to exceed the manufacturer's recommended maximum dose as specified in the approved labeling.

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TABLE 2.2.5.4A Approved Drugs for the Treatment of Atrial Fibrillation

Medication	Route of Administration	Type	Level of Evidence	Minimum Recommended Dose
Dofetilide*	Oral	III	A	500 mcg
Flecainide	Oral	IC	B	200 mg
Propafenone	Oral	IC	B	450 mg
Sotalol	Oral	III	A	240 mg
Quinidine**	Oral	IA	B	600 mg

* The protocol recommended minimum 24 h dose, based on the published ACC/AHA/ESC guidelines.[36] Dosing regimens based on creatinine clearance per ACC/AHA/ESC 2001 practice guidelines
**Dosing was to be divided in doses over 6-12 hours, usually with a rate-slowing drug per ACC/AHA/ESC 2001 practice guidelines and should have been a quinidine based drug.

AADs were defined as class I, class III, or AV nodal blocking agents such as beta blocking agents (BB) or calcium channel blockers (CCB). The addition of BBs, CCBs, or digitalis was allowable for rate control secondary to the proarrhythmia effects of AADs at the beginning of the dosing period so that the dosage was stable for the evaluation period. Such medication was to be maintained for the duration of the subject's involvement in the study unless deemed unnecessary or detrimental by the treating physician.

Control subjects had a 2-week dosing period wherein the subject's medication was dosed for maximum effectiveness for the treatment of PAF. After the dosing period, the subject was to be maintained on the same drug for the entire length of their involvement in the study.

2.2.5.5 Ablation Procedure

Pre-Ablation Procedures

Each investigational ablation procedure was to follow the pre-ablation procedures below:

- Dosimeter badges were placed on the posterior back of the subject to measure and evaluate exposure to radiation from fluoroscopy.
- Anesthesia was delivered per standard electrophysiology (EP) laboratory protocol.
- Urine output during the procedure and/or first void post-ablation procedure was measured.
- Diagnostic catheters, such as coronary sinus and LASSO™ catheters, were appropriately placed. Use of other such catheters was at the discretion of the investigator.
- A routine EP study was performed at the discretion of the investigator
- A single or double transseptal puncture was completed to access the left atrium per standard EP lab protocol.
- Systematic anticoagulation with heparin was administered with the activated clotting time (ACT) checked at least every 30 minutes to maintain a recommended ACT of 250-350 seconds
- Evaluation of the location, morphology and dimensions of each PV by PV venogram or intracardiac echocardiography (ICE) was performed at the discretion of the investigator
- Prior to the ablation in the region of the right superior PV, precautionary measures, such as pacing maneuvers, were recommended to evaluate proximity to the phrenic nerve.
- If the subject was in AF, cardioversion of the subject was performed at the discretion of the investigator.

The following procedures were required:

- The NAVISTAR THERMOCOOL catheter was introduced using fluoroscopic guidance
- The CARTO Navigation System was utilized to map the anatomical location of the PV and RF lesions.
- The circumferential anatomical approach was used to electrically isolate all of the PV. It was recommended that the energy applications were at least 1 to 2 cm outside of the PV ostium to minimize the risk of PV.
- If it was not possible to safely treat the right superior PV due to its proximity to the phrenic nerve, it was documented on the case report form.
- For every application of RF energy, the power, maximum electrode temperature, impedance, irrigation flow rate, and duration of energy application were monitored continuously and recorded.

The following procedures were optional based on clinical findings:

- Non-PV foci initiating AF in the left and/or right atrium were mapped and targeted.
- Ablation along the mitral isthmus between the inferior portion of the left-sided circumferential lesion and the lateral mitral valve annulus was only allowed if left atrial flutter was induced during the ablation procedure.
- Ablation in the cavo-tricuspid isthmus for the ablation of right-sided, isthmus dependent flutter was only allowed if this flutter was induced during the procedure.

Verification of ablation procedure(s):

- Electrical isolation for all PVs targeted was confirmed by demonstrating entrance block into each vein. The Lasso™ catheter technique was recommended for this verification. Atrial electrograms were analyzed in sinus and/or an atrial paced rhythm confirming the absence of PV potentials.
- Termination of all targeted non-PV foci and bi-directional block of linear lesions was verified, where appropriate.
- A PV venogram or intracardiac echocardiography was used post-procedure to evaluate for PV stenosis. If one of these two assessments were used prior to the procedure, the same method was used post-procedure to compare and evaluate if there had been changes to the PV sizes during the procedure.
- Infusion of isoproterenol was recommended post-ablation to confirm that all AF foci had been eliminated or isolated. Isoproterenol was administered in a dosing range of 2 to 20 mcg/min to achieve a ≥ 20 bpm increase in heart rate.
- Pacing maneuvers were recommended to determine whether the ablation eliminated the ability of the atrium to sustain AF, including atrial burst pacing to a cycle length of 200 ms in the absence of isoproterenol.

Post-procedure Assessments and Requirements:

Prior to discharge, a TTE was performed to exclude the presence of intracardiac thrombus, pericardial effusion, or any mechanical injury to cardiac structures. A post-procedure neurological exam was performed and compared to the pre-procedure neurological exam for the purposes of identifying any deficits that may have resulted from the ablation procedure. A 12-lead post-procedure ECG was also taken.

Anticoagulation therapy was required to be administered until the 3-month visit CT/MRA scan was performed. The use of additional medications and anticoagulants during the trial was at the discretion of the investigator.

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2.2.5.7 Follow-up Assessments

THERMOCOOL (Test) Group

Five (5) follow-up visits were required at 1 month, 3 months, 6 months, 9 months, and 1 year following the initial ablation procedure. Subjects also received a health survey by mail to complete 2 years after initial treatment.

The following assessments were performed post-treatment:

- Medical history since the last assessment.
- Medication changes since the last assessment.
- Liver function tests: ALT, AST, ALP (at the 3 and 12-month visits).
- 12-lead ECG (at the 3 , 6 , 9 , and 12-month visits).
- 24-hour Holter Monitor (at the 12-month visit).
- Quality of Life assessment: SF-36 and the Symptom Frequency and Severity checklist (at the 6, 9, and 12-month visits).
- CT/MRA scan to be performed at the 3 and 12-month follow-up visits. The follow-up imaging test was the same type as the pre-ablation imaging test.
- TTE at the 3 and 12-month follow-up visits.
- TTM transmissions for all symptomatic cardiac episodes and weekly asymptomatic transmissions for the first 8 weeks (post-blanking) during the effectiveness assessment period. After the first 8 weeks, asymptomatic episodes would be transmitted once a month until the end of the effectiveness assessment period.

AAD (Control) Group

Five (5) follow-up visits were required at 1 week, 2 weeks, 3 months, 6 months, and 9 months after the dosing of the investigational drug started. The subject also received a health survey by mail to complete 2 years after initial treatment.

The following assessments were performed post-treatment:

- Medical history since the last assessment.
- Medication changes since the last assessment.
- Liver function tests: ALT, AST, ALP (at the 3-month visit).
- 12-lead ECG (at the 2-week, 3-month, 6-month, and 9-month visits).
- 24-hour Holter Monitor (at the 9-month visit).
- Quality of Life assessment: SF-36 and the Symptom Frequency and Severity checklist (at the 3, 6, and 9-month visits).

TTM transmissions for all symptomatic cardiac episodes and weekly asymptomatic transmissions for the first 8 weeks (post-dosing) during the effectiveness assessment period. After the first 8 weeks, asymptomatic episodes would be transmitted once a month until the end of the effectiveness assessment period.

2.2.5.8 AAD Management

THERMOCOOL (Test) Group

During the 90 days following the initial ablation procedure, if symptomatic AF recurred such that the subject warranted AAD therapy, a previously ineffective but tolerated AAD was allowed to be initiated to allow for the assessment of the effectiveness of a previously ineffective AAD. If the subject was changed to a new AAD, had it increased in dose, or if new AADs were added between 91-361 days after the initial ablation, the subject was considered a chronic effectiveness failure.

If the subject was on AV nodal blocking agents such as BBs and/or CCBs during the blanking period, they were to maintain the dose from days 91-361. If these medications were changed to a new medication, increased in dose, or new ones were added during days 91-361, the subject was considered a chronic effectiveness failure.

After the 90-day blanking period, AADs were to be withdrawn (if re-initiated post-ablation) if there was no symptomatic AF recurrence. If a newly prescribed AAD was continued to be used after the 90-day blanking period, the subject was considered a chronic effectiveness failure.

AAD (Control) Group

Subjects that were randomized to the AAD (Control) group had a 2-week dosing period during which the subject's study AAD was dosed for maximum effectiveness for the treatment of PAF. After the 2-week dosing period, the subject's AAD dose was to be fixed and maintained for the remainder of the study. It could not be increased or supplemented by a new AAD for AF or the subject would be considered a chronic effectiveness failure.

Subjects were to receive trial AAD medications and dosing as determined at the discretion of the investigator. Medication dosing, as recommended by the ACC/AHA/ESC 2001 Practice Guidelines for Management of Subjects with Atrial Fibrillation[64] was included in the study protocol and is presented in Table 2.2.5.8A.

TABLE 2.2.5.8A Recommended Dosing of Anti-Arrhythmic Drug Therapy for Subjects in the AAD (Control) Group

Drug	Route of Administration	Type	Level of Evidence	Minimum Recommended Dosage
Dofetilide*	Oral	III	A	500 mcg
Flecainide	Oral	IC	B	200 mg
Propafenone	Oral	IC	B	450 mg
Sotalol	Oral	III	A	240 mg
Quinidine**	Oral	IA	B	600 mg

* The protocol recommended minimum 24 h dose, based on the published ACC/AHA/ESC guidelines.[64] Dosing regimens based on creatinine clearance per ACC/AHA/ESC 2001 practice guidelines
**Dosing was to be divided in doses over 6-12 hours, usually with a rate-slowing drug per ACC/AHA/ESC 2001 practice guidelines and should have been a quinidine based drug.[64]

Under specific circumstances, control subjects could become eligible for an ablation procedure with the investigational device.

- In the first 90 days post-treatment, if a control subject experienced a safety and chronic effectiveness failure, the subject became eligible for an ablation procedure with the investigational device. A safety failure was defined as a category 1 or 2 SAE (see section 2.2.8 for a more detailed

explanation). Recurrence of documented symptomatic AF during the effectiveness evaluation period was considered a failure of chronic effectiveness.

- From days 91-285, if a control subject experienced a documented recurrence of symptomatic PAF (effectiveness failure), the subject gained eligibility.
- Control subjects completing their 9-month observation window without experiencing a documented episode of symptomatic PAF became eligible for the 2 months after their 9-month visit.

If a subject randomized to the control arm underwent an investigational study procedure, the subject was followed according to the parameters of the test group starting with the date of the initial ablation. Table 2.2.5.8B summarizes the eligibility requirements for AAD (Control) subjects to undergo an ablation with the THERMOCOOL catheter.

TABLE 2.2.5.8B AAD (Control) Subject Eligibility Requirements to Undergo an Ablation with the THERMOCOOL Catheter

Study Duration (days)	AAD (Control) Subject Criteria for Ablation Procedure
0-90	Safety and effectiveness failure
91-285	Effectiveness failure
Post-285	Completion of the trial
0-285	Subject withdrawal

2.2.6 Statistical Plan

2.2.6.1 Sample Size Determination and Statistical Methods

The sample size computation was based on the primary effectiveness endpoint of chronic effectiveness. The chronic success rates were compared between the treatment group (NaviStar® THERMOCOOL® Catheter) and the control group (AAD). An adaptive approach to sample size is utilized. The sample size varied from ---- to 230 total subjects.

Detailed sample size, simulation results and operating characteristics are as follows.

Primary Effectiveness Analysis:

The Primary Effectiveness Analysis was based on Bayesian approach with adaptive sample size.

Let P_T be the probability of success for the treatment group and P_C be the probability of success for the control group (no documented symptomatic AF during the 9-month effectiveness evaluation period). The treatment will be considered efficacious if it is shown to be superior to the control. If the posterior probability that the treatment success rate is larger than the control success rate is greater than ---- then the trial will be considered successful in showing effectiveness—the trial will be considered a success

$$\Pr [P_T > P_C \mid \text{Data}] \geq \text{----}$$

The posterior probability above is calculated assuming independent Beta(1,1) prior distributions. The cut-off value of ---- is determined to preserved a type I error.

Adaptive Sample Size and Early Accrual Stopping:

When accrual reaches sample sizes of ---- an interim analysis will be performed. If the predictive probability of trial success is at least ---- then accrual will stop and the sample size will be the final sample size. If the p the current sample size and the maximum sample size (230) are less than ---- then the trial stops for futility.

An independent consultant firm was contracted to conduct the interim analysis for the purpose of potential early stopping.

Operating Characteristics

The operating characteristics for the claim of effectiveness were evaluated and simulations were performed for power computation. The results are based on 10,000 simulated trials per scenario.

Primary Safety Endpoint

The primary safety endpoint was analyzed as a single proportion of subjects experiencing early onset (within 7 days of ablation procedure) primary adverse events. The estimate of proportion and one-sided 95% confidence bound was computed using the Binomial Exact Test.

2.2.7 Core Laboratories

2.2.7.1 Transtelephonic Monitor and Holter Analysis

A core laboratory facilitated the distribution and analyses of TTM and Holter monitors for this study. Per the study protocol, subjects were required to transmit a minimum of 15 TTM recordings during the 9-month chronic effectiveness evaluation period. Subjects were required to record and transmit at least one cardiac episode per week for the first eight weeks of the 9-month evaluation period. After the first 8 weeks, subjects were required to transmit cardiac episodes at least once a month until the efficacy assessment period was completed. If a subject missed a scheduled recording, the core laboratory was responsible for contacting the subject to remind them of their scheduled recording. In addition, subjects were asked to record and transmit all symptomatic cardiac episodes.

Subjects called a toll free phone number to the core laboratory to transmit cardiac episodes. They were asked if the recordings being transmitted were associated with any symptoms. If present, these symptoms were to be annotated in the corresponding report. A notification was sent to the investigator responsible for the subject's care if any of the pre-specified terms listed below were met.

- Symptoms reported included weakness or visual disturbance regardless of the rhythm transmitted
- The transmitted rhythm was found to have a rate of 150 bpm or more for a period of at least 30 seconds
- Subject reported chest pain and shortness of breath with electrocardiographic changes that were different from the subject's normal rhythm

The core laboratory algorithm reported an initial interpretation that was then serially reviewed by 2 certified electrocardiogram technicians at the core laboratory and a report was generated. The report then underwent an independent review by a third party cardiologist. If the cardiologist did not agree with the classified rhythm on the report, the reports were amended per his final interpretation.

Holter Monitor
Holter monitors were given to subjects within the 30 days prior to the initial ablation procedure, if randomized to the RF ablation arm, or within thirty 30 days prior to initial dosing of the assigned study drug, for subjects randomized to the control arm. A repeat Holter recording was also performed at the subject's completion of the efficacy evaluation period. Holter monitor recordings were transmitted from the study center to the core lab. The report was then forwarded to a third-party cardiologist to confirm the proper interpretation was made.

2.2.7.2 CT/MRA

A core laboratory facilitated the processing of CT/MRA scans for this study. Subjects that were scheduled for an ablation procedure were required to have a CT scan in the 30 days prior to their procedure, 3 months after the initial procedure, 12 months after the initial procedure, and before any additional re-ablation procedures. All CT/MRA scans for this clinical trial were reviewed by a board certified radiologist.

2.2.7.3 This Section intentionally left blank

2.2.8 Adverse Events (AEs):

AEs were recorded on the electronic case report forms throughout the study.

The primary safety endpoint is the incidence of early onset (within 7 days of ablation procedure) of the following adverse events (primary AEs):

- 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

Serious Adverse Event (SAE)
An SAE was defined as any clinical event that resulted in death, a life-threatening complication, or a persistent or significant disability/incapacity that required inpatient hospitalization or prolonged hospitalization or required intervention to prevent a permanent impairment of a body function or damage to a body structure.

The following clinical events were not considered as AEs in the THERMOCOOL group for this clinical study:

- Minor bleeding, oozing or ecchymosis from intravenous sites or gums
- Pacemaker implantation for nodal dysfunction rhythms (sick sinus syndrome, sinus bradycardia, sinus arrest or AV blocks) that resulted in symptomatic bradycardia (unrelated to the ablation procedure or related to pre-existing disease states)
- Self-limiting pericarditis attributable to the ablation procedure defined as pleuritic chest discomfort with or without pericardial rub and ECG changes and did not require additional hospitalization

The following clinical event was not considered an AE in the AAD (Control) group for this clinical study:

- Pacemaker implantation for nodal dysfunction rhythms (sick sinus syndrome, sinus bradycardia, sinus arrest or AV blocks) that resulted in symptomatic bradycardia (related to pre-existing disease states)

Secondary Comparative Safety Endpoint

Biosense Webster developed a hierarchical classification of AE based on 2 categories of level of severity to quantify the relative incidence of adverse events across the treatment groups:

All AEs were monitored until they were resolved or explained. Each AE was reported regardless of classification, seriousness, intensity, outcome, or causality. In order to minimize risks to subjects enrolled in the study, the study protocol required that the sponsor convene a Clinical Events Committee (CEC) on an annual basis to review the safety data and determine appropriate action(s) to ensure subject safety.

In order to fulfill this requirement, the sponsor assembled an independent committee that was comprised of the following members:

In addition to reviewing the accumulating safety data, the committee was tasked with independently adjudicating all AEs reported by the investigators in the study, including the causality of the AEs. Details of the scope and the definitions used for adjudication are provided in Appendix 19

3.0 Results

On [redacted] Biosense Webster, Inc. received conditional approval from the agency to begin this study. In October 2004, the first subject was enrolled. In October 2005, 11 subjects were enrolled in the study. After two years (October 2006) of screening over 2100 patients, only 53 subjects were enrolled; representing an approximately 2.5% enrollment rate. In October 2007, the study enrollment was closed with 167 subjects enrolled and approximately 5500 patients screened, representing a 3% overall enrollment rate.

The most common reasons for screening failure were:

- Subjects not meeting the protocol criteria for having sufficient AF episodes in the period prior to enrollment.
- Having a previous ablation for AF.
- Subjects' unwillingness to participate in a randomized study.

In an effort to increase enrollment and complete the study, Biosense Webster, Inc. collaborated with the FDA and revisions of the protocol were approved that expanded inclusion criteria; allowing subjects that previously failed beta-blockers and/or calcium channel blockers and subjects that had three documented episodes in the previous six months to be enrolled in the study (Protocol version [redacted] and [redacted] respectively).

The increase in enrollment accrual between October 2005 and October 2007 was attributed to the modification to the inclusion criteria in the study protocol and the addition of higher volume ablation centers outside the United States.

On [redacted] the company proposed adopting a Bayesian statistics plan. A modified safety endpoint was approved on [redacted] and the Bayesian analysis plan, which included early stopping rules adopted from the "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials - Draft Guidance for Industry and FDA Staff" was fully approved by the agency on [redacted]

The study protocol specified that interim analyses would be conducted when subject accrual reached sample sizes of [redacted] subjects. The interim analysis indicated in Section 3.5 is based on a dataset taken in Septemb

Due to the nature of this Bayesian approach, the presentation of the trial's results utilizes two datasets: September 2007 (N=160) and June 2008 (N=167).

The June 2008 dataset was the basis for the following sections:

- *Section 3.1* – Subject Enrollment and Disposition
- *Section 3.2* – Demographics & Baseline Characteristics
- *Section 3.3* – Protocol Deviations
- *Section 3.4* – Procedural Data

Section 3.5 introduces the first interim analysis based on the September 2007 dataset. This interim analysis was the basis for early stopping of the study and for declaring success. A primary safety endpoint analysis was also included in this section.

Section 3.6 presents the Bayesian and frequentist analyses using the June 2008 dataset for effectiveness outcomes. A primary safety endpoint analysis was also included in this section.

The following protocol classifications were used in all analyses:

Enrolled Subjects were subjects that were eligible for enrollment, signed an informed consent document, and randomized to a treatment group.

Excluded Subjects were enrolled but did not have the study catheter inserted or did not receive the newly prescribed AAD.

Discontinued Subjects were subjects that met the following "discontinued criteria" for their corresponding randomization:

- **THERMOCOOL Group –** Subjects that had the study catheter inserted but did not undergo ablation or attempted ablation with the study catheter, i.e. no RF energy applied; subjects were categorized as "discontinued" if ablation was not possible due to non-study equipment failure or if their arrhythmia was determined at the time of electrophysiological study to be a non-study arrhythmia (e.g. atrial flutter, instead of PAF under investigation).
- **AAD (Control) Group** - Subjects that received a newly prescribed AAD but did not complete the dose-loading period (2 weeks) for reasons other than a safety failure or if their arrhythmia was determined to be a non-study arrhythmia (e.g. atrial flutter).

Overall Safety Cohort is comprised of randomized subjects, in the THERMOCOOL group, that had the study catheter inserted or, in the AAD (Control) group, that began dosing with a newly prescribed AAD as directed in the protocol. This cohort encompasses both discontinued and per-protocol subjects.

Effectiveness Cohort is comprised of subjects received treatment per their randomization assignment (intention to treat) for the specific study-related arrhythmia.

Primary Safety Cohort is comprised of subjects that underwent an ablation procedure with the study catheter. This group includes subjects that were randomized to the ablation arm and underwent RF ablation therapy as well as subjects that were randomized to AAD therapy but, in the course of the study, became eligible for RF ablation and underwent RF ablation therapy with the study catheter.

3.1 Subject Enrollment and Disposition

3.1.1 Study Period

There were 167 subjects enrolled in the study. The first subject was enrolled on October 25, 2004, and the last subject was enrolled on October 11, 2007. Follow-up data were collected on available subjects through the 9-month effectiveness analysis period for subjects randomized to AAD therapy, and the 12-month effectiveness analysis period (after a 3-month blanking period) for subjects randomized to RF Ablation therapy with the THERMOCOOL catheter. The data presented in this section are based on the June 2008 dataset, which included all enrolled subjects.

3.1.2 Subject Enrollment and Disposition

In this analysis, there were 167 subjects that were enrolled at 19 investigational sites. Fifteen (15) of these sites were located in the US and 4 sites were located outside the US.

Table 3.1.2A shows the overall subject enrollment and accountability.

TABLE 3.1.2A Subject Enrollment and Accountability (N=167)

Disposition	Treatment Group		Total
	THERMOCOOL	AAD (Control)	
Enrolled	**106**	**61**	**167**
Excluded	3	4	7
Overall Safety Cohort	103	57	**160**
Discontinued	0	1	1
Effectiveness Cohort	103	56	**159**
AAD (Control) Not Undergoing RF Ablation		20	
Primary Safety Cohort	103	36	**139**

Figure 3.1.2A illustrates how the enrolled subjects were classified per the definitions in the study protocol.

FIGURE 3.1.2A Subject Enrollment and Accountability (N=167)

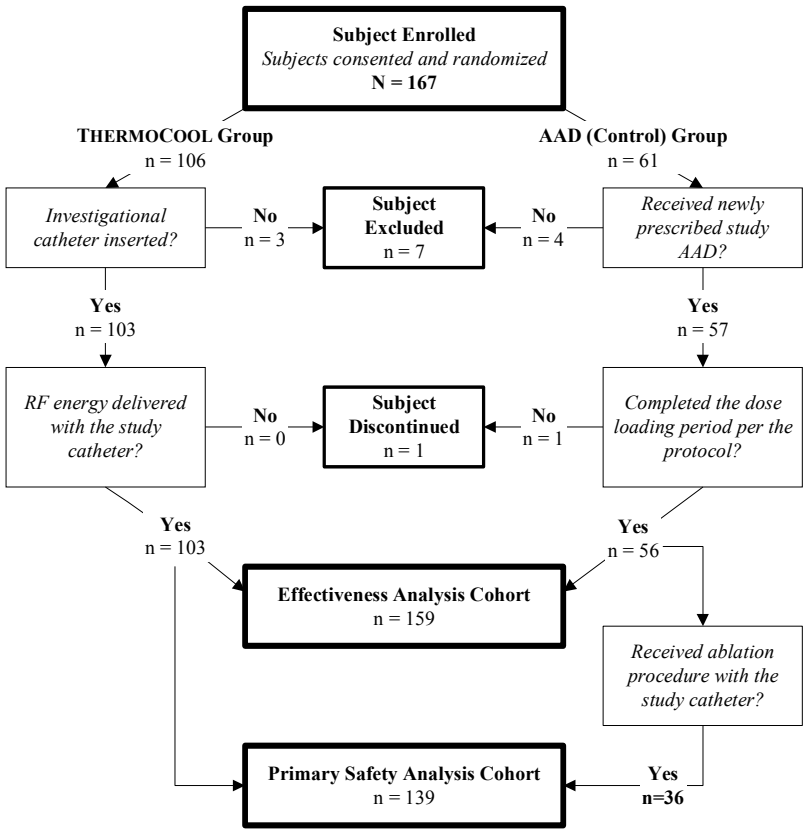

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Table 3.1.2B is a summary of the enrollment and classification distribution by study center in alphabetical order. The highest enrolling center was ---- which enrolled a total of 50 subjects followed by ---- ---- ---- ---- (n = 27) and ---- (n = 13).

TABLE 3.1.2B Subject Enrollment and Disposition (Enrolled Subjects, N=167)

Site	Total Subjects Enrolled n (%)	Excluded Subjects	Discontinued Subjects	Per-Protocol Subjects
----	2 (1.2)	0	0	2
----	9 (5.4)	1	0	8
----	1 (0.6)	0	0	1
----	1 (0.6)	0	0	1
----	27 (16.2)	0	1	26
----	6 (3.6)	0	0	6
----	10 (6.0)	1	0	9
----	12 (7.2)	0	0	12
----	8 (4.8)	0	0	8
----	1 (0.6)	0	0	1
----	13 (7.8)	0	0	13
----	5 (3.0)	1	0	4
----	1 (0.6)	0	0	1
----	2 (1.2)	0	0	2
----	6 (3.6)	2	0	4
----	5 (3.0)	1	0	4
----	2 (1.2)	0	0	2
----	50 (29.9)	1	0	49
----	6 (3.6)	0	0	6
Total	**167 (100.0)**	**7 (4.2)**	**1 (0.6)**	**159 (95.2)**

Code	Site Name	Code	Site Name

The randomization schedule was designed to follow a 2:1 ratio for assigning patients to either the THERMOCOOL group or the AAD (Control) group. Table 3.1.2C presents the subject enrollment by treatment group in alphabetical order.

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TABLE 3.1.2C Subject Enrollment by Site and Treatment Group (Enrolled Subjects, N=167)

Site	Treatment Group		
	THERMOCOOL	AAD (Control)	Total
	n (%)	n (%)	N
----	1 (50.0)	1 (50.0)	2
----	5 (55.6)	4 (44.4)	9
----	1 (100.0)	0 (0.0)	1
----	1 (100.0)	0 (0.0)	1
----	17 (63.0)	10 (37.0)	27
----	4 (66.7)	2 (33.3)	6
----	7 (58.3)	5 (41.7)	12
----	6 (60.0)	4 (40.0)	10
----	5 (62.5)	3 (37.5)	8
----	0 (0.0)	1 (100.0)	1
----	8 (61.5)	5 (38.5)	13
----	3 (60.0)	2 (40.0)	5
----	1 (100.0)	0 (0.0)	1
----	1 (50.0)	1 (50.0)	2
----	5 (83.3)	1 (16.7)	6
----	3 (60.0)	2 (40.0)	5
----	2 (100.0)	0 (0.0)	2
----	31 (62.0)	19 (38.0)	50
----	5 (83.3)	1 (16.7)	6
Total	**106 (63.5)**	**61 (36.5)**	**167**

Excluded Subjects

There were 7 excluded subjects. Three (3) of these subjects were from the THERMOCOOL group and 4 of the subjects were from the AAD (Control) group. Excluded subjects were not included in any of the analyses (Overall Safety Cohort, Effectiveness Cohort, or Primary Safety Cohort). Reasons for exclusion are provided in Table 3.1.2D.

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TABLE 3.1.2D Excluded Subjects (n=7)

Subject ID	Description
THERMOCOOL Group Subjects	
	Physician elected to withdraw the subject after randomization. Subject was diagnosed with persistent AF.
	Insurance denied coverage for an RF ablation procedure with a study catheter and resulted in patient withdrawal.
	Subject withdrew consent.
AAD (Control) Group Subjects	
	Subject withdrew consent after randomization to the AAD (Control) group and elected to have a non-study RF ablation procedure.
	Subject withdrew consent after randomization to the AAD (Control) group. Subject refused hospitalization for dose loading of the assigned study drug.
	Subject withdrew consent after randomization. Subject had been prescribed a new AAD several weeks prior to enrollment. While on this new AAD, the subject was free of symptomatic AF and withdrew consent prior to capturing an episode.
	Subject withdrew consent after randomization and elected to have a non-study RF ablation procedure.

Note: and were withdrawn from the study immediately after randomization. As such, baseline data is unavailable for these subjects.

Discontinued Subjects

There were no subjects randomized to the THERMOCOOL group that were discontinued. However, in the AAD (Control) group, one subject was discontinued from the study as presented in Table 3.1.2E. Discontinued subjects were excluded from the Effectiveness Cohort and Primary Safety Cohort; however, this subject was included in the Overall Safety Cohort.

TABLE 3.1.2E Discontinued Subjects (n=1)*

Subject ID	Description
	Subject withdrew consent from the study. Subject was satisfied with results from the prescribed study AAD.

* At the time of Interim Analysis (September 2007 dataset), subject ( ) was considered discontinued and was subsequently reclassified as an excluded subject in this updated analysis (June 2008 dataset). This subject is described in Table 3.1.2D above.

Lost to Follow-up

There was one subject lost to follow-up in the THERMOCOOL group and no subjects in the AAD (Control) group. Subject (THERMOCOOL group) underwent a study ablation procedure and was subsequently lost to follow-up shortly after the study procedure. Subject did not return phone messages after several attempts. This subject was included in the effectiveness and safety analyses.

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3.2 Demographics & Baseline Characteristics

Table 3.2A presents summary demographics for the enrolled subjects. Nearly all enrolled subjects were white (164/167, 98.2%), one-third of the population was female (56/167, 33.6%). At the time of enrollment, the mean age was 55.7 ± 10.7 years and the age range was from 19 to 77 years. These demographics are comparable between the THERMOCOOL and AAD (Control) groups.

TABLE 3.2A Summary Demographics (Enrolled Subjects, N=167)

	Treatment Group		Total n / 167 (%)	P-value*
	THERMOCOOL n / 106 (%)	AAD (Control) n / 61 (%)		
Gender				0.3997
Female	33 (31.1)	23 (37.7)	56 (33.5)	
Male	73 (68.9)	38 (62.3)	111 (66.5)	
Ethnicity				0.7031
Hispanic	1 (0.9)	0 (0.0)	1 (0.6)	
Other**	2 (1.9)	0 (0.0)	2 (1.2)	
White	103 (97.2)	61 (100.0)	164 (98.2)	
Age† (years)				0.3009
N	106	61	167	
Mean	55.5	56.1	55.7	
Standard Deviation	9.34	12.84	10.72	
Median	56	58	57	
Minimum	32	19	19	
Maximum	76	77	77	

* P-value for comparing THERMOCOOL vs. AAD (Control) group
** Subject [redacted] was of Arab ethnicity and subject [redacted] is a Native American.
† Age when informed consent signed.

3.2.1 Baseline Co-Morbidity Data

Table 3.2.1A summarizes the co-morbidity baseline data collected for 165 of 167 enrolled subjects. There were no statistically significant differences in the baseline co-morbidities between the randomization groups.

- 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.

TABLE 3.2.1A Pre-existing Conditions Reported at Baseline (Enrolled Subjects, N=167)*

Medical History	Treatment Group		p-value**
	THERMOCOOL n/N (%)	AAD (Control) n/N (%)	
Hypertension	51 / 105 (48.6)	30 / 60 (50.0)	0.8729
Diabetes	10 / 105 (9.5)	7 / 60 (11.7)	0.7909
Congestive Heart Failure	3 / 104 (2.9)	2 / 60 (3.3)	1.0000
Arrhythmias			
Atrial Flutter	28 / 103 (27.2)	16 / 56 (28.6)	0.8548
Atrial Tachycardia	7 / 104 (6.7)	6 / 59 (10.2)	0.5492
AV Node Re-entry Tachycardia	3 / 105 (2.9)	1 / 60 (1.7)	1.0000
Accessory Pathway	0 / 105 (0.0)	0 / 60 (0.0)	N/A
Ventricular Tachycardia	1 / 105 (1.0)	0 / 60 (0.0)	1.0000
Ventricular Fibrillation	0 / 105 (0.0)	0 / 60 (0.0)	N/A
Structural Heart Disease			
Ischemic Cardiomyopathy	5 / 105 (4.8)	6 / 60 (10.0)	0.2099
Left Ventricular Hypertrophy	5 / 105 (4.8)	3 / 60 (5.0)	1.0000
Hypertrophic Cardiomyopathy	1 / 105 (1.0)	0 / 60 (0.0)	1.0000
Non-Ischemic Dilated Cardiomyopathy	0 / 105 (0.0)	0 / 60 (0.0)	N/A
Significant Valve Disease/Replacement	0 / 105 (0.0)	1 / 60 (1.7)	0.3636
Congenital Heart Disease	0 / 105 (0.0)	1 / 60 (1.7)	0.3636
Thromboembolic Events			
Cerebrovascular Accident	2 / 105 (1.9)	1 / 60 (1.7)	1.0000
Transient Ischemic Attacks	0 / 105 (0.0)	2 / 60 (3.3)	0.1308
Pulmonary Embolus	1 / 105 (1.0)	0 / 60 (0.0)	1.0000
Other Thromboembolic Events	2 / 105 (1.9)	2 / 60 (3.3)	0.6222
Deep Vein Thrombus	2 / 104 (1.9)	0 / 60 (0.0)	0.5331
Ejection Fraction <40%†	1 / 105 (1.0)	0 / 60 (0.0)	1.0000
Other††	81 / 105 (77.1)	44 / 60 (73.3)	0.5777

* Data not available for all subjects; Subjects could have multiple pre-existing conditions; and were missing data due to the subjects withdrawing consent after randomization.
** Comparison of AAD (Control) vs. THERMOCOOL using Fisher's Exact Test
† Baseline TTE for subject demonstrated a left ventricle ejection fraction (LVEF) <40%, a multiple gated acquisition scan (MUGA) scan obtained on the subject prior to enrollment indicated a LVEF of 50%. The MUGA scan is considered a more reliable and accurate test for ejection fraction measurement.
†† Details of the co-morbidities reported in the "Other" category are provided in Appendix 5.

3.2.2 Baseline Electrocardiogram (ECG)

All subjects enrolled in the study were required to have an ECG performed within the 30 days of the assigned treatment. Table 3.2.2A describes the baseline ECG results for study subjects. There were no statistically significant differences between the two treatment groups for the baseline ECG results.

TABLE 3.2.2A Baseline Electrocardiogram Results (Enrolled Subjects, N=167)*

ECG Findings	Treatment Group		p-value**
	THERMOCOOL n/N (%)	AAD (Control) n/N (%)	
Sinus Rhythm	68 / 104 (65.4)	38 / 57 (66.7)	1.0000
Atrial Fibrillation	19 / 104 (18.3)	10 / 57 (17.5)	1.0000
Sinus Bradycardia	14 / 104 (13.5)	11 / 57 (19.3)	0.3665
1st Degree AV Block	5 / 104 (4.8)	5 / 57 (8.8)	0.3269
Premature Atrial Complexes	5 / 104 (4.8)	0 / 57 (0.0)	0.1621
Premature Ventricular Complexes	5 / 104 (4.8)	1 / 57 (1.8)	0.4246
ST Segment Abnormalities	2 / 104 (1.9)	1 / 57 (1.8)	1.0000
Atrial Flutter	1 / 104 (1.0)	0 / 57 (0.0)	1.0000
Evidence of Previous MI	1 / 104 (1.0)	1 / 57 (1.8)	1.0000
T Wave Abnormalities	1 / 104 (1.0)	1 / 57 (1.8)	1.0000
Intra-ventricular Conduction Defect	0 / 104 (0.0)	1 / 57 (1.8)	0.3540
Other†	13 / 104 (12.5)	5 / 57 (8.8)	0.6044

* Data are not available for all subjects.
** Comparison of AAD (Control) vs. THERMOCOOL using Fisher's Exact Test.
† The majority of the "other" electrocardiographic results were bundle branch blocks and paced rhythms. Refer to Appendix 5

3.2.3 Incidence of Atrial Fibrillation Episodes Prior to Baseline

Subjects were asked to assess the number of symptomatic AF episodes they had experienced in the three and six months prior to their baseline visit. Table 3.2.3A presents the data by randomization assignment. There were no statistically significant differences in the number of reported symptomatic AF episodes between the two treatment groups for either of the time intervals.

TABLE 3.2.3A Subject Reported Atrial Fibrillation Episodes Prior to Baseline* (Enrolled Subjects, N=167)

	Enrolled Subjects (N=167)						
	THERMOCOOL (n=106)			AAD (Control) (n=61)			
	Mean ± SD (n)	Median	Min / Max	Mean ± SD (n)	Median	Min / Max	p-value*,**
In the *6 months* prior to baseline, the number of AF episodes reported by the subject†							
	62.3 ± 89.7 (100)	28	3.0 / 720.0	64.9 ± 98.0 (57)	24	3.0 / 600.0	0.7572
In the *3 months* prior to baseline, the number of AF episodes reported by the subject††							
	33.0 ± 49.6 (98)	17	2.0 / 360.0	35.2 ± 58.8 (58)	12	1.0 / 300.0	0.5785

* Initially the protocol stipulated inclusion criterion as 3 symptomatic AF episodes within 3 months; later protocol revised to stipulate 3 symptomatic AF episodes within 6 months
** Comparison of AAD (Control) vs. THERMOCOOL groups using Wilcoxon Rank-Sum test
† Data not available for 10 subjects
†† Data not available for 11 subjects

Baseline 24-Hour Holter Monitoring:

The study protocol required all enrolled subjects to undergo a 24-hour Holter monitoring assessment in the 30 days prior to receiving or beginning the assigned treatment.

Of the 167 subjects enrolled, a total of 158 baseline Holter recordings were collected. Of the 159 subjects in the Effectiveness Cohort, 156 subjects had baseline Holter recordings (101 in the THERMOCOOL group and 55 in the AAD (Control) group).

Across both groups, 57 subjects recorded episodes of atrial fibrillation on their Holter monitors. Thirty (30) of these 57 subjects reported having AF symptoms. The findings between the two groups were not statistically significant. Table 3.2.3B breaks down the Holter results further by randomization group.

TABLE 3.2.3B 24-Hour Holter Monitor Accountability and Results (Enrolled Subjects, N=167)*

	Enrolled Subjects (N=167)		Total	p-value**
	THERMOCOOL (n=106)	AAD (Control) (n=61)		
Holter monitor recordings not collected	**4**	**5**	**9**	
Holter monitor recordings collected	**102**	**56**	**158**	
Presence of AF unknown or unavailable	2	1	3	
Number of Subjects without AF Episodes	64	34	98	
Number of Subjects with AF Episodes	**36**	**21**	**57**	0.8622
Symptoms reported	20	10	30	0.5698
No symptoms reported	13	10	23	
Symptoms unknown or unavailable	3	1	4	

* Data are not available for all subjects.
** Comparison of AAD (Control) vs. THERMOCOOL using Fisher's Exact Test.

Table 3.2.3C provides an analysis of the 57 baseline Holter recordings in which AF episodes were identified. Of these subject recordings, 36 subjects were from the THERMOCOOL group and 21 subjects were from the AAD (Control) group.

The study protocol defined an "atrial fibrillation episode" as an AF episode lasting 30 seconds or longer in duration. Table 3.2.3C provides an analysis of the mean number of episodes lasting longer than 30 seconds for each group. It also provides the mean total duration of AF, total number of atrial flutter (AFL) episodes, and the total number of pre-atrial complexes (PACs). The findings between the two groups were not statistically significant.

TABLE 3.2.3C Frequency of Arrhythmic Episodes in Holter recordings with AF Episodes (Enrolled Subjects, N=167)

	Enrolled Subjects with AF Episodes in Baseline Holter (n=57)				p-value**
	THERMOCOOL (n=36)		AAD (Control) (n= 21)		
	Mean ± SD (n)	Min/Max	Mean ± SD (n)	Min/Max	
Total Number of AF episodes (≥30 seconds)	6.8 ± 16.5 (33)*	0.0 / 78.0	3.0 ± 4.1 (21)	1.0 / 15.0	0.9436
Total AF Duration (hours)	8.3 ± 8.6 (31)*	0.0 / 24.0	10.9 ± 8.2 (20)*	0.0 / 24.0	0.2132
Total Number of AFL Episodes	3.0 ± 13.6 (33)*	0.0 / 78.0	1.0 ± 4.2 2.0 (20)*	0.0 / 19.0	0.2209
Total Number of PACs	873.7 ± 1695.2 (31)*	0.0 / 6565.0	1658.3 ± 2791.7 (20)*	0.0 / 8181.0	0.4797

* Data are not available for all subjects.
** Comparison of AAD (Control) vs. THERMOCOOL using Wilcoxon Rank-Sum test

3.2.4 Baseline Characteristics - Transthoracic Echocardiogram

The study protocol required all enrolled subjects to undergo a transthoracic echocardiogram (TTE) assessment in the 30 days prior to their study procedure or start of dosing.

Table 3.2.4A and 3.2.4B summarize the findings from the baseline TTE. The LA dimensions and LVEF findings between the two groups were not statistically significant.

TABLE 3.2.4A Baseline Characteristics - Transthoracic Echocardiogram (TTE) (Enrolled Subjects, N=167)*

	Enrolled Subjects (N=167)				
	THERMOCOOL (n=106)		AAD (n=61)		
	Mean ± SD (n)	Min/Max	Mean ± SD (n)	Min/Max	p-value*
LA Dimension (mm)**					
	40.0 ± 5.5 (100)	27.0 / 50.0	40.3 ± 5.3 (52)	26.5 / 49.0	0.7118
LV Ejection Fraction (%)***					
	62.3 ± 9.8 (99)	30.0 / 86.0	63.1 ± 7.4 (54)	44.0 / 80.0	0.467

*** Comparison of AAD (Control) vs. THERMOCOOL using Wilcoxon Rank-Sum test.
** 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).

In their baseline TTE, 4 subjects [1 THERMOCOOL subject and 3 AAD (Control) subjects] presented with clinically insignificant (trace) pericardial effusion.

Left atrial thrombus was not observed in any baseline trans*thoracic* echochcardiograms (TTE). To confirm the absence of left atrial thrombus, a pre-procedure trans*esophageal* echocardiogram (TEE) was required of every subject undergoing a study procedure within 24-hours of the study procedure. Left atrial thrombus was not observed in any pre-procedure TEE.

TABLE 3.2.4B Baseline Characteristics - Transthoracic Echocardiogram Results (TTE, Enrolled Subjects, N=167)

	Enrolled Subjects (N=167)		p-value*
	THERMOCOOL n/N (%) (n=106)	AAD (Control) n/N (%) (n=61)	
TTE Information Unknown	4	7	
TTE Information Available	102	54	
Pericardial Effusion Present**	1 / 100 (1.0)	3 / 48 (6.3)	0.1003
Left Atrial Thrombus Present†	0 / 79 (0.0)	0 / 23 (0.0)	
Tricuspid Valve Regurgitation††			0.4824
No Regurgitation	37 / 101 (36.6)	25 / 54 (46.3)	
Trace/Trivial	30 / 101 (29.7)	12 / 54 (22.2)	
1+ Mild	30 / 101 (29.7)	14 / 54 (25.9)	
2+ Moderate	4 / 101 (4.0)	2 / 54 (3.7)	
4+ Severe	0 / 101 (0.0)	1 / 54 (1.9)	
Mitral Valve Regurgitation††			0.0661
No Regurgitation	27 / 101 (26.7)	24 / 54 (44.4)	
Trace/Trivial	31 / 101 (30.7)	14 / 54 (25.9)	
1+ Mild	35 / 101 (34.7)	14 / 54 (25.9)	
2+ Moderate	8 / 101 (7.9)	1 / 54 (1.9)	
3+ Moderate/Severe	0 / 101 (0.0)	1 / 54 (1.9)	

* Comparison of AAD (Control) vs. THERMOCOOL using Fisher's Exact Test.
** Pericardial effusion was not evaluated for 2 THERMOCOOL subjects and 6 AAD (Control) subjects
† The presence of left atrial thrombus was not evaluated in the pre-assessment trans*thoracic* echocardiogram for 23 THERMOCOOL subjects and 31 AAD (Control) subjects. Subjects undergoing an ablation procedure were required to have a pre-procedure trans*esophageal* echocardiogram to rule out the presence of left atrial thrombus.
†† Valve regurgitation was unknown for [redacted] (THERMOCOOL group).

3.2.5 Baseline Characteristics – NYHA Class

The protocol excluded subjects that were New York Heart Association (NYHA) class III or IV heart failure category. The majority of the enrolled subjects were in the NYHA class I heart failure category. Table 3.2.5.A presents a summary of the baseline NYHA classification of enrolled subjects. The NYHA Classes are comparable between the two treatment groups.

TABLE 3.2.5A Baseline Characteristics - NYHA Class (Enrolled Subjects, N=167)

NYHA Class	Treatment Group		p-value*
	THERMOCOOL (n=106)	AAD (Control) (n=61)	
NYHA Class Unavailable	**13**	**3**	
NYHA Class Available	**93**	**58**	
Class I	81	50	1.0000
Class II	12	8	

* Comparison of AAD (Control) vs. THERMOCOOL using Fisher's Exact Test.

3.2.6 Anti-Arrhythmic Drug Therapy

Baseline Anti-Arrhythmic Drug History

The baseline medication history for both groups included all cardiovascular medications: those prescribed for the treatment of AF and for all other cardiovascular indications. The patient medication history obtained at the baseline visit included all previously failed AADs for the treatment of AF. The two groups had a comparable baseline drug profile.

Table R 3.2.6A compares the two randomization groups by the average number of previously failed AADs at the baseline visit. The mean numbers of AADs that the AAD (Control) group and THERMOCOOL group failed were 2.1 and 2.2, respectively. The AAD definition in the study protocol, which defined AADs as class I, class III, or AV nodal blocking agents such as beta blocking agents (BB) or calcium channel blockers (CCBs), was used in this analysis. The mean numbers of class I/III AADs failed at baseline were also comparable between the two treatment groups.

TABLE R 3.2.6A Mean Number of AAD Drugs Failed at Baseline per Subject (Enrolled Subjects, N=167)*

AAD Drugs Failed	Treatment Group		Total Mean ± SD
	THERMOCOOL Mean ± SD	AAD (Control) Mean ± SD	
Total number of AADs Failed at Baseline	2.2 ± 1.1 (106)	2.1 ± 1.4 (61)	2.2 ± 1.2 (167)
Class I/III AADs Failed at Baseline	1.3 ± 0.9 (106)	1.2 ± 0.8 (61)	1.3 ± 0.8 (167)

*Drugs listed as "failed" at the Baseline visit or "taking now for AF" at the Baseline visit.

Table R 3.2.6B quantifies the number of AADs that subjects failed prior to their enrollment in the study. Subjects were required to have had failed at least one AAD as evidenced by recurrent symptomatic PAF or intolerable side effects due to the AAD. The majority of subjects (89.2%, 149/167) failed between one and three AADs.

TABLE R 3.2.6B Number of AAD Drugs Failed at Baseline per Subject (Enrolled Subjects, N=167)*

AAD Drugs Failed	Treatment Group		Total n/167 (%)
	THERMOCOOL n/106 (%)	AAD (Control) n/61 (%)	
0**	1 (0.9%)	2 (3.3%)	3 (1.8%)
1	29 (27.4%)	20 (32.8%)	49 (29.3%)
2	41 (38.7%)	22 (36.1%)	63 (37.7%)
3	24 (22.6%)	13 (21.3%)	37 (22.2%)
4	6 (5.7%)	2 (3.3%)	8 (4.8%)
5	3 (2.8%)	0 (0.0%)	3 (1.8%)
6	2 (1.9%)	1 (1.6%)	3 (1.8%)
9	0 (0.0%)	1 (1.6%)	1 (0.6%)
Class I/III **AAD Drugs Failed**			
0***	21 (19.8%)	9 (14.8%)	30 (18.0%)
1	48 (45.3%)	33 (54.1%)	81 (48.5%)
2	26 (24.5%)	15 (24.6%)	41 (24.6%)
3	9 (8.5%)	4 (6.6%)	13 (7.8%)
4	2 (1.9%)	0 (0.0%)	2 (1.2%)

*Drugs listed as "failed" at the Baseline visit or "taking now for AF" at the Baseline visit.
** THERMOCOOL subjects and AAD (Control) subject withdrawn from the study after randomization prior to obtaining AAD history. AAD (Control) subject was taking sotalol (120 mg 24 h dose) at the time of enrollment.
*** Of the 30 subjects who did not fail a Class I/III AAD at baseline, 27 were enrolled under version 7 of the protocol allowing failure of only a Class II/IV drug.

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Table 3.2.6C is a comparison of the specific baseline cardiovascular medication histories between the randomization groups. Baseline AAD medication history was similar between randomization groups.

TABLE 3.2.6C Comparison of Baseline Medication History by Enrollment Group (N=167)

AAD Class	Treatment Group		p-value**
	THERMOCOOL (n=106) n (%)*	AAD (Control) (n=61) n (%)*	
Class I and III:			
Propafenone	53 (50.5)	30 (50.8)	1.000
Sotalol	36 (34.3)	22 (37.3)	0.735
Flecainide	33 (31.4)	13 (22.0)	0.211
Amiodarone	7 (6.7)	6 (10.2)	0.548
Disopyramide	3 (2.9)	1 (1.7)	1.000
Dofetilide	3 (2.9)	1 (1.7)	1.000
Quinidine	0 (0.0)	2 (3.4)	0.128
Class II and IV:			
Metoprolol	35 (33.3)	18 (30.5)	0.731
Diltiazem	15 (14.3)	8 (13.6)	1.000
Atenolol	12 (11.4)	2 (3.4)	0.088
Propranolol	2 (1.9)	2 (3.4)	0.619
Verapamil	3 (2.9)	3 (5.1)	0.668
Other Beta Blocker	7 (6.7)	4 (6.8)	1.000
Other Calcium Channel Blocker	4 (3.8)	0 (0.0)	0.297
Acebutolol	0 (0.0)	1 (1.7)	0.359
Other:			
Digoxin	11 (10.5)	7 (11.9)	0.798
ACE Inhibitor	4 (3.8)	1 (1.7)	0.655
Angiotensin Receptor Block	2 (1.9)	2 (3.4)	0.619
Other	3 (2.9)	3 (5.1)	0.668

* Percentage derived using n/N; THERMOCOOL group (N=105) and AAD (Control) group (N=59). [redacted] (THERMOCOOL group) and [redacted] (AAD (Control) group) withdrew from the study after randomization and prior to obtaining AAD history. [redacted] (AAD (Control) group) was taking Sotalol (120 mg 24 h dose) *"not for AF"* at the time of enrollment.
** Comparison of THERMOCOOL vs. AAD (Control) using Fishers Exact test

3.3 Protocol Deviations

Protocol deviations are categorized as major or minor based on the potential of the deviation to affect the scientific validity of the study, or the safety, rights, and welfare of the enrolled subject. Major deviations include, but are not limited to, inclusion and exclusion criteria violations and investigational device violations. Minor deviations include protocol stipulated tests not done and follow-up visits done outside the protocol specified windows.

Table 3.3A lists the major protocol deviation descriptions, study group, and subject ID. None of the major protocol deviations was associated with a SAE was caused by the device.

Major Deviations not captured in Table 3.3A include:

- Investigational Site ---- – two unused randomization envelopes were discovered opened during a routine site-monitoring visit. An investigation revealed that the research staff inadvertently opened the randomization envelopes when they intended to randomize patients in a competing study and failed to notify the sponsor. The sponsor immediately initiated a corrective action by removing the randomization envelopes from the site. In order to carefully monitor randomization the investigator was required to contact the Sponsor when an eligible subject was identified. Randomization envelopes were returned to the investigator after the site had a procedure in place to prevent future reoccurrences.

Table 3.3B lists the minor protocol deviations, study group and the total number of occurrences. The most common deviation was a study visit performed out of window or a study procedure not performed during the patient visit. With additional site training and ongoing monitoring, the number of protocol deviations at each site has decreased over the course of the study.

TABLE 3.3A Major Protocol Deviations

Protocol Deviation	Randomization Group	Subject ID
Subject did not meet all Inclusion/Exclusion Criteria	AAD (Control)	
	THERMOCOOL	
THERMOCOOL device used in non-study subject‡‡	NA	
Power parameters (> 50 W)	THERMOCOOL	
Incorrect informed consent signed§	AAD (Control)	
	THERMOCOOL	
Subjects assigned to a previously failed AAD as the study drug (Refer to section 3.6.1.2 for details.)	AAD (Control)	

* The ECG recordings for subject were out of window, enrollment was approved by BWI as a prospective protocol deviation.

** Subject's had received amiodarone therapy within 6 months of enrollment.

† Subjects did not have documentation of a symptomatic AF episode at time of enrollment. Subject had a documented AF episode prior to the ablation procedure.

†† A left atrial size of 5.0 cm was recorded on the baseline TTE for ----

‡ Subject ---- experienced AF episodes that lasted longer than 30 days and was terminated with cardioversion. The subject was withdrawn prior to undergoing study procedure.

‡‡ An investigational catheter was used in a non-study subject at the Corrective action was put in place to prevent this from recurring.

§ ---- ---- and ---- signed a version of the informed consent that was not approved by the IRB. Randomization envelopes and all investigational devices were immediately removed from the site. Randomization envelopes were returned upon acknowledgement of a IRB-approved informed consent being signed for the next enrolled subject; was withdrawn from the study prior to undergoing any study-related procedures. Subjects and signed an IRB-approved version of the informed consent prior to their study ablation procedures.

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TABLE 3.3B Minor Protocol Deviations

Protocol Deviation	Randomization Group		Total
	THERMOCOOL	AAD (Control)	
Clinic Visit Not Performed	6	6	12
Visit Date Out of Window	44	41	85
Study Procedure Out of Window / Not Done:			
24 Hour Holter monitor	6	5	11
CT/MRA	19	11	30
Dosimeter badges	3	1	4*
ECG	1	4	5
Neurology exam	10	3	13
Pregnancy test	0	4	4
Quality of Life questionnaires	5	2	7
Required labs	15	35	50
TEE	2	3	5
TTE	13	16	29
TTM transmissions	4	1	5
Urimeter to measure urine output	36	15	51
Ablation Parameters not followed:			
CARTO map not collected	1	0	1
Bi-directional block not confirmed	1	1	2
Entrance block not confirmed	0	1	1
Infusion rate parameters	36	10	46
Commercially labeled THERMOCOOL catheter used	2**	0	2
Prophylactic right atrial flutter ablation	24	7	31
PV visualization not done	2	0	2
Temperature parameters (> 50 C)	2	0	2
Anti-coagulation not followed	1	1	1
Administration of Amiodarone during the course of the study	3	1	4
Other†	3	0	3

* Data was listed as not available for 7 additional subjects due to dosimeters being lost in transit to the core lab though placed according to the protocol.
** Commercial THERMOCOOL catheter is identical to the Investigational Catheter except for the "investigational" labeling.
† Other includes: Contrast not used in CT, ECG Source Document not available, Malfunctioned THERMOCOOL catheter not returned to Biosense Webster, Inc.

Deviations associated with ablation parameters not being followed were infrequent except as follows. Infusion rate parameters differed in 46 cases at the physician's discretion to minimize risk of fluid load. The physician used temperature monitoring to ensure the infusion rate remained adequate to maintain patient safety. Prophylactic atrial flutter lines were performed in 31 procedures as the study investigators believed it was in the best interest of these subjects to minimize the risk of a repeat procedure.

3.4 Procedural Data

3.4.1 Accountability

Table 3.4.1A summarizes the number of subjects undergoing a study ablation procedure with the THERMOCOOL catheter. All subjects in the THERMOCOOL group effectiveness cohort (n = 103) underwent at least one ablation procedure. Additionally, 36 subjects enrolled in the AAD group (n = 56) underwent at least one study ablation procedure after reaching the chronic effectiveness endpoint.

TABLE 3.4.1A All Subjects Undergoing an Ablation Procedure (n = 139)

Randomization Group	No. of Subjects n (%)
THERMOCOOL	103 (74.1)
AAD (Control)	36 (25.9)
Total Subjects Undergoing Ablation	**139** (100.0)

3.4.2 Total Number of Atrial Fibrillation Ablation Procedures

Table 3.4.2A summarizes the number of study ablation procedures. There were 167 ablation procedures (including initial and repeat ablation procedures) performed in 139 subjects. The majority of subjects underwent a single AF ablation procedure (79.9%, 111/139).

Per the study protocol, subjects in the THERMOCOOL group could undergo up to 2 repeat ablation procedures within 80 days following the initial AF ablation procedure. Twenty four (24, 23.3%) subjects in the THERMOCOOL group underwent a repeat ablation procedure. No subject underwent a second repeat ablation procedure within the 80 days post initial procedure.

TABLE 3.4.2A Total Number of Ablation Procedures per Subject (Subjects Undergoing Ablation, n = 139)

Number of Ablation Procedures	THERMOCOOL Subjects n/N (%)	AAD (Control) Subjects Undergoing Ablation n/N (%)	Total Subjects n/N (%)	Total Procedures n
1	79 / 103 (76.7)	32 / 36 (88.9)	111 / 139 (79.9)	111
2	24 / 103 (23.3)	4 / 36 (11.1)	28 / 139 (20.1)	56
Total	103 / 103 (100.0)	36 / 36 (100.0)	139 / 139 (100.0)	167

3.4.3 This section intentionally left blank

3.4.4 This section intentionally left blank

3.4.5 This section intentionally left blank

3.4.6 This section intentionally left blank

3.4.7 Ablation Targets

In this study, PV isolation was the required ablation procedure. Optional ablation procedures were allowed based on clinical findings after PV isolation was completed. Any non-PV foci identified in the LA and/or right atrium (RA) that triggered AF were required to be ablated, including the isolation of the superior vena cava (SVC) if AF potentials were identified. Atrial linear lesions were allowed only if an arrhythmia was induced post PV isolation.

Table 3.4.7A summarizes the ablation target sites reported in the study for 102 index ablation procedures plus 23 repeat ablations. PV targets made up the majority of the ablation procedure target sites. Atrial linear lesions were the next most frequent sites targeted during the procedure. Atrial flutter isthmus lines were placed in the right atrium during 34.4% (43/125) of the ablation procedures. LIPV-Mitral valve isthmus lines were the next most common linear targets, being placed in 20.8% of ablation procedures. High left atrial lines were also placed in a number of procedures but less frequently. The SVC was targeted in 16.0% (20/125) and foci were targeted in 16.8% (21/125) of the procedures.

TABLE 3.4.7A Ablation Sites Targeted - Initial or Repeat Procedures (THERMOCOOL Effectiveness Cohort, n = 103; 125 procedures)

Targets	No. of Procedures (Initial or Repeat) (%)
Pulmonary Veins	
Left Inferior PV	117 (93.6)
Left Middle PV	5 (4.0)
Left Superior PV	116 (92.8)
Right Inferior PV	119 (95.2)
Right Middle PV	9 (7.2)
Right Superior PV	120 (96.0)
Other	7 (5.6)
Atrial Linear Lesions	
AFL Isthmus	43 (34.4)
High Atrial Line	8 (6.4)
Left Inferior PV-Mitral Annulus	26 (20.8)
Other	24 (19.2)
SVC	20 (16.0)
Foci	21 (16.8)

*Data is not available for (initial procedure) and ---- (second procedure)

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Table 3.4.7B summarizes the ablation targets from the first procedures. All initial ablation procedures included the isolation of the PV targets as specified in the protocol. The inclusion of an atrial linear target during the initial procedure occurred in 43.1% (44/102) of the subjects in the THERMOCOOL group.

TABLE 3.4.7B Ablation Sites Targeted – 1st Ablation Procedures Only(THERMOCOOL Effectiveness Cohort, n = 103)

Targets	No. of Procedures (Initial only) (%)
PV Only	51 (50.0)
PV + Atrial Linear Lesions	34 (33.3)
PV + Foci	7 (6.9)
PV + Atrial Linear Lesions + Foci	10 (9.8)
Total	102* (100.0)

*Data not available for subject ----

3.5 First Interim Analysis – September 2007 Datas

The FDA approved a Bayesian adaptive sample size on ---- (version 12.2). As discussed in section 3.0, the that interim analyses would be conducted when subject accrual reached sample sizes of ---- subjects. The interim analysis presented in this section is based on a dataset that was taken i (N=160).

An independent consulting group performed the analysis using the September 2007 dataset and the findings are summarized in a report dated October 4, 2007. The results from this report met the protocol's pre-specified effectiveness criteria for stopping enrollment and enrollment was stopped (Appendix 9).

The detailed report of subjects' enrollment and disposition, demographics, chronic effectiveness analyses, safety analyses, and poolability can be found in Appendix 10.

3.6 Updated Analysis – June 2008 Dataset

For the purposes of the PMA supplement, the data were analyzed using a June 2008 dataset to provide a comprehensive clinical report. All previous analyses are updated in this section.

3.6.1 Acute Effectiveness

Table 3.6.1A is an accountability of subjects that underwent an RF Ablation procedure. Of the 106 subjects randomized to RF Ablation therapy, 103 subjects underwent an RF ablation procedure.

The group used for acute effectiveness analysis calculations (n=103) was comprised of only subjects that were randomized to the THERMOCOOL group and underwent a procedure with the study catheter.

TABLE 3.6.1A Accountability of THERMOCOOL GROUP (n=106)

Disposition	THERMOCOOL
Enrolled	106
Excluded	3
Discontinued	0
Effectiveness Cohort	103
Subjects Undergoing RF Ablation Procedure	**103**

3.6.1.1 THERMOCOOL Group

The study protocol defined acute success as the confirmation of entrance block in all targeted PVs.

Subjects were considered acute failures if they met any of the following criteria:

- They did not have confirmation of entrance block into the PV.
- They had a non-study catheter utilized for ablation of any AF targets.
- They received more than 2 repeat ablation procedures.
- They received an ablation procedure beyond day 80 of the blanking period.

Table 3.6.1.1A presents the acute effectiveness results for the subjects in the THERMOCOOL group that had a study procedure.

TABLE 3.6.1.1A 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 subject [redacted] was not available.

Confirmation of Entrance Block

The study protocol defined acute success as the confirmation of entrance block into all targeted PVs. Confirmation of entrance block was achieved for all subjects randomized to the THERMOCOOL group, in both the initial and repeat ablation procedures, with the exception of one subject in which data are pending. Table 3.6.1.1B presents the number of subjects that met the acute success criterion.

TABLE 3.6.1.1B Confirmation of Entrance Block Into all Targeted PVs (THERMOCOOL Group, n=103)

	THERMOCOOL n/N (%)
1st Ablation	102 / 102 (100.0)
2nd Ablation	23 / 23 (100.0)
All Ablations	125 / 125* (100.0)

*End of procedure data for subject ---- (initial ablation) and ---- (second ablation) are pending at this time.

Acute Failures

There were 2 acute failures in the THERMOCOOL group that are described in Table 3.6.1.1C below. These acute failures were not due to investigators not achieving entrance block into the PVs. Rather, the subjects were protocol adjudicated acute failures due to the timing of their re-ablation procedure (beyond Day 80 of the initial ablation procedure).

TABLE 3.6.1.1C Acute Failures (n=2)

Subject ID	Description
THERMOCOOL Group	
----	Subject underwent his initial RF ablation procedure on April 13, 2005 and had a repeat procedure on July 6, 2005, 84 days after the initial procedure. Per the study protocol, if a subject had an ablation procedure beyond 80 days of the initial ablation procedure, the subject was considered an acute effectiveness failure.
----	Subject underwent RF ablation with the study catheter on December 11, 2005. The subject had a repeat procedure on March 2, 2006, 81 days after the initial procedure. Per the study protocol, if a subject had an ablation procedure beyond 80 days of the initial ablation procedure, the subject was considered an acute effectiveness failure.

3.6.1.2 AAD (Control) Group

Anti-Arrhythmic Drug Therapy

Subjects enrolled into the AAD (Control) group were assigned a new AAD drug to assess its effectiveness during their 9-month chronic effectiveness evaluation period. Table 3.6.1.2A summarizes the AAD assignments of this group.

Subjects were to receive trial medications and dosing as determined at the discretion of the investigator. Medication dosing, as recommended by the ACC/AHA/ESC 2001 Practice Guidelines for Management of Subjects with Atrial Fibrillation,[64] was included in the study protocol. Section 2.2.5.4 reviews these recommendations in further detail.

The majority of the subjects were assigned flecainide (35.7 %, 20/56) or propafenone (41.1%, 23/56). This was due in part to the lack of dofetilide use outside the US. Quinidine, which is approved for AF therapy, was allowed by the study protocol but was not prescribed by any study investigator even though subjects had not failed on this drug at time of study entry.

TABLE 3.6.1.2A Summary of Prescribed Anti-Arrhythmic Drug Therapy after Randomization (AAD [Control] Group, n=56)

Drug Treatment	n/56 (%)	Dose Mean ± SD	min (mg)	max (mg)	Protocol Dose (mg)*
Dofetilide (Class III)	2 (3.6%)	0.8 ± 0.4	0.5	1	0.5
Flecainide (Class IC)	20 (35.7%)	190.0 ± 44.7	100.0	300.0	200
Propafenone (Class IC)	23 (41.1%)	594.6 ± 148.1	225.0	900.0	450
Sotalol (Class III)	11 (19.6%)	243.6 ± 72.6	120.0	320.0	240
Quinidine (Class IA)	0 (0.0%)	-	-	-	600

* The protocol recommended minimum 24 h dose, based on the published ACC/AHA/ESC guidelines.[1,64]

At the end of dosing, 4 subjects were prescribed a dose less than the minimum dose recommended by the protocol. Table 3.6.1.2B summarizes the details.

TABLE 3.6.1.2B Subjects Prescribed Less Than the Minimum Protocol Recommended Dose for the Assigned AAD (n=4)

Subject ID	Prescribed AAD	24 h Dose (mg)	Outcome	Reason
	Sotalol	80	Failure	Subject developed a life threatening arrhythmia (bradycardia) after initial dosing of sotalol (240 mg). Failure resulted from the discontinuation of the study drug due to intolerable side effects and subsequent recurrence of AF.
----	Propafenone	300	Success	Subject had previously failed propafenone (300 mg). Dose increase to 450 mg at initial dosing resulted in disabling GI upset, which required dose decrease (300 mg).
----	Flecainide	100	Failure	Subject was also taking diltiazem (240 mg) at the same time flecainide was initiated. Failure resulted from the recurrence of AF during the effectiveness evaluation period.
----	Flecainide	150	Success	Subject started on flecainide (300 mg) at initial dosing. Nausea, fatigue, and lightheadedness after initial flecainide dose required dose a decrease to 150 mg.

Table 3.6.1.2C presents the details for 11 subjects in the AAD (Control) group that were prescribed a previously failed AAD. These subjects were prescribed either an equivalent or higher dose than their historical maximum dose.

TABLE 3.6.1.2C Summary of Subjects Prescribed a Previously Failed AAD (n=11)

Subject ID	Prescribed AAD	Failed 24 h Dose (mg)	Study 24 h Dose (mg)	Chronic Outcome
----	Propafenone	600	900	Failure, AF recurrence
----	Propafenone	300	900	Failure, AF recurrence
----	Propafenone	300	450	Success
----	Propafenone	150	450	Failure, AF recurrence
----	Sotalol	320	320	Failure, AF recurrence
----	Sotalol	240	240	Failure, AF Recurrence
----	Propafenone	450	650	Failure, AF Recurrence
----	Sotalol	60	240	Failure, AF Recurrence
----	Propafenone	600	600	Success
----	Flecainide	200	200	Failure, AF Recurrence
----	Propafenone	N/A*	650	Failure, AF recurrence

* Subject's medical records included documentation of a previous prescription for propafenone (dose unknown), which the investigator believed was non- therapeutic.

Early Protocol Adjudicated AAD Failures

If, at any time, an AAD (Control) subject became intolerant to their assigned AAD and was subsequently discontinued for this reason, the subject was considered a safety and effectiveness failure. Five (5) subjects failed to complete the dosing period on the assigned AAD. Table 3.6.1.2D summarizes the reasons for failure.

TABLE 3.6.1.2D Subjects Did Not Complete the Dosing Period (n=5)

Subject ID	Reason for Failure
----	The subject failed to complete the dosing period on the prescribed study medication. The study AAD was changed at 1 week due to AF Recurrence.
----	The subject experienced AF recurrence during dosing period. The study AAD was discontinued during dosing period due to intolerable side effects.
----	The subject failed to complete the dosing period on the prescribed study medication. The study AAD was changed at 1 week due to intolerable side effects.
----	The subject failed to complete the dosing period on the prescribed study medication. The study AAD was changed at 1 week due to intolerable side effects.
----	The subject failed to complete the dosing period on the prescribed study medication. The study AAD was changed at 1 week due to intolerable side effects.

3.6.2 Chronic Effectiveness

The primary effectiveness endpoint was the chronic success rate of the NAVISTAR THERMOCOOL catheter for the treatment of symptomatic PAF. It was expected that the THERMOCOOL group would be superior in chronic effectiveness to the AAD (Control) group.

Table 3.6.2A provides the subject accountability of the Effectiveness Cohort.
This cohort is comprised of subjects who were considered "per-protocol" and includes subjects that received treatment per their randomization assignment.

When the study closed to enrollment, there were 167 subjects enrolled in the study. Of these, 7 were considered excluded, and 1 subject was considered discontinued. Details of the reasons for exclusions and discontinuations can be found in section 3.1.2 (Tables 3.1.2D and 3.1.2E). The remaining 159 subjects make up the Effectiveness Cohort.

TABLE 3.6.2A Subject Accountability (Effectiveness Cohort, n=159)

Disposition	Treatment Group		Total
	THERMOCOOL	AAD (Control)	
Enrolled	**106**	**61**	**167**
Excluded	3	4	7
Discontinued	0	1	1
Effectiveness Cohort	103	56	**159**

Of the 159 subjects in the Effectiveness Cohort, there were 145 subjects with known effectiveness outcomes. Fourteen (14) subjects in the THERMOCOOL group are still in the effectiveness evaluation period with a mean follow-up of 6.6 ± 3.7 months.

Table 3.6.2B presents the mean follow-up time for both randomization groups at the time of the June 2008 dataset. The study included a follow-up health questionnaire 12 months after the end of the effectiveness evaluation period for both randomization groups.

TABLE 3.6.2B Follow-up Time for Subjects in the Effectiveness Cohort (n=159)*

	THERMOCOOL			AAD (Control)		
	Mean ± SD (n)	Median	Min/Max	Mean ± SD (n)	Median	Min/Max
Follow-up Times (months)	11.2 ± 2.9 (103)	12	0.0 / 20.3	7.3 ± 2.8 (20)	9	0.6 / 9.8

* AAD (Control) subjects who underwent a study ablation procedure were excluded

3.6.2.1 TTM Compliance

Per the study protocol, subjects were required to transmit a minimum of 15 TTM recordings during the 9-month chronic effectiveness evaluation period. Subjects were required to record and transmit at least one cardiac episode per week for the first 8 weeks of the 9-month evaluation period. After the first 8 weeks, subjects were required to transmit cardiac episodes at least once a month until the effectiveness assessment period was completed. If a subject missed a scheduled recording, the core laboratory was responsible for contacting the subject to remind them of their scheduled recording. In addition, subjects were asked to record and transmit all symptomatic cardiac episodes.

Compliance Index

TTM compliance was calculated based on the required number of TTMs per the protocol. Weekly transmissions were based on a 7-day week starting on the first day of the effectiveness evaluation period. Monthly transmissions were based on a 31-day month (34 days was used for the first monthly interval to

account for the transition from weekly to monthly) calculated after week 8 of the effectiveness evaluation period. The compliance index for each subject was calculated as a percentage based on the number of TTM transmissions within an expected timeframe divided by the total number of expected TTM transmissions per subject. The maximum number of expected TTMs was 15 when the subject completed the 9-month effectiveness evaluation period.

TTM transmission data was collected throughout the effectiveness period for both treatment arms. For AAD subjects meeting the effectiveness endpoint and electing to undergo an ablation with the THERMOCOOL catheter, TTM data was collected until the date of the ablation procedure. TTM compliance calculations in these subjects were based on the data collected up to that point.

In this study, subjects transmitted TTM recordings per each hospital's standard practice in addition to any protocol-required timeframes. Compliance was calculated based on the protocol-required timeframes, however data were processed for all TTM recordings transmitted to the core laboratory. There were 4092 additional TTM transmissions collected that followed the same uniform process as the protocol-mandated transmissions, including the review by an independent third party cardiologist (refer to section 2.2.7.1).

Overall Compliance

Table 3.6.2.1A shows the overall mean TTM compliance by randomization group. The overall mean TTM compliance was 88.8%. TTM compliance for the THERMOCOOL Group was 88.5% and 89.2% for the AAD (Control) Group. Detailed information on TTM compliance per subject is provided in Appendix 14.

TABLE 3.6.2.1A Overall Mean TTM Compliance by Randomization Group (Effectiveness Cohort, n=159)

	Treatment Group		
	THERMOCOOL Mean ± SD (n)	AAD (Control) Mean ± SD (n)	Total Mean ± SD (n)
TTM Compliance (%)	88.5 ± 16.3 (102)	89.2 ± 15.4 (56)	88.8 ± 16.0 (158*)

* ---- was lost to follow-up prior to the TTM evaluation.

The overall mean TTM compliance for US sites was 86.8% and the overall mean compliance for non-US sites was 90.1%, as is presented in Table 3.6.2.1B.

TABLE 3.6.2.1B TTM compliance US vs. Non-US (Effectiveness Cohort, n=159)

	US Sites Mean ± SD (n)	Non-US Sites Mean ± SD (n)	Total Mean ± SD (n)
TTM Compliance (%)	86.8 ± 19.7 (63)	90.1 ± 12.8 (95)	88.8 ± 16.0 (158*)

* ---- was lost to follow-up prior to the TTM evaluation.

TTM Compliance by Site

Table 3.6.2.1C presents the mean TTM compliance by site. The majority of the sites showed a mean compliance of > 80%. The lowest mean compliance was reported for site ---- with 2 subjects enrolled. ---- Principal Investigator, Dr. ---- moved from ---- to ---- during the study. Subject ---- completed the 3-month visit at ---- and was followed up at ---- upon study commencement. During the interim, several TTM transmissions were missed. Subject ---- was randomized to the THERMOCOOL Group and is considered a success. Subject ---- withdrew prior to the move to ---- due to insurance

reasons. Subject ---- was randomized to the AAD (Control) Group and is considered a failure after completing the effectiveness endpoint.

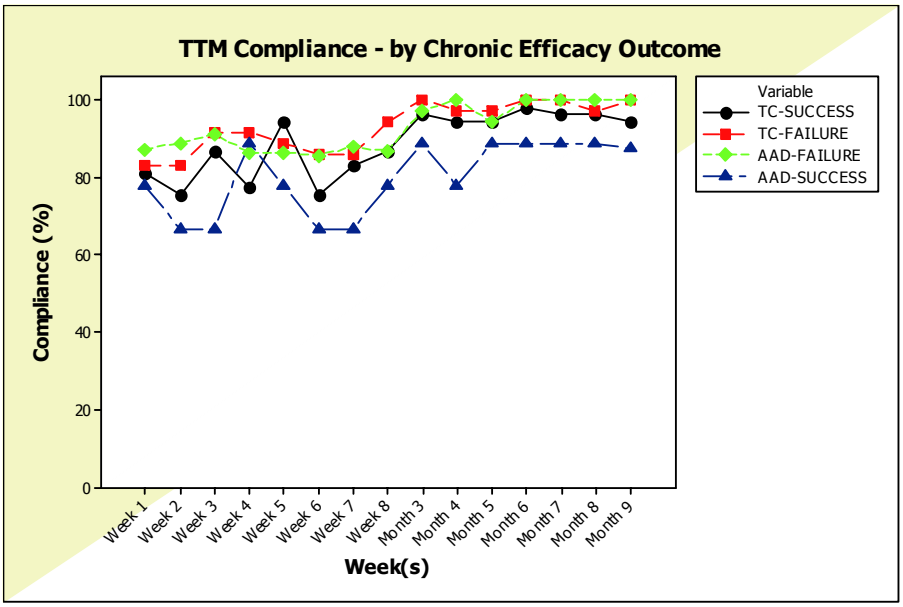
TABLE 3.6.2.1C TTM Compliance by Site (Effectiveness Cohort, n=159)

	Treatment Group		
Site	**THERMOCOOL Mean ± SD (n)**	**AAD (Control) Mean ± SD (n)**	**Total Mean ± SD (n)**
----	80.0 (1)	100.0 (1)	90.0 ± 14.1 (2)
----	86.7 ± 14.1 (5)	84.2 ± 14.1 (3)	85.8 ± 13.1 (8)
----	100.0 (1)	(0)	100.0 (1)
----	100.0 (1)	(0)	100.0 (1)
----	81.2 ± 13.8 (17)	80.5 ± 17.2 (9)	80.9 ± 14.7 (26)
----	81.7 ± 11.4 (4)	83.8 ± 2.8 (2)	82.4 ± 9.0 (6)
----	96.1 ± 3.6 (7)	94.0 ± 8.9 (5)	95.2 ± 6.1 (12)
----	97.3 ± 3.7 (5)	95.0 ± 10.0 (4)	96.3 ± 6.8 (9)
----	95.3 ± 4.5 (5)	97.8 ± 3.8 (3)	96.3 ± 4.2 (8)
----	(0)	90.0 (1)	90.0 (1)
----	89.4 ± 11.5 (7)	92.0 ± 14.5 (5)	90.5 ± 12.2 (12)
----	73.3 ± 40.6 (3)	87.5 (1)	76.9 ± 33.9 (4)
----	100.0 (1)	(0)	100.0 (1)
----	6.7 (1)	66.7 (1)	36.7 ± 42.4 (2)
----	97.2 ± 4.8 (3)	100.0 (1)	97.9 ± 4.2 (4)
----	79.7 ± 17.5 (3)	33.3 (1)	68.1 ± 27.2 (4)
----	100.0 ± 0.0 (2)	(0)	100.0 ± 0.0 (2)
----	92.7 ± 10.3 (31)	92.8 ± 13.7 (18)	92.7 ± 11.5 (49)
----	83.7 ± 28.4 (5)	100.0 (1)	86.4 ± 26.3 (6)
Total	88.5 ± 16.3 (102)	89.2 ± 15.4 (56)	88.8 ± 16.0 (158)

TTM Compliance by Randomization Group and Chronic Effectiveness Outcome

Figure 3.6.2.1E presents the overall mean TTM compliance by randomization group and chronic effectiveness outcome. The THERMOCOOL subjects maintained compliance > 75% throughout the effectiveness period. The AAD subjects showing a successful chronic effectiveness outcome fell to approximately 65% in the first 2 months but approximated 80% or better, on average, in the remainder of the effectiveness period.

FIGURE 3.6.2.1E Overall Mean TTM Compliance by Randomization and Chronic Effectiveness Outcome (Effectiveness Cohort, n=159)



3.6.2.2 Chronic Effectiveness Outcomes

Primary Effectiveness Analysis

As indicated in section 3.5, an interim analysis was performed in October 2007 (using the September 2007 dataset) per the IDE protocol by an independent consulting group. The results from this analysis are summarized in a report dated October 4, 2007 (Appendix 9). The interim analysis demonstrated sufficient statistical evidence of the study meeting the effectiveness endpoint. As a result, enrollment was subsequently stopped and the trial was declared an early success.

This section provides an updated Bayesian analysis of the primary effectiveness endpoint based on the June 2008 dataset. This updated analysis presents data for 167 subjects enrolled: 101 in the THERMOCOOL group and 59 in the AAD (Control) group. Among these 167 enrolled subjects, 7 subjects were excluded and 1 was discontinued. As such, 159 of the 167 subjects were eligible for this updated effectiveness analysis.

The critical results of this 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 ---- (protocol specified level needed for success).

Data Available

There were 159 subjects included in the analyses, with 103 in the THERMOCOOL group and 56 in the AAD (Control) group. Table 3.6.2.2A provides a breakdown of these subjects, showing the exposure time (in months) and failures for each of the three protocol specified intervals.

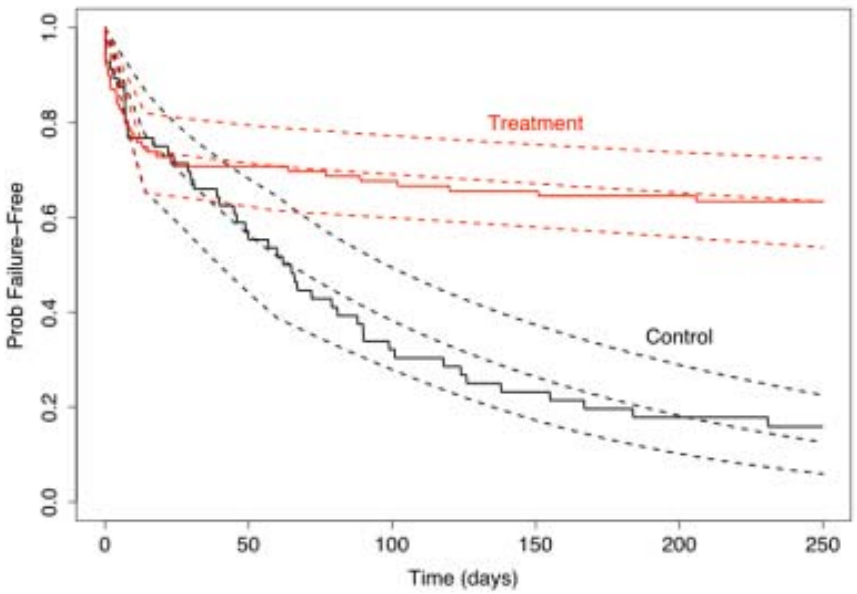
TABLE 3.6.2.2A Subject Exposure Time and Failures – June, 2008 Bayesian Analysis *

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 3.6.2.2B shows the Kaplan-Meier survival curves for each of the treatment groups with their 95% credible intervals.

FIGURE 3.6.2.2B The Posterior Median and 95% Credible Bands for the Time to Failure in Each Treatment Group



The 159 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), as presented in Table 3.6.2.2B.

TABLE 3.6.2.2B Subject Effectiveness Status (June 2008 dataset, n = 159)

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

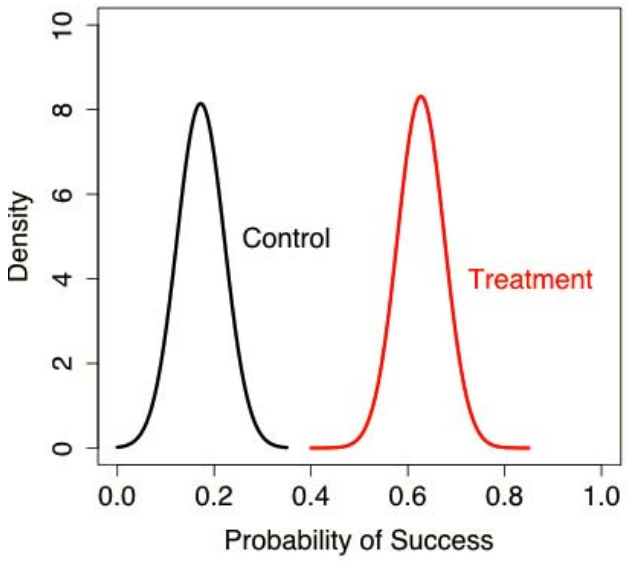
* ---- ---- ---- ---- ---- ---- ---- ---- ---- ---- ---- ---- ---- ----

The posterior mean probability of success for the AAD (Control) group is 0.172, with a posterior standard deviation of 0.049. In the THERMOCOOL group the posterior mean probability of success is 0.627 with a posterior standard deviation of 0.048. The posterior probability that the THERMOCOOL group is superior to the AAD (Control) group is >0.9999. If accrual would have been completed to 230 subjects then the trial would be a success if the posterior probability of superiority for the THERMOCOOL Group was ---- or greater. The predictive probability of this event is >0.9999. The posterior median and 95% credi nds for the time to failure are presented in Figure 3.6.2.2B. The Kaplan-Meier curves from Figure 3.6.2.2B are presented along with the model estimated values for each treatment 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 R 3.6.2.2C shows the plots of the posterior distributions for the 9-month failure-free rates for each treatment group based on the protocol-specified assumptions.

FIGURE R 3.6.2.2C The Posterior Distributions of the Probabilities of 9-month Failure-Free Treatment Success for Each Treatment Group



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Additional Effectiveness Analyses

Table 3.6.2.2C summarizes the chronic effectiveness outcome by treatment groups. In the June 2008 dataset, chronic success was achieved in 60% of the THERMOCOOL subjects eligible for the analysis as compared to 16.1% in the AAD (Control) group. At the time of this analysis, there were 14 subjects from the THERMOCOOL group who were still in the 9-month effectiveness evaluation period and had not achieved the effectiveness endpoint; these subjects were excluded from the analysis.

TABLE 3.6.2.2C Chronic Effectiveness Success (Effectiveness Cohort, n=103)*

	Treatment Group		Total n/N (%)
	THERMOCOOL n/N (%)	AAD n/N (%)	
Chronic Effectiveness Success	53 / 89 (59.6)	9 / 56 (16.1)	62 / 145 (42.8)

* Fourteen (14) subjects in the THERMOCOOL group were censored from this analysis. These 14 subjects have not reached an effectiveness endpoint.

Subjects in the THERMOCOOL group were considered chronic failures if they were given a new Class I or III AAD, beta-blocker, calcium channel blocker, ACE inhibitor, or angiotensin receptor blocker for their AF during the 90-day blanking period and were maintained on it past the end of the blanking period. Also, if a new AAD was begun for a THERMOCOOL subject during their effectiveness evaluation period, the subject was considered a chronic effectiveness failure.

Table 3.6.2.2D describes the primary reason that 36 subjects in the THERMOCOOL group failed for chronic effectiveness. A subject could have more than one mode of failure, i.e. a subject could have failed AAD therapy on day 91 and had an AF recurrence at a later time during the effectiveness evaluation period. The time to occurrence of the first mode of failure was defined as the primary reason for failure and was used in the per-protocol Kaplan-Meier analysis presented in section 3.6.3 below.

There were 23 subjects in the THERMOCOOL group that failed the chronic effectiveness endpoint due to AAD failure. Five (5) of these subjects failed due to the introduction of a new beta-blocker and/or ACE inhibitor in the blanking period that was continued into the effectiveness evaluation period.

TABLE 3.6.2.2D Chronic Effectiveness Endpoint – First Reason for Failure for THERMOCOOL Subjects (Effectiveness Cohort, n=103)

Failure Reasons	n/89* (%)
Total Failures in THERMOCOOL group	**36 (40.4)**
Protocol Adjudicated AAD Failure	23 (25.8)**
AF Recurrence (91-361 Days)	11 (12.4)†
Repeat Ablations (>80 Days)	2 (2.2)
Acute Failure	0 (0.0)
Non-THERMOCOOL Catheter for AF Targets	0 (0.0)

* Fourteen (14) of the 103 subjects in the THERMOCOOL group are still in the effectiveness evaluation period
** Thirteen (13) of the 23 protocol adjudicated AAD failures also had AF recurrence (refer to Figure 3.6.2.2D)
†Five (5) of the 11 subjects observed with AF recurrence also had a subsequent protocol adjudicated AAD failure.

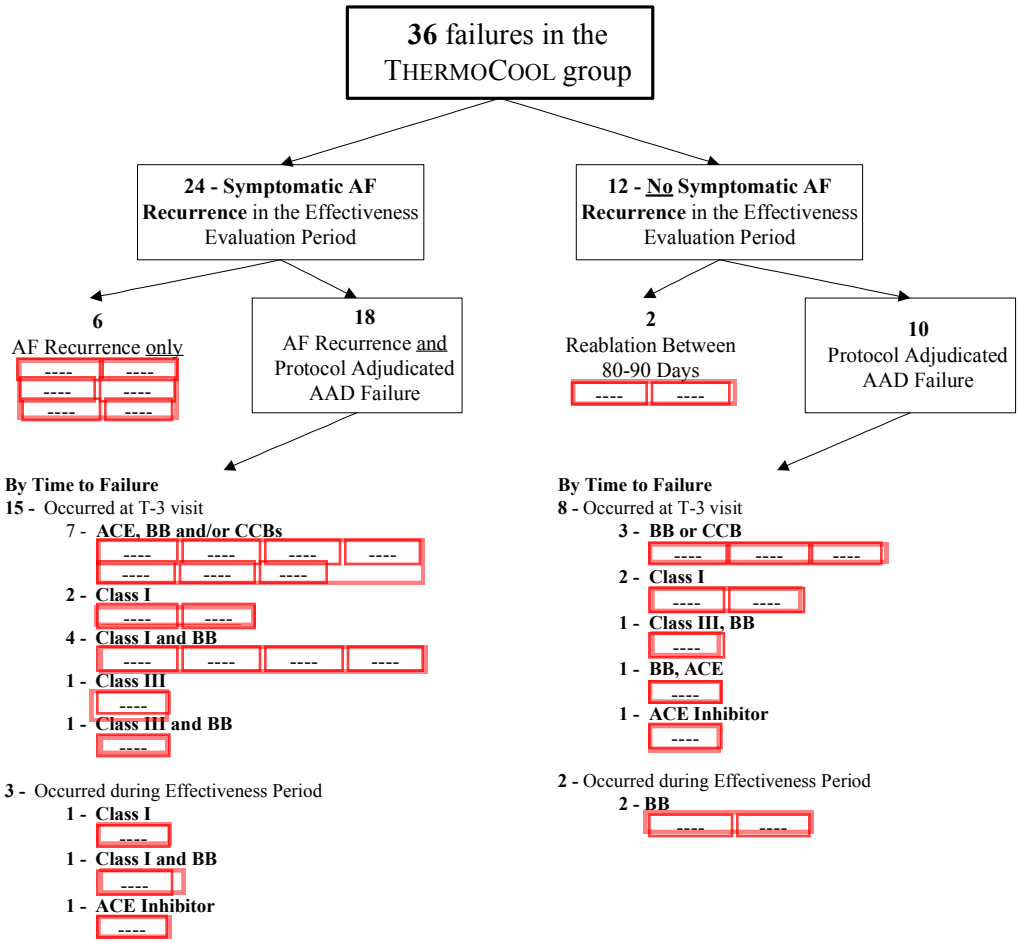
The 36 THERMOCOOL subjects who failed chronic effectiveness may have met the protocol failure criteria for more than one reason. Figure 3.6.2.2D is an illustration of *all* protocol failure criteria that these subjects met, any of which would have caused them to be adjudicated chronic effectiveness failure. The 36 subjects were initially divided into two groups based on whether a documented symptomatic AF episode was captured during their effectiveness evaluation periods (Days 91-361), regardless if that was the primary mode of failure.

Note that 2 subjects, who did have documented symptomatic AF recurrence, failed due to re-ablation procedures that occurred 81 and 84 days post index ablation. Neither subject had a documented symptomatic AF recurrence in the effectiveness evaluation period.

As shown in Figure 3.6.2.2D, 8 subjects, who did not have documented symptomatic AF recurrence, were effectiveness failures at the beginning of their effectiveness evaluation period due to the introduction of a new AAD during the blanking period that was not stopped prior to the start of the evaluation period. Five (5) of the 8 failures were due to BBs and/or ACE Inhibitors only, considered by the protocol to be AADs for the treatment of AF. Additionally, two (2) subjects without documented symptomatic AF recurrence were deemed chronic failures due to introduction to Beta-blocker agents during the effectiveness period. Also note that three (3) subjects, who did not have documented symptomatic AF recurrence, failed at the beginning of their effectiveness evaluation period due to the introduction of a new AAD (Class I or Class III) during the blanking period that was not stopped prior to the start of the evaluation period. Therefore, seven (7) of the ten (10) chronic failure subjects without documented symptomatic AF recurrence failed due to BBs and/or ACE Inhibitors.

Figure 3.6.2.2D reviews the AAD regimens (BBs, CCBs, ACE Inhibitors, Class I, and Class III) that caused subjects to fail by definition of the protocol in the appropriate groups.

FIGURE 3.6.2.2D Reason for Failure in the THERMOCOOL Group



AAD (Control) Group

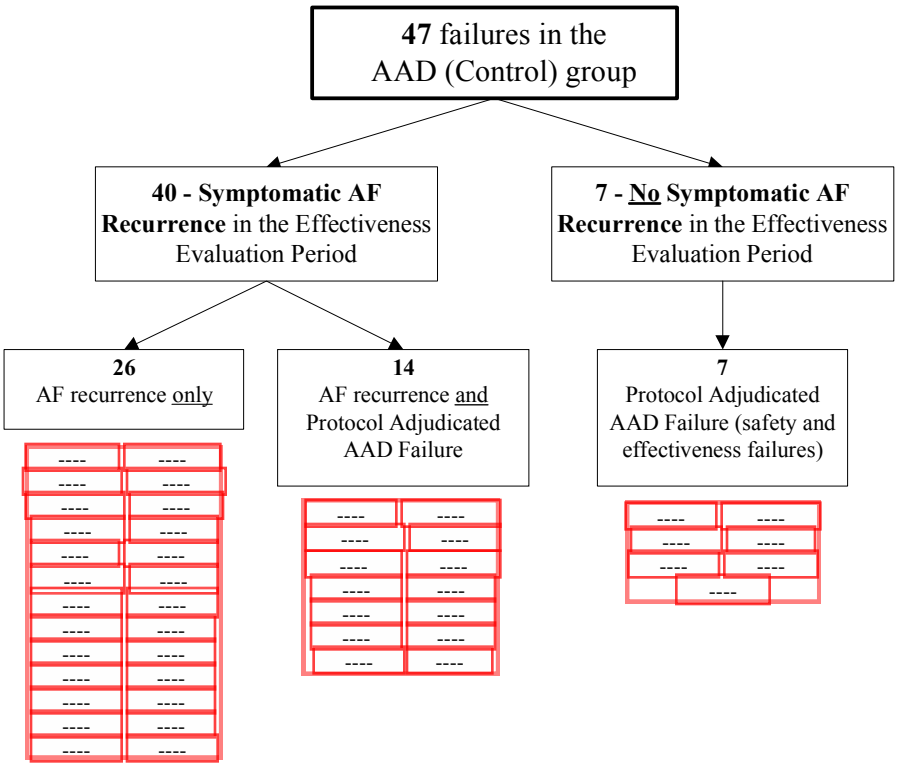
Figure 3.6.2.2E is an illustration of the 47 subjects that failed chronic effectiveness in the AAD (Control) group. The structure follows that of the previous figure, the failures are categorized initially by whether or not the subject had documented symptomatic recurrence of AF during their effectiveness evaluation period.

Of these 40 subjects that experienced such recurrence, 14 failed due to recurrence of AF with a protocol adjudicated failure for the AAD therapy. These subjects either had:

- a discontinuation of their study drug, typically due to intolerable side effects
- the addition of a new drug (other than the prescribed study drug) for AF during their involvement in the trial (day 0-285),
- or had a dose increase in their AF drugs during the effectiveness evaluation period.

Seven (7) subjects did not have documented symptomatic recurrence of AF in their effectiveness evaluation period and were protocol-adjudicated failures for safety and effectiveness. Note that these subjects may have had recurrence of AF during their 14-day dosing-period, prior to the start of the effectiveness evaluation period.

FIGURE 3.6.2.2E Reason for Failure in AAD (Control) Group (n=47)



3.6.3 Additional Kaplan-Meier Analyses

The Kaplan-Meier (KM) analyses presented here estimate the time to chronic failure and the time to recurrence by randomization group. In each analysis, the data were further stratified as follows:

- US vs. Non-US sites
- High (sites enrolling > 20 subjects) vs. Low to Medium Enrolling sites
- Highest Enrolling Site, (---- ---- ---- vs. Remaining Sites (Remaining)

The first analysis, presented in section 3.6.3.1, is based on the protocol specified adjudication of chronic success, which included failures for criteria in addition to symptomatic AF recurrence. This analysis provided statistical evidence demonstrating the chronic effectiveness of the THERMOCOOL catheter (Refer to Table 3.6.2.2C) per the pre-specified definitions for the primary endpoint and further corroborates the conclusions drawn from the September 2007 Bayesian analysis.

To further characterize the data based on clinical outcomes, additional KM analyses were performed for the Time to Recurrence (TTR) of AF and are presented in the following sections:

- 3.6.3.2.1 – Time to Recurrence of documented symptomatic AF
- 3.6.3.2.2 – Time to Recurrence of documented symptomatic or asymptomatic AF

There are a total of 21 additional KM analyses presented in this section. The figures displaying these KM curves are organized as presented in Table 3.6.3A.

TABLE 3.6.3A Organization of KM Figures Presented for All Analyses

	Time to Chronic Effectiveness Failure – Primary Analysis	Time to Recurrence - Symptomatic AF	Time to Recurrence – Symptomatic/ Asymptomatic AF
Randomization Group: THERMOCOOL (TC) Vs. AAD	Fig 3.6.3.1**A**	Fig 3.6.3.2.1**A**	Fig 3.6.3.2.2**A**
US vs. Non-US (NUS)	NUS Fig 3.6.3.1**B** US Fig 3.6.3.1**C**	NUS Fig 3.6.3.2.1**B** US Fig 3.6.3.2.1**C**	NUS Fig 3.6.3.2.2**B** US Fig 3.6.3.2.2**C**
High Enrolling (HE) vs. Low to Medium Enrolling (LME)	HE Fig 3.6.3.1**D** LME Fig 3.6.3.1**E**	HE Fig 3.6.3.2.1**D** LME Fig 3.6.3.2.1**E**	HE Fig 3.6.3.2.2**D** LME Fig 3.6.3.2.2**E**
Highest Enrolling ---- vs. Remaining Sites (RM)	---- Fig 3.6.3.1**F** RM Fig 3.6.3.1**G**	---- Fig 3.6.3.2.1**F** RM Fig 3.6.3.2.1**G**	---- Fig 3.6.3.2.2**F** RM Fig 3.6.3.2.2**G**

For reference purposes only, the KM analyses presented in sections 3.6.3.2.1 and 3.6.3.2.2 provide a p-value based on the log-rank test and should be interpreted with caution since the proportion hazard assumption might not be met. Rather, these post-hoc analyses are included to provide clinical context only.

KM tables are provided in Appendix 12 for each of these KM analyses and include the number of subjects at risk (number of subjects entering number of subjects entering the 9-month effectiveness evaluation period), number of subjects censored (number of subjects who have not experienced chronic failure and still in effectiveness evaluation period), number of events (subjects who experienced chronic failures), point estimate of freedom from chronic failures, standard error (by Peto Method), and 95% two-sided pointwise confidence interval estimation of point estimate of freedom from chronic failures.

The longer duration of the KM curves for the THERMOCOOL group reflects a fraction of the subjects with later final follow up visits. These later results remain within the protocol specified final follow-up visit window. In stratifications where the timing of last observations differs due to pending follow-up or other censoring, outcome comparisons were made at the longest time of follow-up common to both treatment groups.

3.6.3.1 Time to Chronic Failure – Primary Efficacy Endpoint

This KM analysis is based on the protocol specified adjudication of chronic success, which included subject failures without recurrence of AF. The reasons for chronic failure in the THERMOCOOL group were as follows:

- AAD failure [The addition/increased dose of AAD post-blanking. AADs, per the protocol, include Class I, Class III, beta blockers (BB), calcium channel blockers (CCB), digitalis, angiotensin receptor blockers or angiotensin converting enzyme (ACE) inhibitors]
- AF recurrence (91-361 days)
- Repeat ablations (>80 days)
- Acute failure
- Non-THERMOCOOL catheter for AF targets

The reasons for chronic failure in the AAD (control) group were as follows:

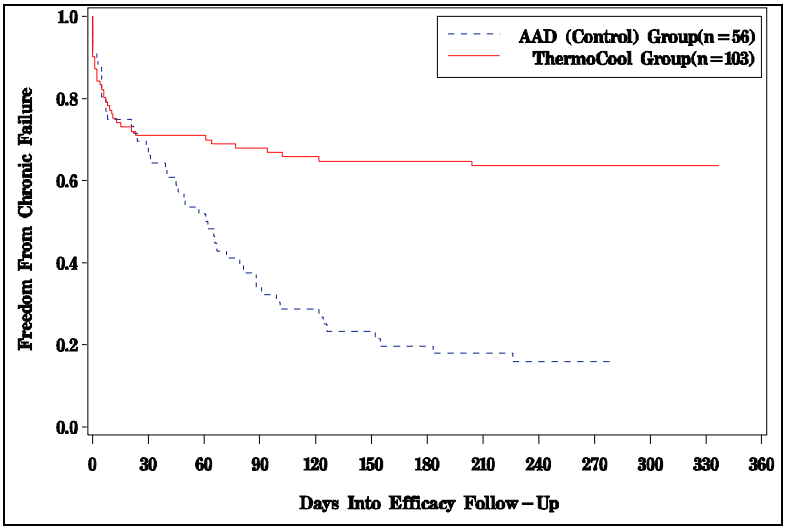
- AAD failure [The addition/increased dose/discontinuation of AAD post-blanking. AADs, per the protocol, included beta blockers (BB), calcium channel blockers (CCB), digitalis, angiotensin receptor blockers or angiotensin converting enzyme (ACE) inhibitors]
- Safety failure requiring discontinuation of the assigned AAD during days 0-285.
- AF recurrence (15-285 days)

Primary Analysis – By Randomization Group

One hundred and fifty-nine (159) subjects were included in this analysis, in which 103 and 56 subjects are from the THERMOCOOL group and AAD (Control) group, respectively.

Figure 3.6.3.1A provides time to chronic failures by randomization group. The results reveal a statistically significant difference between the two randomization groups. Using the stringent protocol definitions, the THERMOCOOL group shows a superior probability of success vs. antiarrhythmic drug (AAD) treatment over time (p-value < 0.0001; Log-Rank test). The difference in probability of treatment success was 48% in favor of the THERMOCOOL group (64% vs. 16%) at 9 months of effectiveness evaluation.

FIGURE 3.6.3.1A KM Curve of Time to Chronic Failures By Randomization Group (Effectiveness Cohort, n=159)



Note: Log rank test p-value < 0.0001. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

US vs. Non-US Sites

Chronic effectiveness outcome data were stratified by US vs. Non-US sites to characterize the regional variation of the effectiveness results (Figures 3.6.3.1B and 3.6.3.1C).

Among the 103 subjects in the THERMOCOOL Group, 43 (43/103, 41.7%) subjects were enrolled from the US sites and 60 (60/103, 58.3%) subjects from the Non-US sites. Among the 56 subjects in the AAD (Control) Group, 21 (21/56, 37.5%) subjects were enrolled from the US sites and 35 (35/56, 62.5%) subjects from the Non-US sites.

Figure 3.6.3.1B presents the time to chronic failure for the Non-US sites. The probability of achieving chronic success is much greater for the THERMOCOOL Group vs. the AAD (Control) group at all but the first few days of the evaluation period, ending with a 62% (76% vs. 14%) difference in the probability of chronic success after 8 months of effectiveness evaluation.

Figure 3.6.3.1C presents the time to chronic failure for the US sites. The THERMOCOOL group had a marked decrease in freedom from chronic failure during the first 30 days post-blanking period, leveling off thereafter. This is initially driven by protocol-adjudicated, non-AF-recurrence failures. In contrast, the chronic failures in the AAD (Control) group occurred more evenly through the evaluation period. At the end of the 9-month evaluation period there was a 26% percent difference in favor of the THERMOCOOL group (44% vs 18%).

In comparing the results between the two strata, it is important to note that the THERMOCOOL catheter has been commercially available at the Non-US sites far longer than in the United States, where treatment of atrial fibrillation remains off-label (see Table 3.6.3.1A).

While differences in the magnitude of the treatment effect are apparent, there is a clear difference in the probability of successful treatment in favor of the THERMOCOOL catheter vs. AADs at both the US and Non-US sites.

TABLE 3.6.3.1A. THERMOCOOL Catheter Approval Dates and Indications for Use by Country

Country	Approval Date	Indications for Use

*The THERMOCOOL catheter was not introduced into .

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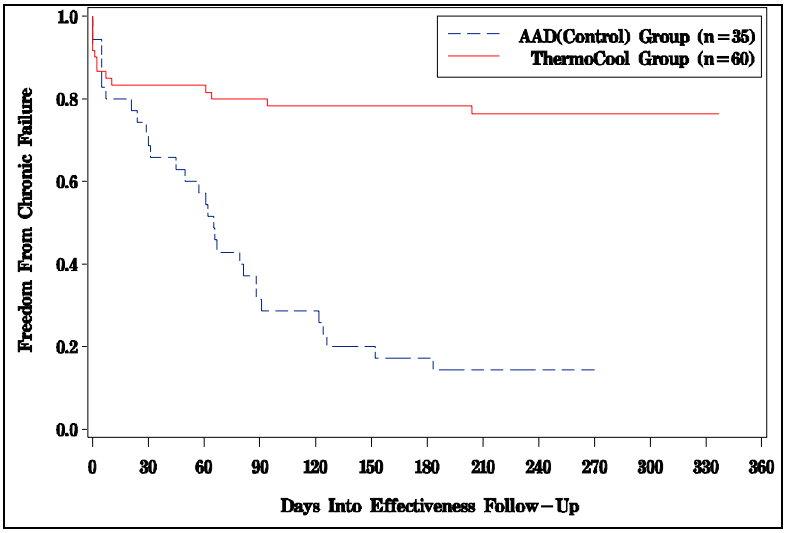
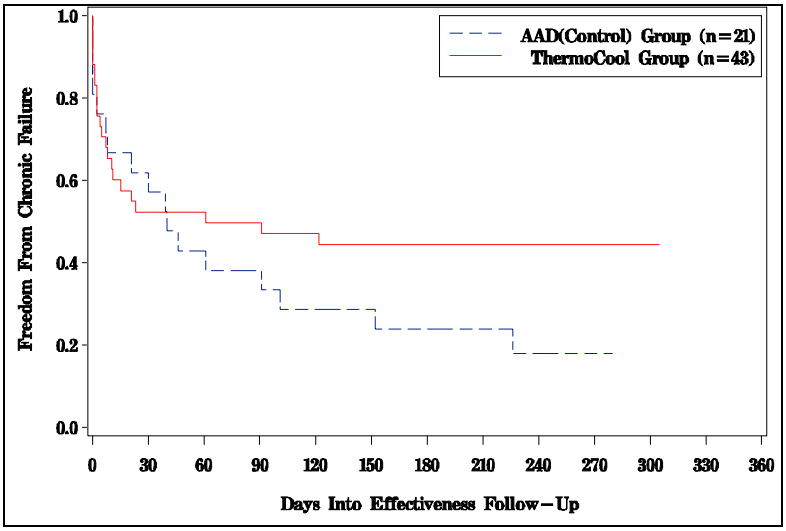
FIGURE 3.6.3.1B KM Curve of Time to Chronic Failures – Non-US Sites (n=95)



Note: Log rank test p-value < 0.0001. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

FIGURE 3.6.3.1C KM Curve of Time to Chronic Failure - US Sites (n=64)



Note: Log rank test p-value = 0.1794. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

High Enrolling vs. Low to Medium Enrolling Sites

Chronic effectiveness outcome data were stratified by High Enrolling vs. Low to Medium Enrolling sites. The study protocol (version 12.2, section 7.2.3), defined sites enrolling greater than 20 subjects as High Enrolling sites and those enrolling 20 subjects or less were categorized as Low to Medium Enrolling sites.

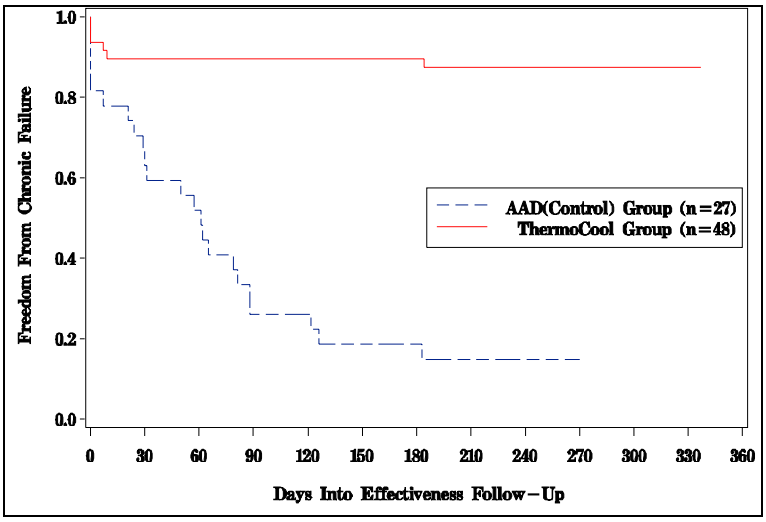
Among 159 subjects enrolled at 19 sites, two (---- ---- and ---- ---- were considered the High Enrolling sites. These two sites enrolled 48 (48/103, 46.6%) subjects in the THERMOCOOL Group and 27 (27/56, 48%) subjects in the AAD (Control) Group. The remaining 17 sites had 55 (55/103, 53.4%) subjects in the THERMOCOOL Group and 29 (29/56, 51.8%) subjects in the AAD (Control) Group.

Figure 3.6.3.1D presents time to chronic failure for the High Enrolling sites.
The treatment effect favors the THERMOCOOL group subjects again, with an increased probability of chronic success of 72% (87% vs. 15%) at 8 months of the evaluation period.

Figure 3.6.3.1E presents the same analysis for the Low to Medium Enrolling sites. There was a high incidence of early chronic failures in the THERMOCOOL group observed for the Low to Medium Enrolling sites. These are attributed in part to the use of a new AAD during the effectiveness period as defined in the study protocol. The number of late chronic failures was relatively modest for subjects in this group. For the AAD (Control) group, there was a more uniform decrease in the probability of freedom from chronic failure over duration of the effectiveness evaluation period. At the end of the 9-month period, there was a differential treatment effect, again in favor of the THERMOCOOL group, with the THERMOCOOL group subjects 24% more likely (41% vs. 17%) to achieve a successful outcome per the protocol than the AAD (Control) group.

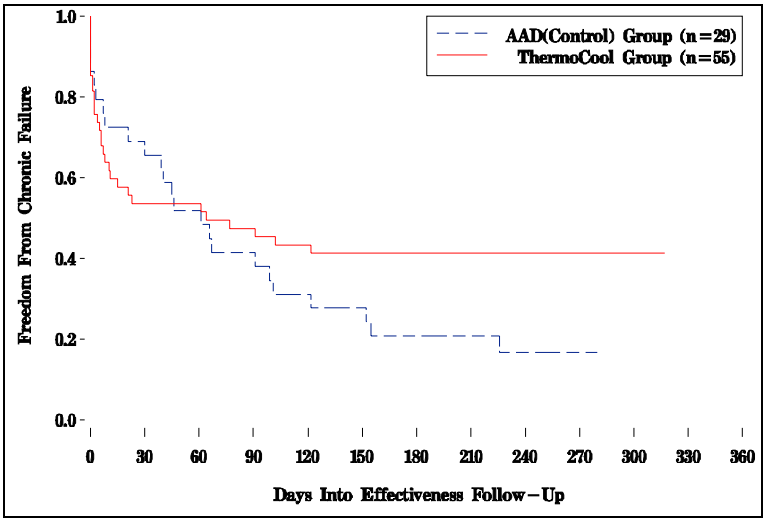
The difference in the magnitudes of the treatment effects across these two strata may again be influenced by investigator experience; both High Enrolling sites are located in ---- and had earlier access to the THERMOCOOL catheter, as discussed previously. Nonetheless, t ion of the treatment effect is consistent, and corroborates the superiority of the THERMOCOOL catheter in the primary effectiveness analysis (refer to section 3.6.2.2).

FIGURE 3.6.3.1D KM Curve of Time to Chronic Failures - High Enrolling Sites (n=75)



Note: Log rank test p-value < 0.0001. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

FIGURE 3.6.3.1E KM Curve of Time to Chronic Failure - Low to Medium Enrolling Sites (n=84)



Note: Log rank test p-value 0.2025. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group

---- ---- (---- vs. Remaining sites

Data were further stratified by ---- ---- (---- vs. Remaining Sites. ---- was selected for further analysis due to the high enrollment and successful outcomes. ---- was the highest enrolling site with 50/167 (29.9%) subjects enrolled.

Among 103 subjects in the THERMOCOOL group, 31 (31/103, 30.1%)subjects were from the ---- site and 72 (72/103, 69.9%) subjects were from the Remaining sites. Among 56 subjects in the AAD (Control) group, 18 (18/56, 32.1%) subjects were from ---- and 38 (38/56, 67.9%) subjects were from the Remaining sites.

Figures 3.6.3.1F and 3.6.3.1G show the time to chronic failures for the ---- vs. Remaining sites, respectively. The results demonstrate a treatment effect in favor of the THERMOCOOL group in both strata, though the magnitude is larger for the ---- site.

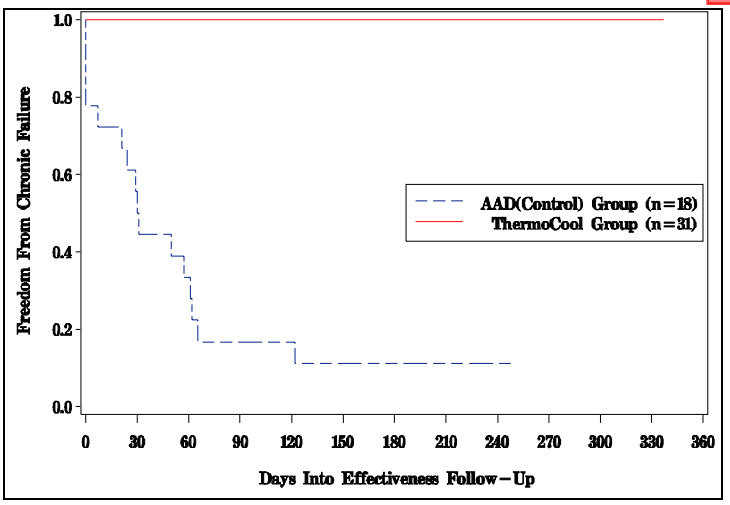
The high incidence of chronic effectiveness success in the THERMOCOOL group at ---- (Figure 3.6.3.1F) is discussed in detail in section 4.5.3. Potential contributors include the following:

1) **No protocol adjudicated failures.** No ---- THERMOCOOL group subject was prescribed a new AAD during the effectiveness period. Subjects were prescribed a previously failed AAD after the ablation procedure (during the blanking period) and weaned off the drug during the effectiveness period, all within the specified parameters of the study protocol (refer to section 3.6.4.2 for details)
2) **Investigator experience.** Early commercial availability of the THERMOCOOL catheter for the treatment of AF in the ---- giving the study investigator several years of experience using the THERMOCOOL catheter.

The AAD (Control) group at ---- shows increased failures at approximately day 0, 30 and 60 days into the effectiveness period. The difference in effectiveness between the two treatment groups was 89% (100% vs. 11%) in favor of the THERMOCOOL Group after 8 months of effectiveness evaluation.

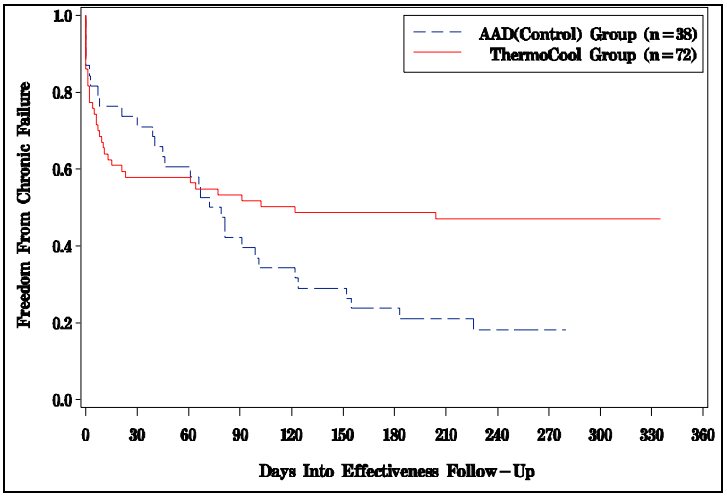
The THERMOCOOL group at the Remaining sites (Figure 3.6.3.1G) had a rapid decrease in freedom from chronic failure during the first 30 days post-blanking period, and plateaus thereafter. Again, this is driven in part by the protocol-adjudicated failures. In contrast, the chronic failures in the AAD (Control) group occurred more evenly through the evaluation period. At the end of the 9-month evaluation period there was a 29% (47% vs. 18%) difference in favor of the THERMOCOOL group.

FIGURE 3.6.3.1F KM Curve of Time to Chronic Failure - ---- Site (n=49)



Note: Log rank test p-value < 0.0001. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

FIGURE 3.6.3.1G KM Curve of Time to Chronic Failures - Remaining Sites (n=110)



Note: Log rank test p-value =0.0528. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

To further characterize the effect of site variation on the overall results, an additional Bayesian analysis was conducted excluding the ---- site (refer to Appendix 26). The resulting posterior mean probabilities of success for the AAD and THERMOCOOL ablation groups were 0.200 (posterior standard deviation of 0.062) and 0.460 (posterior standard deviation of 0.060) respectively. The posterior probability that the THERMOCOOL ablation group is superior to the AAD group is 0.9975. Thus, the superiority of the THERMOCOOL ablation vs. AAD group with respect to the primary effectiveness endpoint was further confirmed, independent of the contribution of the highest enrolling site.

3.6.3.2 Time to AF Recurrence Analyses

The additional KM analyses estimate the Time to Recurrence of AF based on clinical AF recurrence. These post-hoc analyses do not address protocol success or failure, and are provided for clinical context only.

- 3.6.3.2.1 – Time to Recurrence of Documented Symptomatic AF
- 3.6.3.2.2 – Time to Recurrence of Documented Symptomatic or Asymptomatic AF

3.6.3.2.1 Time to Recurrence of Documented Symptomatic AF Episode

In these analyses, the time to recurrence of documented symptomatic AF is presented. This analysis was based on the protocol definition of documented symptomatic AF recurrence (AF episode lasting at least 30 seconds and associated with symptoms).

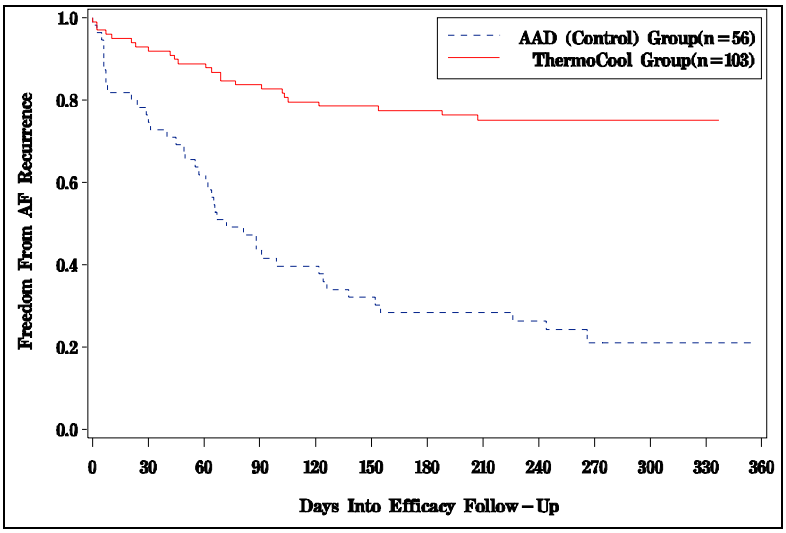
As presented in the previous section, the data were stratified by:

- Randomization Group
- US vs. Non-US sites
- High (sites enrolling > 20 subjects) vs. Low to Medium Enrolling sites
- Highest Enrolling Site, (---- ---- ---- vs. Remaining Sites

By Randomization Group

This analysis includes only documented symptomatic AF recurrence as an event. Figure 3.6.3.2.1A shows the time to recurrence of documented symptomatic AF episodes by randomization group. The main difference between this analysis and the KM curve for protocol specified adjudication of chronic success is the 10 THERMOCOOL group subjects considered protocol failures without recurrence of AF (refer to section 3.6.2.2 and Figure 3.6.3.1A, KM Curve of Time to Chronic Failures By Randomization Group). The data demonstrate that the THERMOCOOL group subjects had a 54% (75% – 21%) higher probability of freedom from AF recurrence at 9 months after initiation of the evaluation period.

FIGURE 3.6.3.2.1A KM Curve of Time to Recurrence of Documented Symptomatic AF by Randomization Group (Effectiveness Cohort, n=159)



Note: Log rank test p-value < 0.0001; "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

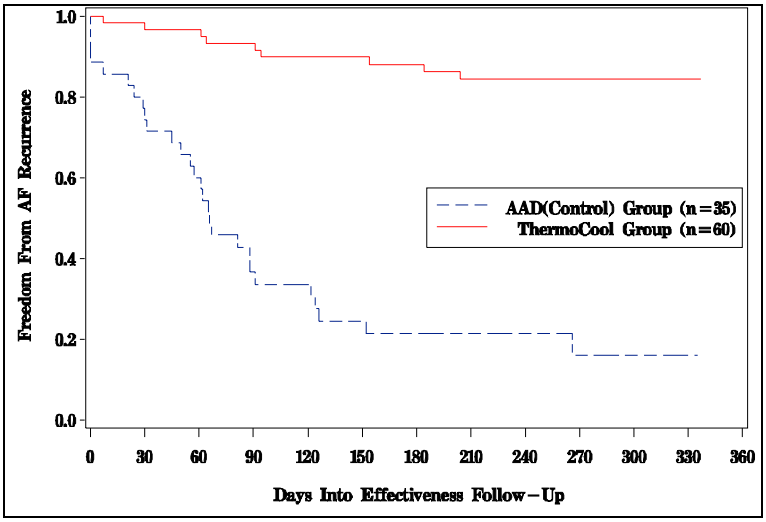
US vs. Non-US Sites

Figure 3.6.3.2.1B and 3.6.3.2.1C stratify the time to recurrence of documented symptomatic AF episodes by US vs. Non-US. The results again reveal that the THERMOCOOL group subjects experienced a higher probability of freedom from symptomatic AF recurrence across both strata, though the magnitude of the treatment effect varied.

Figure 3.6.3.2.1B presents time to recurrence of documented symptomatic AF episodes for non-US sites. There was a 68% (84% vs. 16%) greater probability of freedom from symptomatic AF recurrence in favor of the THERMOCOOL group following 9 months of effectiveness evaluation.

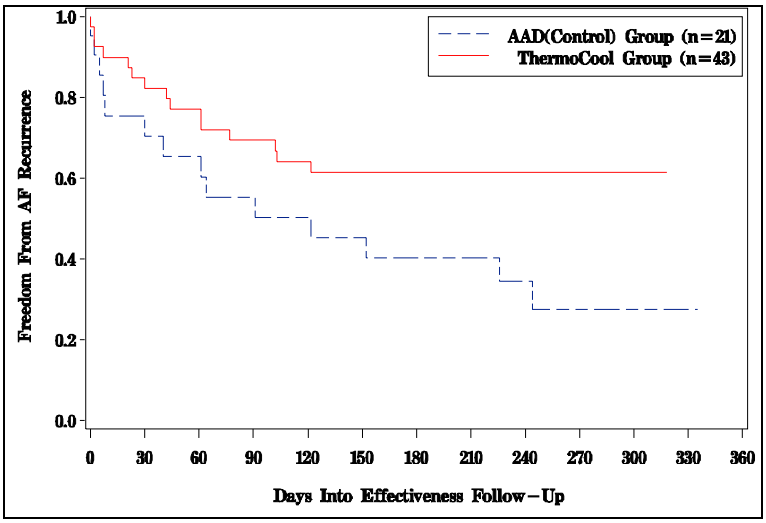
Figure 3.6.3.2.1C shows the time to recurrence of documented symptomatic AF episodes for US sites. At all times throughout the evaluation period, the THERMOCOOL group subjects had a higher probability of being free from symptomatic AF recurrence. At the end of 9 months of effectiveness evaluation, the difference was 33% (61% vs. 28%) in favor of the THERMOCOOL group.

FIGURE 3.6.3.2.1B KM Curve of Time to Recurrence of Documented Symptomatic AF - non-US Sites (n=95)



Note: Log rank test p-value < 0.0001. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

FIGURE 3.6.3.2.1C KM Curve of Time to Recurrence of Documented Symptomatic AF -US Sites (n=64)



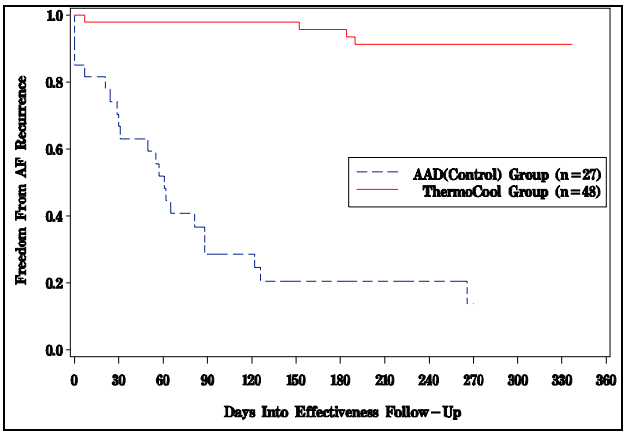
Note: Log rank test p-value = 0.0345. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

High Enrolling vs. Low to Medium Enrolling Sites

Figures 3.6.3.2.1D and 3.6.3.2.1E stratify the time to recurrence of documented symptomatic AF episodes by High Enrolling (HE) vs. Low to Medium Enrolling (LME) sites.

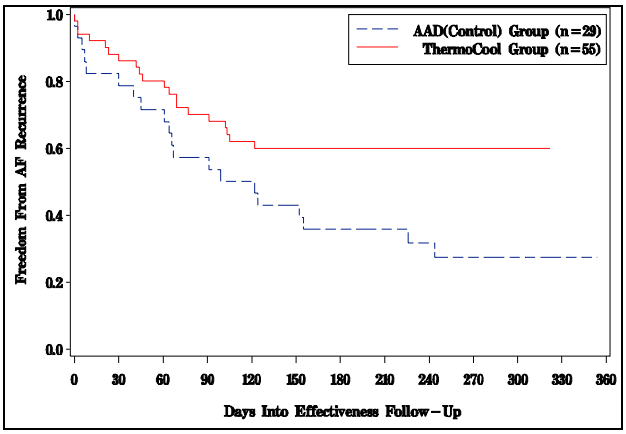
In the High Enrolling sites (Figure 3.6.3.2.1D), the results demonstrate that the THERMOCOOL group subjects had a higher probability of freedom from symptomatic AF recurrence throughout the effectiveness evaluation period. The treatment effect for the Low to Medium Enrolling sites (Figure 3.6.3.2.1E) is again in favor of the THERMOCOOL group, though the magnitude is smaller (71%, 91% vs. 20%; and 33%, 60% vs. 27%); HE and LME sites respectively, after 8 and 9 months of effectiveness evaluation). As discussed above, the High Enrolling sites subset is comprised of two [redacted] with earlier commercial availability of the THERMOCOOL catheter.

FIGURE 3.6.3.2.1D KM Curve of Time to Recurrence of Documented Symptomatic AF - High Enrolling Sites (n=75)



Note: Log rank test p-value < 0.0001. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

FIGURE 3.6.3.2.1E KM Curve of Time to Recurrence of Documented Symptomatic AF - Low to Medium Enrolling Sites (n=84)



Note: Log rank test p-value = 0.0168. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

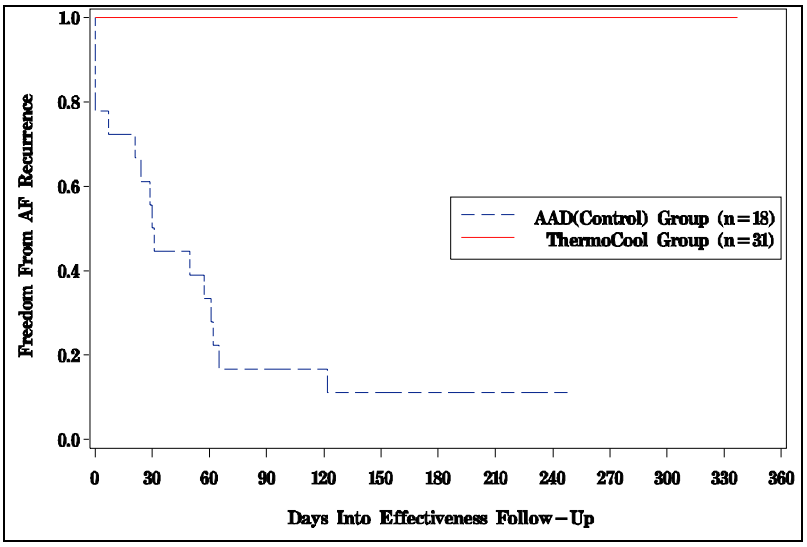
---- vs. Remaining Sites

Figures 3.6.3.2.1F and 3.6.3.2.1G show the time to recurrence of documented symptomatic AF by ---- vs. Remaining sites. The direction of treatment effect is again the same, in favor of the THERMOCOOL Group, though of greater magnitude at the ---- site.

Figure 3.6.3.2.1F is identical to Figure 3.6.3.1F (KM Curve of Time to Chronic Failure – ---- Site), as all chronic failures at this site resulted from symptomatic AF recurrence. The difference in probability of freedom from symptomatic AF recurrence after 8 months of effectiveness evaluation was 89% (100% vs. 11%).

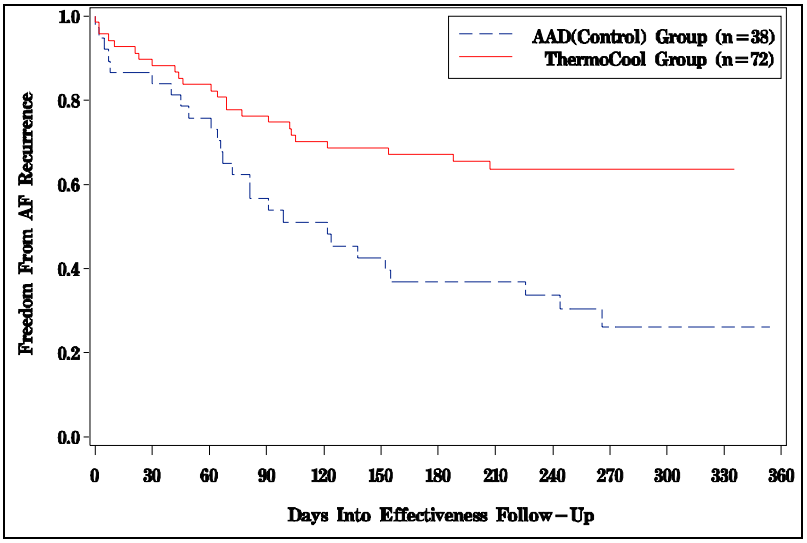
For the Remaining sites (Figure 3.6.3.2.1G), a greater fraction of the THERMOCOOL group subjects were free from symptomatic AF recurrence at all times throughout the evaluation period. The magnitude of the difference in freedom from symptomatic AF recurrence at the end of the follow-up period was 38 % (64% vs. 26%) in favor of the THERMOCOOL Group at 9 months following start of the effectiveness period.

FIGURE 3.6.3.2.1F KM Curve of Time to Recurrence of Documented Symptomatic AF - ---- Site (n=49)



Note: Log rank test p-value < 0.0001. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

FIGURE 3.6.3.2.1G KM Curve of Time to Recurrence of Documented Symptomatic AF - Remaining Sites (n=110)



Note: Log rank test p-value = 0.0011. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

3.6.3.2.2 Time to Recurrence of Any Documented AF Episode

In these analyses, the time to recurrence of any documented AF episodes, symptomatic or asymptomatic, is presented. This analysis was based on the clinical finding of documented AF (episode > 30 sec) regardless of symptoms.

As presented in the previous sections, data are stratified by:

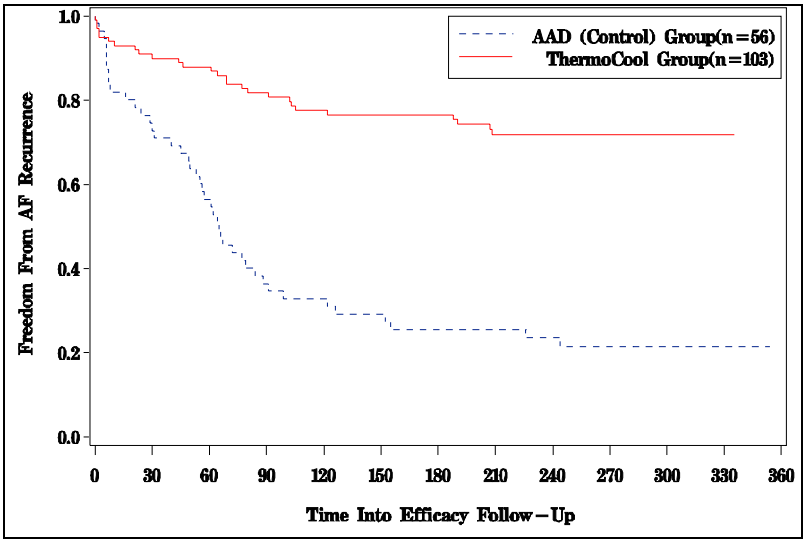
- Randomization Group
- US vs. Non-US sites
- High (sites enrolling > 20 subjects) vs. Low to Medium Enrolling sites
- Highest Enrolling Site, (---- ---- ---- vs. Remaining Sites (Non- ----

By Randomization Group

Figure 3.6.3.2.2A presents the time to recurrence of documented symptomatic or asymptomatic AF episodes by randomization group.

The data demonstrate that the THERMOCOOL group has a higher probability of freedom from any AF recurrence over time. The difference in likelihood of AF recurrence after 9 months of effectiveness evaluation is 51% (72% vs. 21%) in favor of the THERMOCOOL catheter treatment group.

FIGURE 3.6.3.2.2A KM Curve Of Time To Recurrence Of Documented Symptomatic Or Asymptomatic AF By Randomization Group (Effectiveness Cohort, n=159)

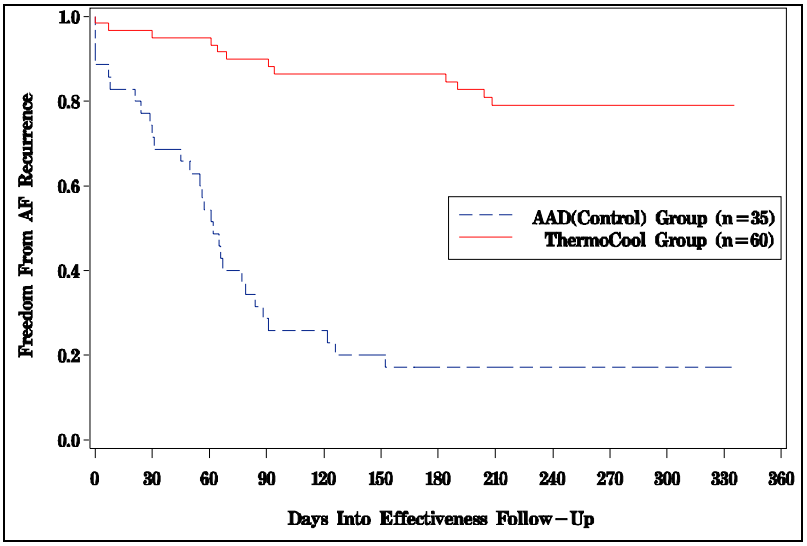


Note: Log rank test p-value < 0.0001. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

By US vs. Non-US Sites

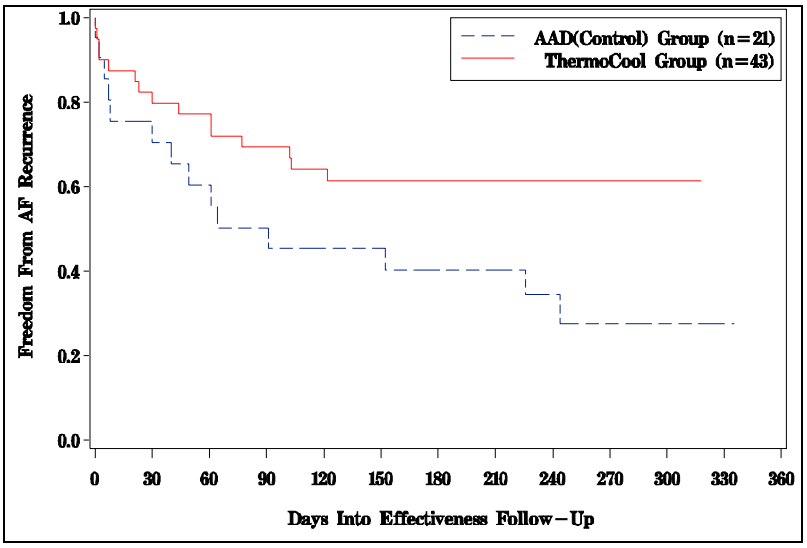
Figures 3.6.3.2.2B and 3.6.3.2.2C stratify the time to recurrence of documented symptomatic or asymptomatic AF by the US vs. Non-US sites. Again the results reveal consistent directionality of the treatment effect in favor of the THERMOCOOL group. In both strata, subjects treated with the THERMOCOOL catheter had a greater probability of freedom from AF recurrence, symptomatic or asymptomatic, throughout the effectiveness evaluation period. The magnitude of the effect was larger for the Non-US sites, such that Non-US subjects were 62% (79% vs. 17%) more likely and US THERMOCOOL subjects 33% (61% vs. 28%) more likely to be AF recurrence free than their AAD (Control) group counterparts at the end of 9 months of effectiveness evaluation.

FIGURE 3.6.3.2.2B KM Curve of Time to Recurrence of Documented Symptomatic or Asymptomatic AF - Non-US Sites (n=95)



Note: Log rank test p-value <0.0001. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

FIGURE 3.6.3.2.2C KM Curve of Time to Recurrence of Documented Symptomatic or Asymptomatic AF - US Sites (n=64)



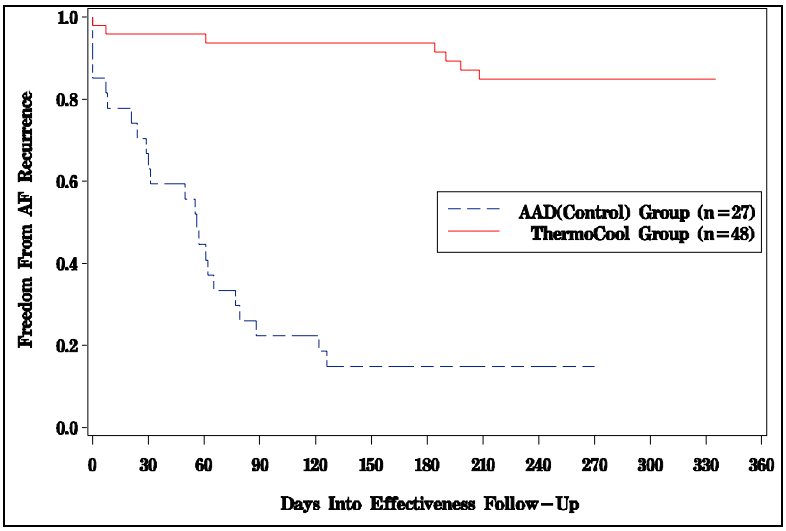
Note: Log rank test p-value = 0.0324. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

By High Enrolling vs. Low to Medium Enrolling Sites

Figures 3.6.3.2.2D and 3.6.3.2.2E stratify the time to recurrence of documented symptomatic or asymptomatic AF. Again the results demonstrate consistent directionality of the treatment effect in favor of the THERMOCOOL group. In both strata, subjects treated with the THERMOCOOL catheter had a greater probability of freedom from AF recurrence, symptomatic or asymptomatic, throughout the effectiveness evaluation period. The magnitude of the effect was larger for the High Enrolling sites, such that High Enrolling (HE) sites' THERMOCOOL subjects were 70% (85% vs. 15%) more likely and Low to Medium enrolling (LME) sites' THERMOCOOL subjects 33% (60% vs. 27%) more likely than their AAD (Control) group counterparts to be AF recurrence free after 8 (HE) and 9 months (LME) of effectiveness evaluation, respectively.

As previously stated in section 3.6.3.1 and 3.6.3.2.1, the magnitude of the difference in the observed treatment effect was attributed at least in part to the availability of the THERMOCOOL catheter in [redacted] for the treatment of AF. The study investigators at these two clinical sites had prior experience with the HERMOCOOL catheter.

FIGURE 3.6.3.2.2D KM Curve of Time to Recurrence of Documented Symptomatic or Asymptomatic AF - High Enrolling Sites (n=75)



Note: Log rank test p-value <0.0001. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

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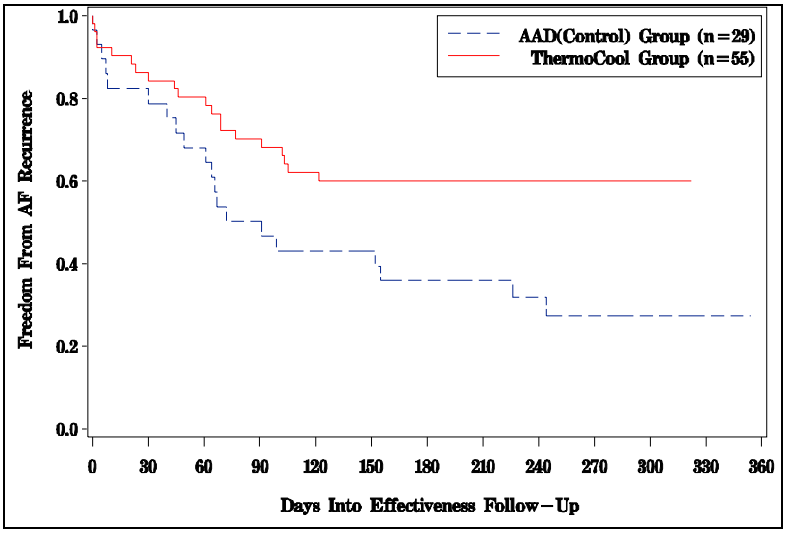
FIGURE 3.6.3.2.2E KM Curve of Time to Recurrence of Documented Symptomatic or Asymptomatic AF - Low to Medium Enrolling Sites (n=84)



Note: Log rank test p-value = 0.0129. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

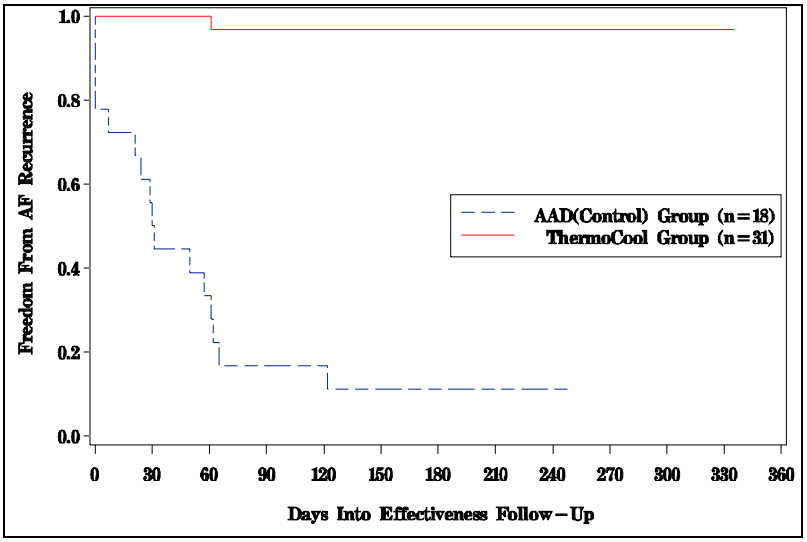
By ---- vs. Remaining Sites

Figures 3.6.3.2.2F and 3.6.3.2.2G stratify the time to recurrence of documented AF, whether symptomatic or asymptomatic, by ---- vs. Remaining sites. As before, the direction of the treatment effect remains strongly in favor of the THERMOCOOL Group across both strata.

In Figure 3.6.3.2.2F, the KM curve for the ---- site reveals a small drop in freedom from AF recurrence part way through the evaluation period. The KM curve for the AAD (Control) group remains comparable to that in Figure 3.6.3.2.1F (KM Curve of Time to Recurrence of documented symptomatic AF - ---- Site). At the end of 8 months of effectiveness evaluation, the difference in probability of being AF recurrence free was 86% (97% vs. 11%).

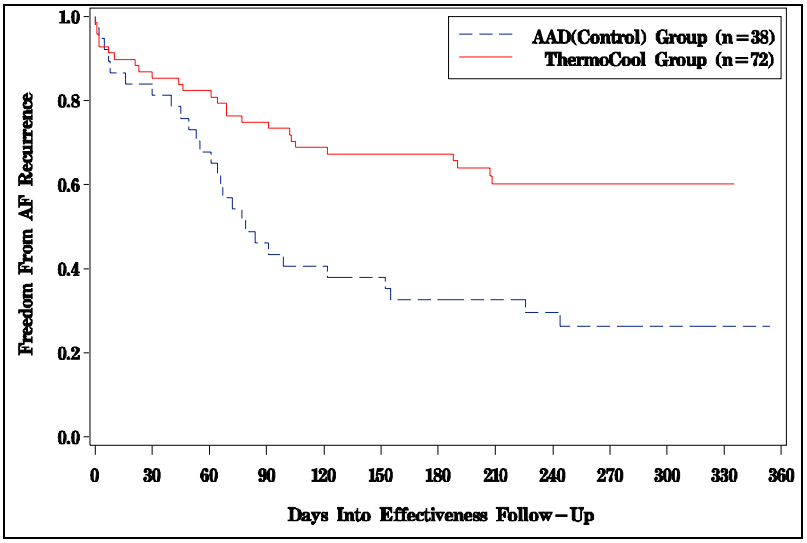
Figure 3.6.3.2.2G shows the time to recurrence of documented symptomatic AF for the Remaining sites. A substantially greater probability of freedom from documented AF recurrence, symptomatic or asymptomatic, was observed for the THERMOCOOL group at all times except the first week throughout the 9 month effectiveness evaluation period. At the end of the 9 month effectiveness evaluation period, THERMOCOOL group subjects were 34% (60% vs. 26%) more likely to be AF recurrence free.

FIGURE 3.6.3.2.2F KM Curve of Time to Recurrence of Documented Symptomatic or Asymptomatic AF - ---- Site (n=49)



Note: Log rank test p-value <0.0001. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

FIGURE 3.6.3.2.2G KM Curve Of Time To Recurrence Of Documented Symptomatic or Asymptomatic AF - Remaining Sites (n=110)



Note: Log rank test p-value = 0.0009. "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group.

3.6.4 Additional Chronic Effectiveness

3.6.4.1 Outcomes in THERMOCOOL Group by Procedures and Targets

Chronic Outcomes By Number of Ablation Procedures – THERMOCOOL Group

Table 3.6.4.1A presents and compares chronic outcomes in subjects undergoing either one or two ablation procedures for AF with the study catheter. Out of 24 THERMOCOOL subjects that underwent a second ablation procedure, 7 (29.2%, 7/24) achieved a successful chronic outcome. Successful chronic outcomes occurred in 70.1% (46/65) of subjects who underwent only one ablation procedure.

TABLE 3.6.4.1A Chronic Effectiveness Outcome by Total Number of Ablation Procedures per Subject (THERMOCOOL Group Subjects, n=103*)

Number of Ablation Procedures	THERMOCOOL Group		
	Success n	Fail n	Total n
1 Procedure	46	19	65
2 Procedures	7	17	24
Total	53	36	89

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

Chronic Outcomes By Ablation Targets – THERMOCOOL Group

Investigators performing procedures were required to follow the circumferential anatomical approach to isolate the PVs. The study protocol allowed investigators to perform additional optional ablation procedures based on clinical findings and specific conditions outlined in the protocol. The parameters for the required and optional ablation procedures are explained in greater detail in this document in section 2.2.5.5.

Chronic effectiveness was evaluated by type of ablation targets and the results are provided in Table 3.6.4.1B. Subjects were stratified based on the lesions sets applied to subjects during the ablation procedure. The most successful outcomes included both the isolation of the PVs and the addition of left side and right side atrial lines.

TABLE 3.6.4.1B 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 are still within the effectiveness evaluation period and were not included in this analysis.

3.6.4.2 AADs and Chronic Outcomes

Chronic Outcomes by AAD Class Failed at Baseline by Randomization Group

Twenty-six (26) subjects were enrolled into the study who failed only a Class II or IV AAD for the treatment of AF. Of these subjects, 19 were randomized to the THERMOCOOL group and 7 to the AAD (Control) group. Six (6) subjects in the THERMOCOOL group have not reached an effectiveness endpoint.

Table 3.6.4.2A presents a comparison of the chronic outcomes in subjects by the class of the previously failed AAD. The number of subjects enrolled who failed only a Class II or IV AAD at enrollment was 15.6% (26/167). The chronic effectiveness outcomes were not statistically significant comparing the groups (Class I/III vs. Class II/IV subjects).

TABLE 3.6.4.2A Chronic Effectiveness Outcome by AAD Failed at Baseline (Effectiveness Cohort, n=159*)

Chronic Outcome	Randomization Group			
	THERMOCOOL group (n=103)		AAD (n=56)**	
	Class I & III n/76 (%)	Class II & IV n/13 (%)	Class I & III n/48 (%)	Class II & IV n/7 (%)
Success	48 (63.2)	5 (38.5)	7 (14.6)	2 (28.6)
Failure	28 (36.8)	8 (61.5)	41 (85.4)	5 (71.4)
p-Value***	0.128		0.321	

* 14 Subjects are still within the effectiveness evaluation period and were not included in this analysis.
** AAD (Control) group subject [redacted] is excluded from this analysis pending data clarification.
*** Fisher's Exact test.

AAD Therapy During the Effectiveness Period – THERMOCOOL Group

Table 3.6.4.2B summarizes the subject outcomes for the THERMOCOOL subjects by the AAD therapy taken during the effectiveness evaluation period. At the beginning of the effectiveness evaluation period, 54% (55/102) of the THERMOCOOL group subjects were prescribed a Class I or III AAD for AF. Of these 55 subjects, 31 had a successful chronic outcome at the end of the effectiveness evaluation period. As described in the protocol and in section 2.2.5.8 above, a subject could be adjudicated a chronic success if the AAD currently prescribed was a previously failed therapy with a dose equal to or less than the maximum historical dose. All 31 subjects deemed to have chronic success were prescribed a previously failed AAD.

The study investigator at [redacted] was careful to prescribe a previously failed AAD after the ablation procedure (during the blanking period) to be within the specified parameters of the study protocol. The Non- [redacted] sites were more likely to prescribe a new (not previously failed) AAD after the ablation procedure and continue administration into the effectiveness period. In addition [redacted] subjects remained on a previously failed Class IC drug for a longer time period in the effectiveness period.

As the effectiveness period continued, some investigators began to remove Class I or III AAD Therapy from these subjects. By the 3-month visit of the effectiveness period only 33% (33/99) of the subjects remained on a Class I or III AAD. The majority of the subjects (66.7%, 66/99) were not taking a Class I or III AAD for the remaining 6-months of the effectiveness evaluation period.

TABLE 3.6.4.2B Chronic Outcome by AAD Prescribed During Effectiveness Period (THERMOCOOL Group Subjects, n=103)*

	Effectiveness Evaluation Period			
	Day 0	**Day 90**	**Day 180**	**Day 270**
Number of Subjects/Visit	102	99	95	76
Taking a Class I and/or III AAD at Visit Date				
Number of Subjects (% of subjects at visit)	55 (53.9)	33 (33.3)	19 (20.0)	15 (19.7)
Number of Subjects with Success	31	16	4	3
Off a Class I and/or III AAD at Visit Date				
Number of Subjects (% of subjects at visit)	47 (46.1)	66 (66.7)	76 (80.0)	61 (80.3)
Number of Subjects with Success	22	37	49	50

* There are 14 THERMOCOOL group subjects that have not reached the effectiveness endpoint.

3.6.4.3 Follow-up 24 Hour Holter Results

No subject in either the THERMOCOOL or AAD (control) group reached the end of the effectiveness evaluation period without documented symptomatic AF by TTM or ECG documentation only to then fail effectiveness because of the recurrence of symptomatic AF during the 24 hour Holter monitoring.

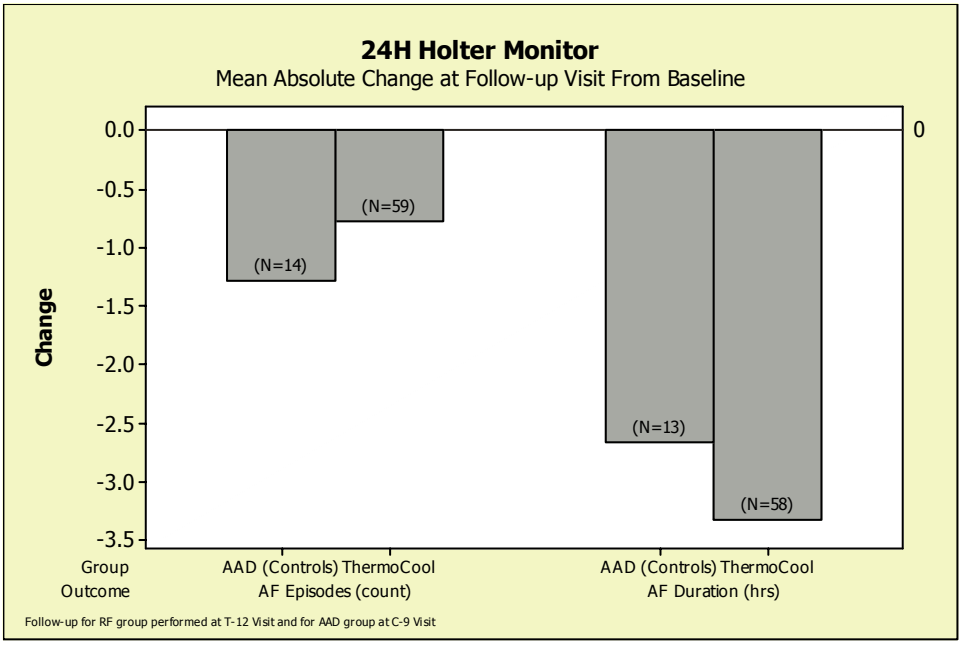
Where available, within subject comparisons in the AF duration and the number of AF episodes between the baseline and the end of the effectiveness evaluation period Holter monitor recordings were analyzed. Figure 3.6.4.3A presents the results of the within subject comparisons.

A mean reduction (within subject comparisons) in the number of AF episodes recorded during the final 24 h Holter monitoring was observed for both the THERMOCOOL and AAD (control) groups. The THERMOCOOL group (n=59) had a mean reduction of 0.8 episodes per 24 h, while in the AAD (control) group (n=14) the mean reduction was 1.3 episodes per 24 h.

Additionally, a mean within subject reduction of 3.3 hours in AF duration was seen in the THERMOCOOL group (n=58) between baseline and final effectiveness follow-up visit. A similar result was also seen in the AAD (Control) group (n=13) were an average reduction of 2.7 hours in AF duration was recorded.

Statistically the reduction in the number of AF episodes and in AF duration seen on the final 24 h Holter monitor recording were not different between randomization groups, p-values of 0.6263 and 0.7604 respectively (Wilcoxon Rank-Sum test). This can be attributed to the to the small number of subjects remaining in the AAD (Control) cohort, many of whom had a successful effectiveness outcome (n=9).

FIGURE 3.6.4.3A Within Subject Comparison of the Number of AF Episodes and AF Duration (Hours) by 24-Hour Holter Monitor (Effectiveness Analysis Cohort, n=159)



3.6.4.4 Quality of Life and Symptoms Check List Analysis

The Quality of life was measured using the generic health survey short-form questionnaire, SF-36 Version 2, and the arrhythmia-specific Symptom Frequency and Severity Checklist. In this analysis, no distinction was made within groups between subjects with recurrence of AF and those subjects that did not have recurrence. AAD (Control) group subjects who underwent an ablation procedure with the study catheter (36/56) were censored at the time of the ablation procedure and are not included in analysis of SF-36 Version 2 or the Symptoms Checklist scores for any subsequent time points.

Figures 3.6.4.4A and 3.6.4.4B present the absolute change from baseline in the mental (MCS) and physical (PCS) component summary scores for each visit period in the effectiveness evaluation period. Research in patients with chronic diseases indicates that a 3- to 5- point improvement in SF-36 Version 2 subscales is considered to be clinically important.[66] Changes in mean within-subject aggregate scores for both the mental and physical component in the AAD (Control) group were not significant, ranging from a high of 1.3 to a low of -1.0. In the THERMOCOOL group the mean within-subject absolute change in aggregate scores for both the mental and physical component of the SF-36 instrument demonstrated a clinically important increase above baseline at each visit period. The increases in the mental component aggregate scores ranged from 7.7 to 9.8 while those of the physical component ranged from 5.2-6.7.

The observed improvements in both the mental and physical quality of life scores expressed by the THERMOCOOL group subjects at the 3-month visit were maintained throughout the effectiveness evaluation period. Whereas, in the AAD (Control) group subjects the absolute change from baseline in aggregate scores varied between small positive (<2 units) and negative changes from baseline scores for both aggregate components. None of the expressed changes reached the level of clinical importance seen in the THERMOCOOL group.

FIGURE 3.6.4.4A Mean Within-Subject Absolute Change from Baseline in the SF-36 Aggregate Mental Component Score (Effectiveness Cohort, n=159)

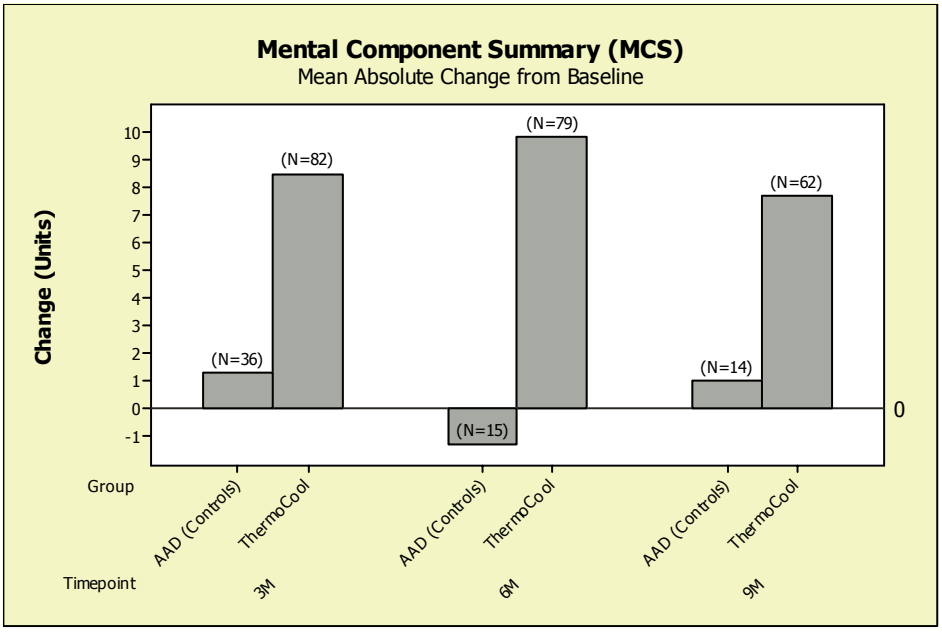


FIGURE 3.6.4.4B Mean Within-Subject Absolute Change from Baseline in the SF-36 Aggregate Physical Component Score (Effectiveness Cohort, n=159)

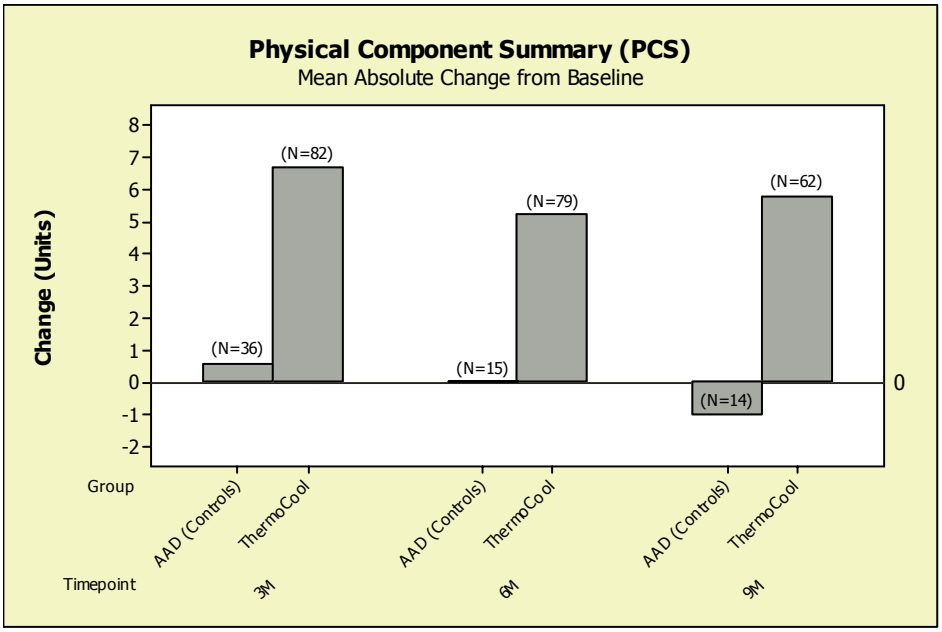


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Table 3.6.4.4A details and compares the mean within-subject percent change from baseline over time in the SF-36 Version 2 aggregate mental and physical component summary scores (MCS and PCS). Baseline aggregate scores for both the mental and physical component were comparable between the THERMOCOOL and AAD (Control) groups and exhibited a below normal quality of life score. This can be seen in the baseline aggregate score for the mental and physical component of the SF-36, which was below the 50-unit quality of life population norm standard.[67]

Similar to the mean absolute change, the mean within-subject percent change improved beginning at the 3-month visit in both SF-36 Version 2 aggregate components for each randomization group. The improvement persisted throughout the 9-month effectiveness evaluation period. Overall, the percent improvements were modest in the AAD (Control) group, ranging from 6.0% at the 3-month visit to 7.1% at the 9-month visit. Conversely, subjects who underwent a study ablation procedure demonstrated a significant and positive percent increase in their quality of life scores at each evaluation period when compared to AAD (Control) subjects. The percent change ranged from a 28.8% increase at the 3-month visit to a 26.1% increase at the 9-month visit for the THERMOCOOL group.

TABLE 3.6.4.4A SF-36 Baseline Score and Mean Within-Subject Percentage Change from Baseline in the Aggregate Mental and Physical Component Summary (Effectiveness Cohort, n=159)

Treatment Group	Baseline Aggregate Score (n)	% Change From Baseline (n)		
		3-Month	6-Month	9-Month
SF-36 Aggregate *Mental* Component Summary (MCS)				
THERMOCOOL	44.5 ± 11.1 (96)	28.8 ± 47.2 (82)	32.2 ± 49.7 (79)	26.1 ± 48.7 (62)
AAD (Control)	44.0 ± 12.1 (51)	6.0 ± 26.0 (36)	3.2 ± 40.0 (15)	7.1 ± 34.7 (14)
p-value*	0.9984	0.0033	0.0045	0.0496
SF-36 Aggregate *Physical* Component Summary (PCS)				
THERMOCOOL	46.2 ± 8.5 (96)	17.7 ± 23.3 (82)	14.1 ± 24.7 (79)	14.1 ± 18.5 (62)
AAD (Control)	47.9 ± 8.6 (51)	1.5 ± 17.4 (36)	3.0 ± 26.4 (15)	0.3 ± 21.1 (14)
p-value*	0.1659	<0.0001	0.0271	0.0039

* Based on Wilcoxon Rank Sum Test.

Figures 3.6.4.4C and 3.6.4.4D present the absolute change from baseline in the arrhythmia symptoms checklist for frequency and severity scores. As mentioned above, no distinction was made within groups between subjects with recurrence of AF and those that did not have recurrence. AAD (Control) group subjects undergoing a study ablation procedure were censored from this analysis.

Subjects in the THERMOCOOL group demonstrated improvement in both symptoms frequency and severity. The improvement is depicted by the negative change in absolute scores, which correspond with a decrease in both symptom frequency and severity. Similar to the SF-36 aggregate scores, improvement occurred at the 3-month visit and persisted throughout the effectiveness evaluation period.

With the exception of the 12-month symptom severity score, AAD (Control) group subjects showed no improvement in either symptom frequency or severity. The improvement observed at the 12-month assessment in symptom frequency and severity in the AAD (Control) group may be due in part to the small number of subjects remaining in the analysis cohort at that time-point. The majority of AAD (Control) group subjects (64.3 %, 36/56) underwent a study ablation procedure after the chronic effectiveness endpoint was met.

Additionally, 9 of the 20 remaining subjects had a successful chronic effectiveness outcome, which can be seen in the improved symptom frequency and severity at the 9-month visit. Thus, the AAD (Control) group subjects analyzed at the 9-month visit were likely not representative of the true response to AAD therapy, since most patients who did poorly on AAD therapy had crossed over to ablation by then.

FIGURE 3.6.4.4C Symptoms Checklist – Absolute Change in the Symptom Frequency Score (Effectiveness Cohort, n=159)

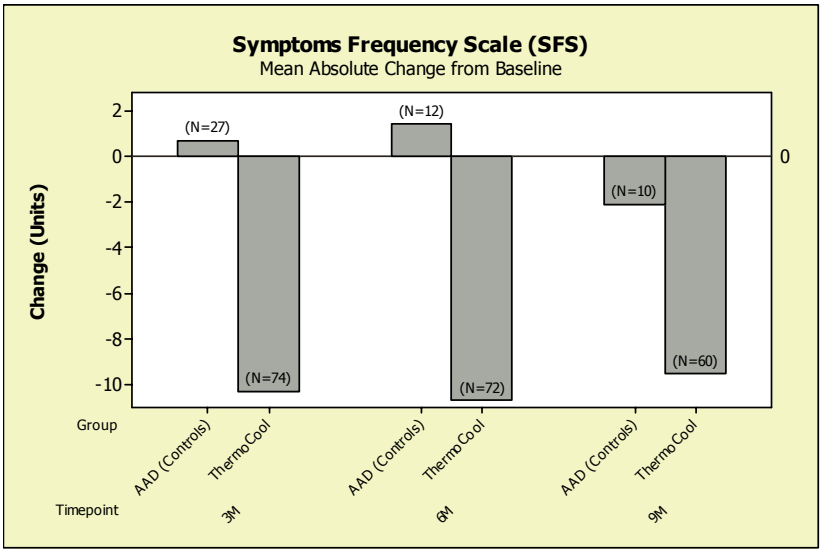

FIGURE 3.6.4.4D Symptoms Checklist – Absolute Change in the Symptom Severity Score (Effectiveness Cohort, n=159)

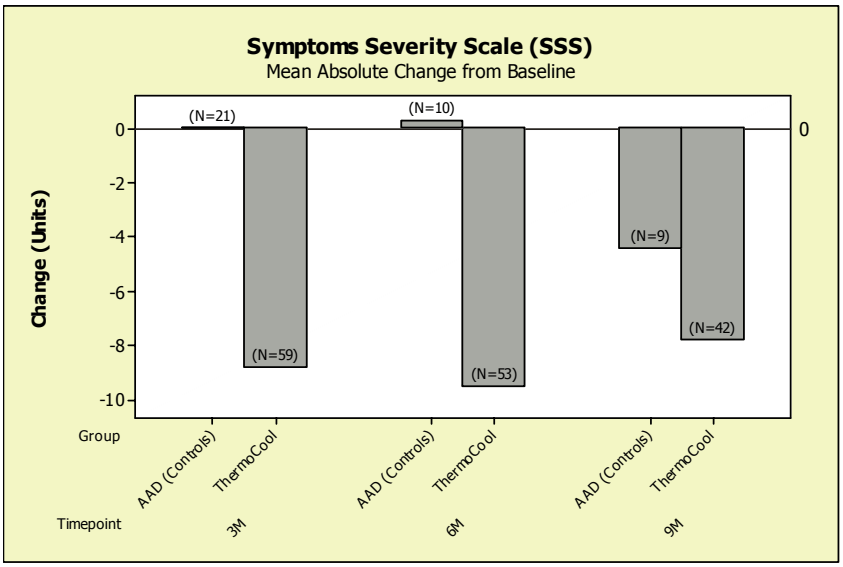

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Table 3.6.4.4B presents and compares the percent change over time in the arrhythmia symptoms checklist for frequency and severity scores.

Similar to the absolute change, the percent change in symptom frequency and severity in the THERMOCOOL group began at the 3-month visit and was maintained throughout the effectiveness evaluation period.

AAD (Control) group subjects showed no improvement in either symptom frequency or severity until the 9-month visit. Percent change results differed from the absolute change in that only the symptom severity was improved in the AAD (Control) group subjects. The percent improvement seen at the 9-month assessment in symptom severity in the AAD (Control) group may be due in part to the small number of subjects remaining in the analysis cohort, many of whom had a successful effectiveness outcome (45%; 9/20).

TABLE 3.6.4.4B Symptoms Checklist – Symptom Frequency and Severity Score (Effectiveness Cohort, n=159)

Treatment Group	Baseline Score (n)	% Change From Baseline (n)		
		3-Month	6-Month	9-Month
Symptoms *Frequency*				
THERMOCOOL	20.5 ± 9.1 (94)	-54.1 ± 35.8 (74)	-52.4 ± 34.1 (72)	-50.2 ± 32.8 (60)
AAD (Control)	18.4 ± 8.6 (50)	6.2 ± 65.2 (27)	33.7 ± 103.6 (12)	11.2 ± 102.8 (10)
p-value*	0.2209	<0.0001	0.0003	0.0224
Symptoms *Severity*				
THERMOCOOL	17.1 ± 7.0 (76)	-54.5 ± 33.5 (59)	-55.3 ± 35.2 (53)	-52.3 ± 30.3 (42)
AAD (Control)	15.9 ± 7.8 (43)	9.9 ± 78.5 (20)	44.0 ± 155.0 (10)	-22.9 ± 61.9 (9)
p-value*	0.4108	<0.0001	0.0043	0.1740

* Comparison of THERMOCOOL vs. AAD (Control) using Wilcoxon Rank-Sum test.

Overall, no improvement was demonstrated in symptom frequency and/or severity in the AAD (Control) group at the 3-month and 6-month visits. However, at the 9-month visit there was an improvement in symptom severity for this group. Conversely, subjects that underwent a study ablation procedure demonstrated on average a significant improvement in symptom frequency and severity.

3.6.4.5 This section intentionally left blank

3.6.4.6 AAD (Control) Subjects Undergoing Ablation

Subjects who were randomized to the AAD (Control) group were eligible for an ablation procedure with the study catheter if they failed the effectiveness and safety endpoints in the first 90 days post-dosing. The chronic effectiveness endpoint, in both groups, was met if the subject had a documented symptomatic episode of AF in the 9-month effectiveness evaluation period. Safety failure was the documentation of a category 1 or 2 AE (see section 3.6.5.2.1).

After Day 90, the protocol allowed subjects to undergo a procedure with the study catheter if the primary effectiveness endpoint was documented. Subjects who failed the chronic effectiveness endpoint, but did not fail the safety endpoint in the first 90 days post-initial dosing, were required to wait 90 days from the day of their initial dosing before being eligible for an ablation procedure with the study catheter.

AAD (Control) subjects who underwent an ablation procedure with the study catheter were held to the same follow-up visit and testing requirements as subjects randomized to the THERMOCOOL group for the purposes of long-term safety (required in all versions of the protocol). This group also was required to follow the same asymptomatic and symptomatic TTM transmission requirements as the THERMOCOOL group. Because of these requirements, the procedural data, acute success, and chronic outcomes are presented in the section.

Version 12.2 of the protocol proposed inclusion of these subjects in the primary safety cohort.

3.6.4.6.1 This section intentionally left blank

3.6.4.6.2 This section intentionally left blank

3.6.4.6.3 Acute Success

AAD (Control) subjects that underwent an ablation procedure had an acute effectiveness success rate of 94.4% as seen in Table 3.6.4.6.3A

TABLE 3.6.4.6.3A Acute Effectiveness Success (n=36)

	AAD Subjects Undergoing Ablation n/36 (%)*
Acute Effectiveness Success	**34 (94.4)**
Entrance Block Confirmed	34
Ablation Procedure >80 days	0
Non-study Catheter Utilized for AF Targets	0
>2 Repeat Ablation Procedures	0

* Percentages derived from the following N-values: AAD Subjects Undergoing Ablation (N=36)

Acute Failures

Two acute failures were identified in the AAD (Control) subjects that underwent an ablation procedure. Table 3.6.4.6.3C explains the reasons for acute failure for these two AAD (Control) subjects.

TABLE 3.6.4.6.3C Reasons for Acute Failure in the AAD (Control) Group Undergoing an Ablation Procedure (n = 2)

Subject	Reason for Chronic Effectiveness and/or Safety Failure	Reason for Acute Failure
----	Subject experienced a documented symptomatic AF episode after initiation of AAD protocol therapy. The subject reported daily episodes of intolerable symptomatic AF despite more than one increase in the prescribed propafenone dose (450 to 850 mg, 24 h dose).	The subject underwent an ablation procedure on November 7, 2007. While exit block was confirmed for all targeted PVs, entrance block was not confirmed for the targeted PVs.
----	The subject had a documented episode of symptomatic AF during an emergency room visit 59 days after starting their study AAD, resulting in both a failure of the safety and effectiveness endpoints.	The ablation procedure was prematurely stopped due to the appearance, on the intracardiac echocardiogram (ICE), of a possible thrombus or the tearing of atrial septum. Entrance block was not confirmed.

3.6.4.6.4 Chronic Effectiveness Outcomes

Table 3.6.4.6.4A presents the chronic effectiveness outcomes for the AAD (Control) subjects that underwent an ablation procedure with the THERMOCOOL catheter. At the time of the June 2008 dataset, 3 of the 36 AAD (Control) subjects who underwent an ablation procedure with the study catheter were in their effectiveness evaluation. Of the 33 remaining AAD (Control) subjects in this group, 21 subjects had successful chronic effectiveness outcomes. This represents a 63.6% chronic effectiveness success rate, comparable to the 59.6% chronic effectiveness success rate that was observed for subjects in the THERMOCOOL group (see section 3.6.2.2).

The study protocol mandated that AAD (Control) subjects who were undergoing an ablation procedure be followed for 12-months post-procedure for evaluation of safety. These subjects followed the same effectiveness assessments as the THERMOCOOL group in their post-procedure follow-up period; this included the TTM transmission requirements. The overall mean compliance for TTM transmissions for these subjects was 86.1 ± 15.9%.

TABLE 3.6.4.6.4A Chronic Outcomes in AAD (Control) Subjects undergoing Ablation (n=36*)

	AAD (Control) Subjects Undergoing Ablation n/33 (%)
Chronic Effectiveness Success	21 (63.6)

* Three (3) subjects have not reached the effectiveness endpoint.

3.6.5 Safety Data

In this section the safety data will be presented in two analyses, the Primary Safety Analysis (Section 3.6.5.1) and Secondary Safety Analysis (Section 3.6.5.2) with corresponding cohorts. Table 3.6.5A presents the accountability of the overall safety cohort for these analyses.

The primary safety endpoint (section 3.6.5.1) for this study was defined as the incidence of specific early-onset (within 7 days of ablation procedure) adverse events (primary AEs) 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).

Secondary safety analyses (section 3.6.5.2) compared the THERMOCOOL and AAD (Control) randomization groups rates of the early-onset (≤90 days) and late-onset (>90 days) category 1 and category 2 SAEs. These analyses were done based on the Overall Safety Cohort (n=160), which included all subjects not excluded prior to therapy. This cohort was comprised of the following:

- Subjects randomized to the THERMOCOOL group and undergoing insertion of study catheter (n=103)
- Subjects randomized to AAD (Control) group who received at least one dosing treatment (n=57).

TABLE 3.6.5A Accountability for Safety Analysis (Enrolled Subjects, N=167)

Subject Disposition	Treatment Group		Total
	THERMOCOOL	AAD (Control)	
Total Number of Subjects Enrolled	106	61	**167**
Subjects Excluded	3	4	7
Overall Safety Cohort	103	57	**160**
Subjects Discontinued	0	1	1
Subjects not Undergoing Ablation	0	20	20
Primary Safety Cohort (Subjects undergoing ablation)	103	36	**139**

All AEs reported in this study have been evaluated by an independent Clinical Events Committee/Data Safety Monitoring Board (CEC/DSMB). The CEC/DSMB was comprised of 3 expert physicians and a statistician who did not otherwise participate in the trial (refer to section 2.2.8 for details). All AEs were monitored until they were resolved or explained. Each AE was reported regardless of classification, seriousness, intensity, outcome, or causality.

3.6.5.1 Primary Safety Analysis

The primary safety endpoint was defined as the incidence of serious primary AEs that occurred within 7 days of a study ablation procedure. There were 18 categories of primary AEs prospectively established in the study protocol and presented in Table R 3.6.5.1B. The details are described in the Methods section (see section 2.2.8 for details).

Table R 3.6.5.1A below 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%). Though the primary AE incidence did not meet the protocol-established primary safety endpoint for this study, the nature and types of adverse events nonetheless represent an acceptable safety profile.

- No deaths, stroke, cardiovascular accident, atrial perforation, esophageal fistula, myocardial infarction, and thromboembolism occurred within 7 days of the ablation procedure.

TABLE R 3.6.5.1A 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 R 3.6.5.1B summarizes the early-onset serious primary AEs for the Primary Safety Cohort. There were 16 reported serious primary AEs in 15 subjects. One subject expired ( ) 284 days post study ablation procedure and was not considered by definition a primary AE (refer to section 3.6.5.1.3 for details). Seven (7/139, 5.0%) subjects experienced primary AEs that resulted in hospitalizations that were either extended post-procedure or occurred after discharge and within 7 days of the ablation procedure. Of the remaining 8 subjects, one (1) subject developed late-onset cardiac tamponade with pleural effusion, one (1) subject developed pericardial effusion, one (1) subject had pulmonary edema, and five (5) subjects developed vascular access complications that required intervention or extended their hospital stay. For details, see primary AE summaries in Appendix 15.

TABLE R 3.6.5.1B 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 (%)	Subject ID
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 %)	---- ---- ---- ---- ----

* Note: Subject was hospitalized on two occasions.
** Subject ---- was also reported to have cardiac tamponade with pleural effusion 17 days after the study ablation procedure.

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Primary Adverse Events by Causality

Table R 3.6.5.1C summarizes all primary AEs by causality (i.e. device-related, possibly device-related, procedure-related, possibly procedure-related, and unrelated to the device or procedure).

- No primary AE was classified as device-related by the investigator.
- One subject (0.7%; 1/139) experienced a primary AE that was classified as potentially attributable to the device.
- Nine subjects (6.5% (9/139) experienced primary AEs that were classified as procedure related.
- Five subjects (3.6%, 5/139) experienced primary AEs that were classified as unrelated to the device and unrelated to the procedure.

TABLE R 3.6.5.1C Primary Adverse Events by Causality (Primary Safety Cohort, n=139)

Description	Number of Subjects Experiencing Primary AEs*	% Subjects Experiencing Primary AEs	Total No. of Primary AEs
All Serious Primary AEs	**15**	**10.8**	**16**
Device-related	0	0.0	0
Possibly Device-related	1	0.7	1
Procedure-related	9	6.5	10
Possibly Procedure-related	0	0.0	0
Unrelated to Device or Procedure	5	3.6	5

* Some subjects experienced more than one AE and multiple causalities. Causality for subject [redacted] was listed as both possibly device-related and possibly procedure-related.

Table R 3.6.5.1G summarizes primary AEs that resulted in an impairment of a body function or damage to a body structure by severity, causality, and outcome. The majority of the primary AEs did not result in impairment to a body function (n=12). There was a total of three (3) primary AEs that were assessed as having mild (n=2) or moderate (n=1) impairment or damage to a body structure. Of these three (3) primary AEs, the outcomes were reported as improved (n=1), resolved (n=1), and unchanged (n=1). The outcome of the one (1) primary AE that was reported as severe was reported as resolved prior to the subject's hospital discharge.

Severity, Causality, and Outcomes of Primary Adverse Events

Complete resolution was reported in 93.8% (15/16) of the primary AEs. The outcome of the one (1) remaining primary AEs was reported as improved (1/16; 6.3%).

TABLE R 3.6.5.1G Primary Adverse Events by Impairment of a Body Function or Damage to a Body Structure by Severity, Causality, and Outcome (Primary Safety Cohort, n=139)

Impairment	Causality	Outcome	Description	Subject ID
Severe (n=1)	Possibly Device and Procedure Related	Resolved	Pulmonary Edema	----
Moderate (n=1)	Procedure Related	Resolved	AV Fistula	----
Mild (n=2)	Procedure Related	Resolved	Edema	----
	Procedure Related	Resolved	Hematoma	----
None (n=12)	Unrelated to Device or Procedure	Resolved	AF Recurrence	----
	Procedure Related	Resolved	Decreased Hemoglobin	----
	Procedure Related	Resolved	AV Fistula	----
	Procedure Related	Resolved	Pseudoaneurysm	----
	Procedure Related	Resolved	Hematuria	----
	Unrelated to Device or Procedure	Resolved	AF Recurrence	----
	Procedure Related	Improved	Pericarditis	----
	Unrelated to Device or Procedure	Resolved	AF Recurrence	----
	Procedure Related	Resolved	Access Site Bleeding	----
	Unrelated to Device or Procedure	Resolved	Pneumonia	----
	Unrelated to Device or Procedure	Resolved	Atrial Flutter	----
	Procedure Related	Resolved	Pericardial Effusion	----

* Subject ---- experienced two (2) primary AEs.

3.6.5.1.1 SAEs: Non-Primary ≤ 7 Days Post Ablation

Table R 3.6.5.1.1A summarizes the SAEs that were not classified as primary AEs by protocol definition. See section 2.2.8 for a detailed listing of the primary AEs.

There were seven (7) SAEs reported in five (5) subjects that were considered not related to the study catheter by protocol definition. None of the reported SAEs were deemed to be device related or possibly device-related. Of the seven (7) SAEs:

- Two (2) events were considered procedure-related;
- One (1) was considered possibly related to the procedure;
- The remaining four (4) non-primary SAEs were considered not related to the device or procedure.

Case histories of all SAEs that were deemed not related to the study catheter are provided in Appendix 16.

TABLE R 3.6.5.1.1A SAEs Occurring Within (≤) 7 Days of the Ablation Procedure by Relatedness, Body System, Category, and Subject ID (Primary Safety Cohort, n=139)

Description	Total Number of Serious Non-primary AEs	Subject ID
Non-Primary SAEs	**7**	
Device-Related	0	
Possibly Device-Related	0	
Procedure-Related	2	
Cardiac Disorder		
LA Thrombus or Tearing of Atrial Septum	1	----
Infection and Infestations		
Urinary Tract Infection	1	----
Possibly Procedure-Related	1	
Respiratory/Renal & Urinary Disorder		
Hemoptysis/Right Kidney Stone	1	----
Not Related	4	
Renal Disorder/Neoplasm		
Neoplasm/Kidney Nodule	2	---- (x2)*
Cardiac Disorder		
Emergency Room Visit – AF/Atrial Flutter	1	----
Renal and Urinary Disorder		
Hematuria	1	----

* Subject ---- experienced 3 SAEs that were not catheter related.

3.6.5.1.2 Non-Serious AEs within 7 Days Post Ablation

Non-SAEs were evaluated in all 139 subjects included in the Primary Safety Cohort. Non-SAEs were defined as, "All AEs not meeting the definition of a SAE, including events resulting in a transient impairment of a body function that resolves with minimal intervention."

Table 3.6.5.1.2B summarizes all non-SAEs that were reported within 7 days post-procedure. A total of 30 subjects (30/139; 21.6%) developed non-serious AEs. Only 3 AEs in 2 subjects were classified as device-related (2/139; 1.4%) and 4 AEs in 3 subjects were classified as possibly device-related (3/139; 2.2%).

TABLE 3.6.5.1.2B Non-SAEs Occurring Within 7 Days of the Ablation Procedure by Causality and Subject ID (Primary Safety Cohort, n=139)

Description	Total Subjects with non-SAEs	Total Number of non-SAEs	Subject ID
Non-SAEs	**30* (21.6%)**	**53**	
Device-Related	**2 (1.4%)**	**3**	
Pain During RF Application	1	1	----
Hematoma/Incessant AF	1	2	
Possibly Device-Related	**3 (2.2%)**	**4**	
Chest Pain	1	1	----
Groin Pain/Bruising	1	1	----
Decreased Hematocrit and BP	1	2	
Procedure-Related	**14 (10.1%)**	**20**	
Hematoma/ Bleeding/Groin Pain	3	5	
Chest Pain	1	1	
Pericardial Effusion (trace)	2	2	
Pericardial Effusion (mild)/Chest Pain	1	1	
Bronchospasm	1	1	----
Arm Pain	1	1	----
Back Pain	1	1	----
Nausea, Vomiting/Rigors	2	6	
UTI	1	1	----
Hematuria	1	1	----
Possibly Procedure-Related	**11 (7.9%)**	**11**	
Hypotension/Pericardial Effusion	1	1	----
Hematuria	1	1	----
Neurologic Side Effects	1	1	----
Hematoma	2	2	---- ----
Dyspnea	1	1	----
Back Pain	2	2	---- ----
Breathing Difficulties	1	1	----
Epistaxis	1	1	----
SOB/Pleuritic Pain/Fever	1	1	----
Not Related	**14 (10.1%)**	**15**	
Congestive Heart Failure	1	1	----
GI Upset	1	1	----
Kidney Stone	1	1	----
Shoulder Pain	1	1	----
Hematuria	1	1	----
Epigastrium Pain	1	1	----
Cardioversion/Atrial Flutter	1	1	----
Anxiety	1	1	----
Shortness of Breath	3	3	
Backache/Shoulder Pain	1	2	
Neurologic Side Effects	2	2	

* Note: Subjects may have more than one AE and be represented in more than one causality classification.

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3.6.5.1.3 Subject Death

One subject (---- in the THERMOCOOL group expired on March 3, 2008 during the effectiveness evaluation period. This event occurred several months (284 days) after the ablation procedure.

Case History
Subject ----
Category 1 – Death

related to device treatment and not related to the ablation procedure.

3.6.5.1.4 Additional Safety Analyses

Procedural Parameters Safety Analyses

Additional safety analyses include presentation of procedural parameters as predictors of primary AEs.

Procedural parameters were analyzed to determine if there were differences in subjects who experienced primary AEs and those that did not. As shown in Table R 3.6.5.1.4A, subjects who experienced primary AEs had a significantly longer procedure times, longer periods of time during which RF was applied, greater numbers of RF applications during the procedure, and the maximum durations of RF applications were shorter. The maximum duration of an RF application was not stipulated in the study protocol. The length of duration is attributed to physicians' preferred techniques of delivering continuous lesions or discrete lesions and the data were not normally distributed.

During RF application, maximum temperature and the saline volume delivered via the investigational catheter were similar between subjects that developed primary AEs and those subjects that did not. The average maximum power was less in subjects with primary AEs than in those without primary AEs. Subjects with atrial lines targeted during the ablation procedure were not more likely to experience a primary AE than those without such lines.

TABLE R 3.6.5.1.4A Primary Adverse Events by Procedural Parameters – Initial Procedure (Primary Safety Cohort, n=139)

Procedural Parameters	With primary AEs	Without primary AEs	p-value
Maximum Power (W)	35.4 ± 5.4 (15)	38.6 ± 6.0 (123)	0.0245*
Maximum Temperature (C)	42.0 ± 4.0 (15)	42.3 ± 4.5 (123)	0.7682*
Maximum Ablation Duration (sec)	176.7 ± 222.9 (15)	238.3 ± 184.2 (123)	0.0163*
Number of RF Applications	76.8 ± 43.0 (15)	51.8 ± 34.2 (124)	0.0041*
Saline Volume Delivered via the Catheter (mL)	1979.0 ± 1194.2 (15)	1582.1 ± 702.2 (124)	0.3877*
Total RF Time (min)	167.1 ± 95.1 (15)	103.4 ± 56.2 (124)	0.0017*
Procedure Time (min)	280.7± 112.3(15)	201.5 ± 84.7 (124)	0.0032*
Atrial Lines Targeted	5 / 15 (33.3%)	55 / 124 (44.4%)	0.5826**

* P-value calculated by Wilcoxon Rank Sum Test.
** P-value calculated by Fisher's Exact Test.

Primary Safety Comparison by AAD Class Failed at Baseline

Nineteen (19) subjects in the THERMOCOOL group were enrolled into the study failing only a Class II or IV AAD for the treatment of AF.

Table R 3.6.5.1.4B presents a comparison of the primary adverse events in the THERMOCOOL subjects by the class of the previously failed AAD. The number of THERMOCOOL subjects enrolled failing only a Class II or IV AAD at enrollment was 18.4% (19/103) and the rates of AEs were not significantly different between groups.

TABLE R 3.6.5.1.4B Primary Safety Comparison by AAD Failed at Baseline (THERMOCOOL Group, n=103)

AE Category	THERMOCOOL (N=103)		p-Value*
	Class I & III n/84 (%)	Class II & IV n/19 (%)	
Primary AEs	8 (9.5)	2 (10.5)	1.0000
Non-primary AEs	76 (90.5)	17 (89.5)	

* Fisher's Exact test.

3.6.5.1.5 Pulmonary Vein Stenosis Post-Ablation

Table R 3.6.5.1.5A summarizes the incidence of PV stenosis in subjects who underwent a study ablation procedure. Pulmonary vein stenosis was defined in the study protocol as ≥ 70% reduction in the diameter of the PV from baseline. To date, no PV stenosis as defined in the protocol has been reported. This includes all subjects undergoing an ablation procedure (with follow-up CT/MRA data available at the time of the June 2008 dataset). This includes subjects with 3-month scan data (AAD (Control) group, n=16 and THERMOCOOL subjects, n=68) and subjects with 12-month scan data (AAD (Control) group, n=4 and THERMOCOOL subjects, n=25).

TABLE R 3.6.5.1.5A Incidence of Pulmonary Vein Stenosis ≥ 70% (Primary Safety Cohort, n=139)

	Treatment Groups		Total n / N
	THERMOCOOL n / N	AAD (Control) Undergoing Ablation n / N	
PV Stenosis ≥ 70% at 3 Months	0 / 68	0 / 16	0 / 84
PV Stenosis ≥ 70% at 12 Months	0 / 25	0 / 4	0 / 29

CT/MRA Results

Table 3.6.5.1.5B, 3.6.5.1.5C and 3.6.5.1.5D summarize the degree of PV stenosis by severity in the targeted veins. The severity scale is based on the recommended guideline proposed by the HRS/EHRA/ECAS expert consensus statement on catheter and surgical ablation of AF.[13]

Pulmonary Vein Status - 3-Month CT/MRA Results

At 3 months post-ablation, no subject undergoing an ablation procedure with the study catheter had developed severe PV stenosis. The majority of THERMOCOOL group subjects (48/68, 70.6%) developed mild PV narrowing (<50%) in all targeted PVs, while in the AAD (Control) undergoing an ablation procedure the majority developed mild PV narrowing in 3 PVs (12/16, 75.0%). In this group only 31.3% (5/16) developed mild PV narrowing in the RIPV. No individual PV was found to have narrowing > 50%. Table 3.6.5.1.5B summarizes the 3-month CT/MRI results by targeted PV.

TABLE 3.6.5.1.5B Pulmonary Vein 3-Month CT/MRA Data [THERMOCOOL group, n=68 and AAD (Control) Subjects Undergoing Ablation, n=16]

Pulmonary Vein	Treatment Groups	
	THERMOCOOL n / 68 (%)	AAD (Control) Undergoing Ablation n / 16 (%)
LSPV		
None	20 (29.4%)	4 (25.0%)
Mild (<50%)	48 (70.6%)	12 (75.0%)
Moderate (50%-<70%)	0 (0.0%)	0 (0.0%)
Severe (≥70%)	0 (0.0%)	0 (0.0%)
LIPV		
None	21 (30.9%)	5 (31.3%)
Mild (<50%)	47 (69.1%)	11 (68.8%)
Moderate (50%-<70%)	0 (0.0%)	0 (0.0%)
Severe (≥70%)	0 (0.0%)	0 (0.0%)
RSPV		

Pulmonary Vein	Treatment Groups	
	THERMOCOOL n / 68 (%)	AAD (Control) Undergoing Ablation n / 16 (%)
None	24 (35.3%)	5 (31.3%)
Mild (<50%)	44 (64.7%)	11 (68.8%)
Moderate (50%-<70%)	0 (0.0%)	0 (0.0%)
Severe (≥70%)	0 (0.0%)	0 (0.0%)
RIPV		
None	23 (33.8%)	11 (68.8%)
Mild (<50%)	45 (66.2%)	5 (31.3%)
Moderate (50%-<70%)	0 (0.0%)	0 (0.0%)
Severe (≥70%)	0 (0.0%)	0 (0.0%)

Pulmonary Vein Status - 12-Month CT/MRA Results

Table 3.6.5.1.5D summarizes the 12-month CT/MRA results by targeted PV. At 12 months post ablation, no subject undergoing an ablation procedure with the study catheter had developed severe PV stenosis. One (1) subject developed moderate narrowing (50%-<70%) in the RSPV. As seen with the 3 month CT/MRA data, the majority of subjects continued to exhibit mild PV narrowing in the LS, LI and RI PVs.

TABLE 3.6.5.1.5D Pulmonary Vein 12-Month CT/MRA Data (THERMOCOOL group, n=25 and AAD (Control) Subjects Undergoing Ablation, n=4)

Pulmonary Veins	Treatment Groups	
	THERMOCOOL n / 25 (%)	AAD (Control) Undergoing Ablation n / 4 (%)
LSPV		
None	10 (40.0%)	0 (0.0%)
Mild (<50%)	15 (60.0%)	4 (100.0%)
Moderate (50%-<70%)	0 (0.0%)	0 (0.0%)
Severe (≥70%)	0 (0.0%)	0 (0.0%)
LIPV		
None	5 (20.0%)	3 (75.0%)
Mild (<50%)	20 (80.0%)	1 (25.0%)
Moderate (50%-<70%)	0 (0.0%)	0 (0.0%)
Severe (≥70%)	0 (0.0%)	0 (0.0%)
RSPV		
None	13 (52.0%)	2 (50.0%)
Mild (<50%)	11 (44.0%)	2 (50.0%)
Moderate (50%-<70%)	1 (4.0%)	0 (0.0%)

Pulmonary Veins	Treatment Groups	
	THERMOCOOL n / 25 (%)	AAD (Control) Undergoing Ablation n / 4 (%)
Severe (≥70%)	0 (0.0%)	0 (0.0%)
RIPV		
None	10 (40.0%)	3 (75.0%)
Mild (<50%)	15 (60.0%)	1 (25.0%)
Moderate (50%-<70%)	0 (0.0%)	0 (0.0%)
Severe (≥70%)	0 (0.0%)	0 (0.0%)

3.6.5.2 Secondary Safety Analysis (Early- and Late-Onset SAEs)

Overall Safety Cohort

A secondary safety analysis was performed to characterize and compare the early-onset (≤ 90 days) and late-onset (>90 days) AEs by severity (category 1 and category 2 SAEs) in the Overall Safety Cohort (n=160). This cohort was comprised of:

- Subjects randomized to the THERMOCOOL group and undergoing insertion of study catheter (n=103)
- Subjects randomized to AAD (Control) group who received at least one dosing treatment (n=57).

Table 3.6.5.2A summarizes the subject accountability for the Overall Safety Cohort.

TABLE 3.6.5.2A Overall Safety Cohort (n=160)

Subject Disposition	Treatment Groups		Total
	THERMOCOOL	AAD (Control)	
Overall Safety Cohort	**103**	**57**	**160**

In the following secondary safety analysis, subjects in the AAD (Control) group undergoing a study ablation procedure (n=36) were censored from the analysis at the time of their initial study ablation procedure (see section 3.6.4.6 for additional details). The results of early- and late-onset category 1 and 2 SAEs following the first ablation procedure in these subjects are presented after the analysis of the ablation and AAD (Control) groups in each section below. These data are presented to demonstrate that AAD (Control) group subjects undergoing an ablation procedure have a similar safety profile to the subjects randomized to the THERMOCOOL group.

3.6.5.2.1 Early-Onset Category 1 and 2 SAEs by Treatment Arm

SAEs were classified as category 1 if the event resulted in permanent injury or impairment to the subject. Adverse events were classified as a category 2 if the event resulted in a temporary or reversible injury to the subject. Refer to section 2.2.8 for a more detailed description.

Table 3.6.5.2.1A summarizes the secondary safety outcome defined as the presence of early-onset SAEs. There were no category 1 SAEs that occurred ≤ 90 days of initial therapy. There was a higher proportion of subjects experiencing category 2 early-onset SAEs in the AAD (Control) group (20/57, 35.1%) compared to the THERMOCOOL group (19/103, 18.4%).

TABLE 3.6.5.2.1A Secondary Safety Endpoint – Early-Onset of Serious Adverse Events by Subject (Overall Safety Cohort, n=160)

Group	Early-Onset of Serious Adverse Events		
	Category 1	Category 2	Other
THERMOCOOL (n=103)	0 (0.0%)	19 (18.4%)	2 (1.9%)
AAD (Control) (n=57)	0 (0.0%)	20 (35.1%)	1 (1.8%)
AAD (Control) Subjects Undergoing Ablation (n=36)	0 (0.0%)	7 (19.4%)	4 (11.1%)

The "Other" SAE category represents SAEs occurring during the specified time period that do not meet the protocol specified criteria for either a category 1 or category 2 SAE but were considered to be a SAE by the investigator at the time the AE occurred.

Table 3.6.5.2.1B presents a comparison of the number of early onset category 1 and category 2 SAEs between the randomization groups. Early onset SAEs were defined as a combination of early onset category 1 and category 2 SAEs. The number of early-onset SAEs was statistically different between the THERMOCOOL and AAD (Control) group with a favorable result observed in the THERMOCOOL group.

TABLE 3.6.5.2.1B Percentage of Early Onset SAEs by Randomization Group (Overall Safety Cohort, n=160)

Randomization Group	% of SAEs (n/N)	p-value**
THERMOCOOL Group	18.4 (19/103)	0.0221
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.
** Fisher's Exact test

Table 3.6.5.2.1C summarizes the number of early-onset SAEs by category and relatedness that have been reported to date for the THERMOCOOL group.

- No early-onset category 1 events were reported.
- Nineteen (19/103; 18.4%) subjects experienced a total of 24 category 2 SAEs.
- None of the SAEs were considered device related.

Of the 24 category 2 SAEs:

- Two (2) were classified as possibly device-related.
- Eight (8) SAEs were considered procedure-related (n=5) or possibly procedure related (n=3).
- The remaining 13 category 2 SAEs were classified as not related to device or procedure.
- One (1) category 2 SAE was unclassified.

TABLE 3.6.5.2.1C Early-Onset Serious Adverse Events by Category, Relatedness and AE Description (THERMOCOOL Group, n=103)

Description	Number of Subjects n / 103 (%)	Number of SAEs
Serious Adverse Events – Category 1	**0**	**0**
No Category 1 SAEs were observed		
Serious Adverse Events – Category 2	**19 (17.5%)***	**24***
Device-Related	**0 (0.0%)**	**0**
Possibly Device-Related	**2 (1.9%)**	**2**
Hospitalization		
Pulmonary Edema		1
AF Recurrence/Cardioversion		1
Procedure-Related	**4 (3.9%)**	**5**
Hospitalization		
Pericardial Effusion		1
Decreased Hb Level		1
Access Site Complication		1
Edema		1
Hematuria		1
Possibly Procedure-Related	**3 (2.9%)**	**3**
Hospitalization		
AF Recurrence		3
Not Related	**11 (10.7%)**	**13**
ER Visit		
AF Recurrence		1
A Flutter Recurrence		1
Hospitalization		
AF Recurrence		4
A Flutter Recurrence		5
Neurological (Dysarthria & Vertigo)		1
Pneumonia		1
Serious Adverse Events – Other	**2 (1.9%)**	**4**
Device Related	**0 (0.0%)**	**0**
Possibly Device-Related	**0 (0.0%)**	**0**
Procedure Related	**1 (1.0%)**	**1**
Urinary Tract Infection		1
Possibly Procedure Related	**1 (1.0%)**	**1**
Hemoptysis		1

Description	Number of Subjects n / 103 (%)	Number of SAEs
Not Related	**1 (1.0%)**	**2**
Tumor between R Kidney and R Hepatic Lobe Nodule on L Kidney		1 1
Serious Adverse Events – Category 2 (Causality not reported)	**1 (1.0%)**	**1**
Hospitalization Steven Johnson Syndrome		 1

* Subject [redacted] experienced a category 2 SAE (Hospitalization) that was unclassified.
** Note: AEs could be classified in more than one relatedness group and a subject could have more than one AE.

Table 3.6.5.2.1D summarizes the number of early-onset SAEs by category and relatedness that have been reported to date for the AAD (Control) group. No category 1 events were reported. A total of 27 early-onset category 2 SAEs have been reported in 14 subjects. Eleven (11) category 2 SAEs were classified as treatment-related and the remaining 7 category 2 SAEs were classified as not related.

TABLE 3.6.5.2.1D Early-Onset Serious Adverse Events by Category, Relatedness and AE Description (AAD (Control) Group, n=57)

Description	Number of Subjects n / 57 (%)	Number of SAEs
Serious Adverse Events – Category 1	**0**	**0**
No Category 1 SAEs were observed		
Serious Adverse Events – Category 2	**14 (24.6%)***	**27***
Treatment-Related	**7 (12.3%)**	**11**
EMD Visit AF Recurrence Exercise Intolerance Disabling Fatigue Disabling Visual Disturbance Life Threatening Arrhythmia Neurologic Side Effects		 1 2 3 1 3 1
Possibly Treatment-Related	**0 (0.0%)**	**0**
Not Related	**7 (12.3%)**	**7**
EMD Visit AF Recurrence Hospitalization AF Recurrence Diabetes Exercise Intolerance Disabling Fatigue Life Threatening Arrhythmia		 1 2 1 1 1 1

Description	Number of Subjects n / 57 (%)	Number of SAEs
Serious Adverse Events – Other	**1 (1.8%)**	**1**
Treatment Related	**1 (1.8%)**	**1**
Intolerable Side Effects		1
Possibly Treatment-Related	**0 (0.0%)**	**0**
Not Related	**0 (0.0%)**	**0**
Serious Adverse Events – Category 2 (Causality not reported)**	**8 (14.0%)**	**9**
EMD Visit		
AF Recurrence (x4)		4
Hospitalization		
AF Recurrence (x2)		2
Pneumonia		1
Exercise Intolerance		1
Life Threatening Arrhythmia		1

* Note: AEs could be classified in more than one relatedness group, and a subject could have more than one AE.
** Eight (8) AAD (Control) group subjects experienced a category 2 SAE that was missing causality;

Table 3.6.5.2.1E summarizes the number of early-onset SAEs by category and relatedness that have been reported to date for the AAD (Control) subjects undergoing an ablation procedure. No category 1 events were reported in this group. A total of 11 early-onset category 2 SAEs have been reported in 7 subjects. Category 2 SAEs were classified procedure related (n=6) or possibly procedure-related (n=1). The remaining 4 category 2 SAEs were classified as not related to device or procedure.

TABLE 3.6.5.2.1E Early-Onset Serious Adverse Events by Category, Relatedness and AE Description (AAD (Control) Subjects Undergoing Ablation, n=36)

Description	Number of Subjects n / 36 (%)	Number of SAEs
Serious Adverse Events – Category 1	**0**	**0**
No Category 1 SAEs were observed		
Serious Adverse Events – Category 2	**7 (19.4%)***	**11***
Device Related	**0 (0.0%)**	**0**
Possibly Device-Related	**0 (0.0%)**	**0**
Procedure-Related	**5 (13.9%)**	**6**
Hospitalization		
Hematoma		1
Pleural effusion		1
Pericarditis		1
Vascular Access Complication		3

Possibly Procedure-Related	**1 (2.8%)**	**1**
Respiratory Insufficiency		1
Not Related	**3 (8.3%)**	**4**
EMD Visit		
AF Recurrence		2
Hospitalization		
AF Recurrence		1
Hypotension		1
Serious Adverse Events – Other	**4 (11.1%)**	**5**
Device Related	**0 (0.0%)**	**0**
Possibly Device-Related	**0 (0.0%)**	**0**
Procedure Related	**1 (1.0%)**	**1**
LA Thrombus or Possible Atrial Septal Tear		1
Possibly Procedure Related	**0 (0.0%)**	**0**
Not Related	**3 (8.3%)**	**4**
AF Recurrence		2
Hematuria		1
Hospitalization		
CHF		1

* Note: AEs could be classified in more than one relatedness group and a subject could have more than one AE.

3.6.5.2.2 Late-Onset Category 1 and 2 SAEs by Treatment Arm

Table 3.6.5.2.2A summarizes the preliminary secondary safety outcome defined as the presence of late-onset SAEs. There was one (1) category 1 late-onset SAEs. One (1) subject death (according to death certificate), was due to acute myocardial infarction, ischemic cardiomyopathy, systemic arterial hypertension, and diabetes mellitus, occurred in the THERMOCOOL group at Day 284 (refer to section 3.6.5.1.3 for details). There was a higher proportion of subjects experiencing category 2 late-onset SAEs in the AAD (Control) group (8/57, 14.0%) compared to the THERMOCOOL group (8/103, 7.8%).

TABLE 3.6.5.2.2A Secondary Safety Endpoint – Late-Onset of Serious Adverse Events (Overall Safety Cohort, n=160)

Group	Late-Onset of Serious Adverse Events		
	Category 1	Category 2	Other
THERMOCOOL (n=103)	1 (1.0%)	8 (7.8%)	4 (3.9%)
AAD (Control) (n=57)	0 (0.0%)	8 (14.0%)	1 (1.8%)
AAD (Control) Subjects Undergoing Ablation (n=36)	0 (0.0%)	1 (2.8%)	3 (8.3%)

Table 3.6.5.2.2B summarizes the number of late-onset SAEs by category and relatedness that have been reported to date for the THERMOCOOL group. One (1/103, 1.0%) category 1 event (death) has been reported that was considered not related to the device or procedure. Eight subjects (8/103; 7.8%) experienced a total of 15 category 2 SAEs. Two (2) category 2 SAEs were classified as device-related (n=1) or possibly device-related

(n=1) and one (2) category 2 SAEs was classified as procedure related (n=1) and possibly procedure-related (n=1). The remaining 12 category 2 SAEs were considered not related to device or procedure.

TABLE 3.6.5.2.2B Late-Onset Serious Adverse Events by Category, Relatedness and AE Description (THERMOCOOL Group, n=103)

Description	Number of Subjects n / 103 (%)	Number of SAEs
Serious Adverse Events – Category 1	**1 (1.0%)**	**1**
Not Related	**1 (1.0%)**	**1**
Death		1
Serious Adverse Events – Category 2	**8 (7.8%)***	**15***
Device-Related	**1 (1.0%)**	**1**
Hospitalization		
CHF		1
Possibly Device-Related	**1 (1.0%)**	**1**
Abnormal Liver Function test		1
Procedure-Related	**0 (0.0%)**	**0**
Possibly Procedure-Related	**1 (1.0%)**	**1**
EMD Visit		
Atrial Tachycardia		1
Not Related	**7 (6.8%)**	**12**
EMD Visit		
Chest pain/Sort of Breath		1
Hospitalization		
AF Recurrence		1
Atrial Flutter		2
Coronarography		1
Syncope		1
ICD Upgrade		1
Epigastric Pain		1
Chronic Sinusitis		1
Cholecystectomy		1
Choledocholithiasis		1
Life Threatening Arrhythmia/VT		1
Serious Adverse Events – Other	**4 (3.9%)**	**4**
Device Related	**0 (0.0%)**	**0**
Possibly Device-Related	**0 (0.0%)**	**0**
Procedure Related	**1 (1.0%)**	**1**
Atrial Flutter Ablation/Hypotension Post		1
Possibly Procedure Related	**0 (0.0%)**	**0**

Description	Number of Subjects n / 103 (%)	Number of SAEs
Not Related	**3 (2.9%)**	**3**
Atrial Flutter		1
Bradycardia/Pacemaker Implant		1
Dizziness Post Flecainide Therapy		1

* Note: AEs could be classified in more than one relatedness group and a subject could have more than one AE.

Table 3.6.5.2.2C summarizes the number of late-onset SAEs by category and relatedness that have been reported to date for the AAD (Control) group. No category 1 events were reported in this group. A total of 9 late-onset category 2 SAEs have been reported in 7 subjects. Two (2) category 2 SAEs were classified as treatment-related (n=1) or possibly treatment- related (n=1). The remaining 7 category 2 SAEs were classified as not related to treatment or procedure.

TABLE 3.6.5.2.2C Late-Onset Serious Adverse Events by Category, Relatedness and AE Description (AAD (Control) Group, n=57)*

Description	Number of Subjects n / 57 (%)	Number of SAEs
Serious Adverse Events – Category 1	**0**	**0**
No Category 1 SAEs were observed		
Serious Adverse Events – Category 2	**7 (12.3%)***	**9****
Treatment-Related	**1 (1.8%)**	**1**
EMD Visit		
AF Recurrence		1
Possibly Treatment-Related	**1 (1.8%)**	**1**
Hospitalization		
AF Flutter		1
Not Related	**5 (8.8%)**	**7**
Hospitalization		
AF Recurrence		2
AF Ablation		2
Pacemaker Implant		1
Epigastric Pain		2
Serious Adverse Events – Other	**1 (1.8%)**	**1**
Treatment-Related	**0 (0.0%)**	**0**
Possibly Treatment-Related	**0 (0.0%)**	**0**
Not Related	**1 (1.8%)**	**1**
Disorientation with Walking		1
Serious Adverse Events – Category 2 (Causality not reported)	**1 (1.8%)**	**1**
Hospitalization		

AF Recurrence		1

* AEs could be classified in more than one relatedness group and a subject could have more than one AE. Subject [redacted], SAE Cat-2 hospitalization for an ablation procedure at an outside hospital is missing causality.

Table 3.6.5.2.2D summarizes the number of late-onset SAEs by category and relatedness that have been reported to date for the AAD (Control) subjects undergoing an ablation procedure. No category 1 events were reported in this group. A total of 2 late-onset category 2 SAEs have been reported in 1 subject. No category 2 SAEs were classified as device-related, possibly device-related, procedure-related or possibly procedure-related. The 2 category 2 SAEs were classified as not related to device or procedure.

TABLE 3.6.5.2.2D Late-Onset Serious Adverse Events by Category, Relatedness and AE Description (AAD (Control) subject Undergoing Ablation, n=36)

Description	Number of Subjects n / 36 (%)	Number of SAEs
Serious Adverse Events – Category 1	**0**	**0**
No Category 1 SAEs were observed		
Serious Adverse Events – Category 2	**1 (2.8%)**	**2**
Device-Related	**0 (0.0%)**	**0**
Possibly Device-Related	**0 (0.0%)**	**0**
Procedure-Related	**0 (0.0%)**	**0**
Possibly Procedure Related	**0 (0.0%)**	**0**
Not Related	**1 (2.8%)**	**2**
Hospitalization		
Fever and Chills		2
Serious Adverse Events – Other	**3 (8.3%)**	**4**
Device Related	**0 (0.0%)**	**0**
Possibly Device-Related	**0 (0.0%)**	**0**
Procedure Related	**0 (0.0%)**	**0**
Possibly Procedure Related	**0 (0.0%)**	**0**
Not Related	**3 (8.3%)**	**4**
AF Recurrence		1
Atrial Flutter		1
Hematuria		1
Cardiac Catheterization		1

* Note: SAEs could be classified in more than one relatedness group and a subject could have more than one SAE.

3.7 Poolability

The primary justification for poolability of results from multiple investigational sites is made on the following clinical basis (Meinert, 1986): that there was a uniform study protocol with well-defined inclusion/exclusion criteria, and data collection methods, endpoints, and sites were monitored to verify protocol compliance across study sites. Participating sites included in this clinical report were in the US, Latin America, Canada, and Europe. Observed differences among sites principally reflect variability in the overall subject population and clinical practice patterns.

3.7.1 Statistical Methods

Different sites may admit different types of patients, within the trial inclusion / exclusion criteria. These differences are likely to be reflected in patient characteristics and eventual outcomes.

Comparability of the results sites was assessed statistically. The baseline prognostic factors, including co-morbid conditions that were addressed by these analyses, were the following:

- Demographics: Gender, age
- Medical History: SVT (AVNRT, accessory pathway, atrial tachycardia), atrial flutter, congenital heart disease, congestive heart failure, deep vein thrombus, diabetes, hypertension, hypertrophic cardiomyopathy, ischemic cardiomyopathy, left ventricular hypertrophy, non-ischemic dilated cardiomyopathy, pulmonary embolus, significant valve disease/replacement, cerebrovascular accident (cerebrovascular accident possibly secondary to thromboembolism & cerebrovascular accident not secondary to thromboembolism), transient ischemic attacks, ventricular fibrillation, ventricular tachycardia, NYHA heart failure class.
- AF History: Number of symptomatic AF episodes within the 6 months prior to randomization, any previous catheter ablation procedures for arrhythmias other than AF
- Liver Function: Baseline ALT, AST, ALP
- Cardiac Medical History: AAD and/or cardiac medications as follows:
  - Class I: Disopyramide, Flecainide, Propafenone, Quinidine
  - Class III: Amiodarone, Dofetilide, Sotalol
  - Beta-Blocker: Acebutolol, Atenolol, Metoprolol, Propranolol, other Beta-Blocker
  - Calcium Channel Blocker: Diltiazem, Verapamil, other Calcium Channel Blocker
  - Digoxin
- Neurology Exam: Baseline neurological exam outcome.
- TTE: Baseline left atrial dimension and LVEF

We included a factor for "site" in our analyses to assess the statistical significance of any differences by clinical site. In view of the many sites with small to moderate sample sizes we grouped sites as follows:

- Group 1 (10 sites, 22 subjects): sites enrolling 5 or fewer subjects each
- Group 2 (5 sites, 37 subjects): sites enrolling between 6 and 10 subjects
- Group 3 (2 sites, 25 subjects): sites enrolling between 11 and 15 subjects
- The remaining sites (---- (49 subjects) and ---- (26 subjects) were large and were considered separately in our analyses.

We used three different grouping methods for "site" in logistic regression analyses:

(a) Non-US vs. US sites: We used an indicator variable set equal to 1 for Non-US sites and 0 for US sites. The Non-US sites included 95 subjects from ---- ---- ---- and ---- The US sites included 64 subjects from the remaining 15 sites.

(b) High Enrolling vs. Low to Medium Enrolling Sites: Consistent with section 7.2.3 in the study protocol (version 12.2), we created a "site" indicator variable that equaled 1 for sites having 20 or more subjects (High enrollers) and 0 for others (Low to Medium enrolling sites). The high enrolling sites include 75 subjects from ---- and ---- The Low to Medium enrolling sites included 84 subjects from the remaining 17 sites.

(c) vs. the remaining sites (Non- ---- sites): Since ---- had the highest enrollment, we carried out alysis comparing that site to the others. ---- site included 49 subjects and Non- ---- sites included 110 subjects.

Comparison Among Sites

As a preliminary analysis we compared subjects characteristics among the sites. For categorical variables, such as gender (male/female) and SVT (yes/no), we judged statistical significance using Fisher's Exact test. The Monte Carlo method was used, with 10,000 samples (the SAS default), because of the size of the tables. Comparisons among sites for continuous covariates, such as age and LVEF, were performed using a Kruskal-Wallis test in view non-normality of the data.

Logistic Regression Analysis of Chronic Success Outcome

To further assess the comparability across sites and to account for potentially significant predictors of a successful outcome that may vary by site, we carried out a formal evaluation of baseline prognostic factors and co-morbid conditions using logistic regression analyses. To screen these potential covariates, comparison analyses among sites and a univariate logistic regression analysis for each covariate with an adjustment of randomization group were performed separately and the summary is provided in Table 3.7.2A.

An arbitrary cut-off of p-value < 0.20 was used for the purpose of screening covariates from comparison analyses among sites and univariate logistic regression analyses. Multivariate logistic regression analyses with an adjustment of randomization group were then conducted using those covariates that survived the initial screening process.

A forward selection algorithm was used for the covariates to enter into the multivariate logistic regression model starting with the lowest p-value from the univariate logistic regression analysis. A cut-off of p-value < 0.05 was used for the covariates to remain in the final model.

3.7.2 Comparison Analyses Among Sites & Univariate Logistic Regression

All enrolled subjects (n=167) were evaluated for the comparison among sites since the primary emphasis in these analyses was the baseline characteristics. The subjects in the Effectiveness Analysis Cohort (n=159), for whom their chronic efficacy outcome was determined, were included in the logistic regression for the prediction of chronic success. Among them, 14 subjects are still in the 9-month follow-up effectiveness assessment period and have not met the chronic effectiveness endpoint at the time of data received. Therefore, logistic regressions were based on 145 subjects in which 89 subjects are from the THERMOCOOL Group and 56 subjects are from the AAD (Control) Group.

Table 3.7.2A shows the results of the comparison among sites and also summarizes the potential predictors of chronic success in the univariate logistic regression models. Based on the comparison analyses among sites, the p-value less than 0.05 indicates there were statistically significant site differences for the corresponding covariate. Age, SVT, NYHA heart failure class, symptomatic AF episodes, class I AAD usage, beta-blocker

usage, outcome of neurological exam, LA dimension, and LVEF were statistically significant across sites in the preliminary analyses.

TABLE 3.7.2A Comparison of Covariates Among Sites and Univariate Logistic Regression Model of Chronic Success Outcome

Covariate	Comparison of Covariate Among Sites (All Enrolled Subjects, n=167)		Covariate As a Univariate Predictor of Chronic Success Adjusting For Randomization Group (Efficacy Analysis Cohort, n=159)	
	Number of Subjects in the Analysis[a]	p-value [a]	Number of Subjects in the Analysis[a]	p-value
Age	167	0.0112*	145	0.7820
Gender	167	0.2675	145	0.1386*
SVT	165	<0.0001*	145	0.1050*
AFL	159	0.1070*	140	0.3631
Congenital Heart Disease	165	0.6979	145	N/A[c]
Congestive Heart Failure	164	0.5934	144	0.8956
Deep Vein Thrombus	164	0.6187	144	N/A[c]
Diabetes	165	0.3627	145	0.7572
Hypertension	165	0.6981	145	0.2497
Hypertrophic Cardiomyopathy	165	0.3295	145	N/A[c]
Ischemic Cardiomyopathy	165	0.9189	145	0.6111
Left Ventricular Hypertrophy	165	0.1541*	145	N/A[c]
Non-Ischemic Dilated	165	N/A[b]	145	N/A[c]
Pulmonary Embolus	165	0.6979	145	N/A[c]
Significant Valve Disease	165	0.3295	145	N/A[c]
Cerebrovascular Accident	165	0.5708	145	0.9122
Transient Ischemic Attacks	165	0.0841*	145	N/A[c]
Ventricular Fibrillation	165	N/A[b]	145	N/A[c]
Ventricular Tachycardia	165	0.6979	145	N/A[c]
NYHA Heart Failure Class	151	<0.0001*	132	0.3968
Symptomatic AF Episodes (6 months prior to enrollment)	157	0.0003*	137	0.7364
Previous Catheter Ablation	165	0.1032*	145	0.2822
ALT Value Normal	145	0.2030	128	0.3348
AST Value Normal	144	0.2176	127	0.4079
ALP Value Normal	136	0.2830	120	0.4375
Class I AAD Usage	167	0.0352*	145	0.0919*
Class III AAD Usage	167	0.2061	145	0.2135
Beta Blocker Usage	167	<0.0001*	145	0.0055*
Calcium Channel Blocker Usage	167	0.0529*	145	0.1333*
Digoxin	167	0.3509	145	0.9988
Outcome of Neurological Exam	136	<0.0001*	122	N/A[c]
LA Dimension	152	0.0186*	136	0.9443
LVEF	153	<0.0001*	137	0.0510*
Grouped Sites			145	0.0007*

Covariate	Comparison of Covariate Among Sites (All Enrolled Subjects, n=167)		Covariate As a Univariate Predictor of Chronic Success Adjusting For Randomization Group (Efficacy Analysis Cohort, n=159)	
	Number of Subjects in the Analysis[a]	p-value [a]	Number of Subjects in the Analysis[a]	p-value
Non-US vs. US Sites			145	0.0042*
High Enrolling vs. Low to Medium Enrolling Sites			145	< 0.0001*
---- vs. Non- ---- Sites			145	<0.0001*

a P-value based on Fisher's exact test for discrete covariates and Kruskal Wallis test for continuous covariates
b Analysis not performed due to no subjects with the specific medical condition
c Analysis not performed due to complete/quasicomplete data in the logistic regression analysis
* Denote p-value less than 0.20

3.7.3 Multivariate Logistic Regression Analysis

The covariates with a p-value less than 0.20 either from comparison analyses among sites or univariate logistic regression (refer to Table 3.7.2 A) were considered as potential covariates for entering into the multivariate logistic regression model. The covariates that survived the screening process include: age, gender, SVT, AFL, left ventricular hypertrophy, transient ischemic attacks, NYHA heart failure class, symptomatic AF episodes, previous catheter ablation, class I AAD usage, beta-blocker usage, calcium channel blocker usage, outcome of neurological exam, LA dimension, LVEF, new grouped sites (<=5, ≥ 6 to ≤10, ≥ 11 to ≤15, and the remaining sites), Non-US vs. US sites, High Enrolling vs. Low to Medium Enrolling sites, and ---- vs. Non- ---- sites. Three of these covariates (left ventricular hypertrophy, transient ischemic attacks, and outcome of neurological exam) were not included in the model building process due to a small number of subjects in some cells of the logistic regression model.

After screening, LVEF, randomization group, and a site term (High Enrolling vs. Low to Medium Enrolling sites) were included in the final multivariate logistic regression model.
All interaction terms were examined and only the interaction between randomization group and High Enrolling vs. Low to Medium Enrolling sites was significant. Table 3.7.3 A presents the final model including the interaction term. Adjusting for the remaining covariates, there was a significant interaction between randomization group and High Enrolling vs. Low to Medium Enrolling sites (p=0.0209).

A significant treatment effect was observed within each stratum of the sites (high enrolling and low to medium enrolling sites):

- In the high enrolling sites, the THERMOCOOL Group demonstrated superior chronic effectiveness compared to the AAD Group [OR=44.19; 95% CL=(10.45, 186.92)]
- Same trend favoring THERMOCOOL Group was also observed in the low to medium enrolling sites [OR=4.19; 95% CL=(1.02, 17.11)]

TABLE 3.7.3A Final Multivariate Logistic Regression Model of Chronic Success (Effectiveness Analysis Cohort, n=159*)

Covariate	Odds Ratio	95% CL	p-value
LVEF	0.93	0.88-0.98	0.0058
Randomization Group (THERMOCOOL vs. AAD Group)			0.0462
High Enrolling vs. Low to Medium Enrolling Sites			0.4704
Randomization*High vs. Low to Medium Enrolling Sites			0.0209
Randomization (THERMOCOOL vs. AAD Group) | High Enrolling Sites	44.19	10.45-186.92	< 0.001
Randomization (THERMOCOOL vs. AAD Group) | Low to Medium Enrolling Sites	4.19	1.02-17.11	0.046

* 137 subjects with chronic outcome and covariate data available

In conclusion, the site variation of the chronic success outcome were observed in this study, however, the treatment effect of chronic success outcome in favor of the THERMOCOOL Group was consistent between High Enrolling and Low to Medium Enrolling sites [OR=44.19; 95% CL=(10.45, 186.92) and OR=4.19; 95% CL=(1.02, 17.11), respectively; Table 3.7.3 A]. Thus, it is reasonable to pool the High Enrolling and Low to Medium Enrolling sites recognizing site variations and accounting for site differences.

3.8 Additional Logistic Regression Analyses of Study Outcomes

Additional logistic regression analyses were conducted to better understand how baseline characteristics, co-morbid conditions, and ablation parameters impact the chronic success endpoint and report of primary AEs. The analyses for acute endpoint and mortality were not performed since there were only 4 acute failures and 1 death in this study.

To identify the risk factors for these endpoints, logistic regression analyses were performed. The baseline prognostic factors, co-morbid conditions, and ablation parameters that were included in these analyses consisted of following:

- *Demographics*: Gender, age
- *Medical History*: SVT (AVNRT, accessory pathway, atrial tachycardia), atrial flutter, congenital heart disease, congestive heart failure, deep vein thrombus, diabetes, hypertension, hypertrophic cardiomyopathy, ischemic cardiomyopathy, left ventricular hypertrophy, non-ischemic dilated cardiomyopathy, pulmonary embolus, significant valve disease/replacement, cerebrovascular accident (cerebrovascular accident possibly secondary to thromboembolism & cerebrovascular accident not secondary to thromboembolism), transient ischemic attacks, ventricular fibrillation, ventricular tachycardia, NYHA heart failure class.
- *AF History:* Number of symptomatic AF episodes within the 6 months prior to randomization, any previous catheter ablation procedures for arrhythmias other than AF
- *Liver Function:* Baseline ALT, AST, ALP
- *Cardiac Medical History:* AAD and/or cardiac medications as follows:
  - Class I: Disopyramide, Flecainide, Propafenone, Quinidine
  - Class III: Amiodarone, Dofetilide, Sotalol

  - Beta-Blocker: Acebutolol, Atenolol, Metoprolol, Propranolol, other Beta-Blocker
  - Calcium Channel Blocker: Diltiazem, Verapamil, other Calcium Channel Blocker
  - Digoxin
- *Neurology Exam:* Baseline neurological exam outcome.
- *TTE:* Baseline left atrial dimension and left ventricular ejection fraction (LVEF)
- *Ablation Procedure:* Total procedure time, total ablation time, total fluoroscopy duration, fluid delivered via the catheter, fluid balance (fluid output minus fluid input), linear sites ablated
- *End of Procedure Verification:* Burst pacing performed, and Isoproterenol infusion.
- *Site Term:* Due to the finding of site variation in the poolability section 3.7.3, a site term (High Enrolling vs. Low to Medium Enrolling sites) was included as a covariate in the analysis. According to section 7.2.3 of the study protocol (version 12.2), a site that enrolled more than 20 subjects was considered as a high enrolling site and a site that enrolled less than or equal to 20 subjects was considered as a low to medium enrolling site.

Univariate logistic regression models were conducted in each of the baseline characteristics, co-morbid variables, ablation parameters, and the site term to identify potential predictors of the outcomes. An arbitrary cut-off of p-value < 0.20 was used for the purpose of screening covariates.

A forward selection algorithm was used for the covariates to enter into the multivariate logistic regression model starting with the lowest p-value from the univariate logistic regression analysis. A cut-off of p-value < 0.05 was used for the covariates to remain in the final model. Interaction terms were examined based on those covariates survived in the final model.

3.8.1 Logistic Regression Analysis for Chronic Success

The per-protocol subjects in the THERMOCOOL group (n=103), for whom their chronic efficacy was determined, could be included in the logistic regression for the prediction of chronic success. Table 3.8.1 A shows the results from the univariate logistic regression analyses of chronic success.

TABLE 3.8.1 A Univariate Logistic Regression Model and Predictors of Chronic Success (THERMOCOOL Effectiveness Cohort, n=103)

Co-Morbid Variable	Number of Subjects Used in the Analysis[a]	P-value
Age	89	0.1004*
Gender	89	0.0149*
SVT	89	0.1914*
AFL	87	0.4268
Congenital Heart Disease	89	N/A[b]
Congestive Heart Failure	88	0.3565
Deep Vein Thrombus	88	N/A[b]
Diabetes	89	0.6476
Hypertension	89	0.1210*
Hypertrophic Cardiomyopathy	89	N/A[b]
Ischemic Cardiomyopathy	89	0.5279
Left Ventricular Hypertrophy	89	N/A[b]
Non-Ischemic Dilated Cardiomyopathy	89	N/A[b]

Co-Morbid Variable	Number of Subjects Used in the Analysis[a]	P-value
Pulmonary Embolus	89	N/A[b]
Significant Valve Disease	89	N/A[b]
Cerebrovascular Accident	89	N/A[b]
Transient Ischemic Attacks	89	N/A[b]
Ventricular Fibrillation	89	N/A[b]
Ventricular Tachycardia	89	N/A[b]
NYHA Heart Failure Class	78	0.1608*
Symptomatic AF Episodes (6 months prior to enrollment)	84	0.2782
Previous Catheter Ablation	89	0.4301
ALT Value Normal	87	0.1912*
AST Value Normal	87	0.7220
ALP Value Normal	87	N/A[b]
Class I AAD Usage	89	0.0716*
Class III AAD Usage	89	0.3658
Beta Blocker Usage	89	0.0008*
Calcium Channel Blocker Usage	89	0.1609*
Digoxin	89	0.3368
Outcome of Neurological Exam	86	0.5472
LA Dimension	85	0.4765
LVEF	84	0.0220*
Procedure Time	89	0.0004*
Ablation Time	89	0.0005*
Fluoroscopy Time	89	0.0011*
Fluid via Catheter	89	0.0144*
Fluid Balance	89	0.0171*
Linear Site Ablated	89	0.0452*
Burst Pacing Done	89	0.0264*
Isoproterenol Infusion	89	0.0063*
High vs. Low to Medium Enrolling Sites	89	< 0.0001*

[a] 14 subjects are still in the 9-month follow-up effectiveness assessment period and have not met the chronic effectiveness endpoint at the time of data received. Some subjects did not have co-morbid data available.
[b] Analysis not performed due to a small number of subjects with the co-morbid condition. This caused the complete/quasicomplete separation data.
* Denote the covariates with a p-value < 0.20 in the univariate logistic regression analyses were considered in the multivariate logistic regression model.

Table 3.8.1B shows the final results from the multivariate logistic regression analysis. High vs. Low to Medium Enrolling sites and LVEF are significant predictors of chronic success outcome ($p < 0.0001$, and = 0.0019, respectively). Subjects from the High Enrolling sites had a greater chance to achieve chronic success outcome than those from the Low to Medium Enrolling sites [OR=25.80; 95% CL=(6.61, 100.70)]. A lower LVEF at baseline was associated with chronic success outcome [OR=0.90, 95% CL=(0.84, .096)]. It was noticed from this logistic regression model that a lower LVEF was associated with higher successful chronic outcome. This is partly due to the variability of the measurement of LVEF. For example, one site (---- used the Teicholz method to calculate the LVEF, which tends to overestimate the LVEF when compared to the Simpson method used by other sites.

TABLE 3.8.1B Final Multivariate Logistic Regression Model for Chronic (THERMOCOOL Group, n=103)

Risk Factor	Odds Ratio	95% CL	P-value
High vs. Low to Medium Enrolling Sites	25.80	6.61-100.70	< 0.0001
LVEF (%)	0.90	0.84-0.96	0.0019

* Analysis was based on 84 subjects with chronic outcome and risk factor data available.

3.8.2 Logistic Regression Analysis for Primary Adverse Events (Updated – 15 Subjects with Primary Adverse Events)

The Primary Safety Analysis Cohort (n=139) was used in the logistic regression analyses of the Primary Adverse Events. This cohort is comprised of per-protocol subjects from the THERMOCOOL Group (n=103) and per-protocol subjects undergoing an RF ablation procedure from the AAD (Control) Group (n=36). Table R 3.8.2 A shows the results for the univariate logistic regression analyses of primary AE.

TABLE R 3.8.2 A Univariate Logistic Regression Model and Predictors of Primary Adverse Events (Primary Safety Analysis Cohort, n =139)

Co-Morbid Variable	Number of Subjects Used in the Analysis[a]	P-value
Age	139	0.5103
Gender	139	0.1700*
SVT	139	0.4975
Atrial Flutter	134	0.4330
Congenital Heart Disease	139	N/A[b]
Congestive Heart Failure	138	0.0322*
Deep Vein Thrombus	138	N/A[b]
Diabetes	139	N/A[b]
Hypertension	139	0.6316
Hypertrophic Cardiomyopathy	139	N/A[b]
Ischemic Cardiomyopathy	139	N/A[b]
Left Ventricular Hypertrophy	139	N/A[b]
Non-Ischemic Dilated Cardiomyopathy	139	N/A[b]
Pulmonary Embolus	139	0.9890
Significant Valve Disease	139	N/A[b]
Cerebrovascular Accident	139	N/A[b]
Transient Ischemic Attacks	139	N/A[b]
Ventricular Fibrillation	139	N/A[b]
Ventricular Tachycardia	139	N/A[b]
NYHA Heart Failure Class	127	0.2406
Symptomatic AF Episodes (6 months prior to enrollment)	133	0.3941
Previous Catheter Ablation	139	0.9019
ALT Value Normal	125	0.4485
AST Value Normal	124	N/A[b]
ALP Value Normal	118	0.5717
Class I AAD Usage	139	0.9331

Class III AAD Usage	139	0.4440
Beta Blocker Usage	139	0.7309
Calcium Channel Blocker Usage	139	0.7670
Digoxin	139	0.0577*
Neurological Exam	136	0.0625*
LA Dimension	134	0.4468
LVEF	133	0.0476*
Procedure Time	139	0.0033*
Ablation Time	139	0.0013*
Fluoroscopy Time	139	0.0205*
Fluid via Catheter	139	0.0714*
Fluid Balance	139	0.0132*
Linear Site Ablated	139	0.3086*
Burst Pacing Done	137	0.0980*
Isoproterenol Infusion	137	0.0589*
High vs. Low to Medium Enrolling Sites	139	0.2755

a Subjects with co-morbid condition data available

b Analysis not performed due to a small number of subjects with the co-morbid condition. This caused the complete/quasicomplete separation data.

* Denote the covariates with a p-value < 0.20 in the univariate logistic regression analyses were considered in the multivariate logistic regression model.

Table R 3.8.2 B presents the final results of multivariate logistic regression model for primary AE. Ablation time, CHF, and neurological exam findings at baseline are significant predictors of primary AE (p=0.0006, 0.0065, and 0.0227, respectively). An increased ablation time is associated with an incidence of primary AE [OR=1.01; 95% CL=(1.01, 1.02)]. Subjects with a normal neurological exam at baseline had a lower chance to experience a primary AE than those with an abnormal assessment [OR=0.16; 95% CL=(0.03, 0.77)]. Subjects with a medical history of CHF had a higher chance to experience a primary AE than those without a medical history of CHF [OR=43.90; 95% CL=(2.88, 668.21)].

The odds ratio and confidence limits for CHF were relatively large since there were only 4 subjects who had a medical history of CHF. A model excluding CHF was performed and the results are presented in Table R 3.8.2 C. This shows the consistent results indicating an increased ablation time and abnormal baseline neurological exam are associated with increased incidence of primary AEs.

Table R 3.8.2 B Final Multivariate Logistic Regression Model for Primary Adverse Events (Primary Safety Analysis Cohort, n =139*)

Risk Factor	Odds Ratio	95% CL	P-value
Ablation Time (min)	1.01	1.01-1.02	0.0006
CHF (Yes vs. No)	43.90	2.88-668.21	0.0065
Neuro Exam (Normal vs. Abnormal)	0.16	0.03-0.77	0.0227

* Analysis was based on 135 subjects with risk factors data available.

Table R 3.8.2 C Final Multivariate Logistic Regression Model for Primary Adverse Events, Excluding CHF (Primary Safety Analysis Cohort, n =139*)

Risk Factor	Odds Ratio	95% CL	P-value
Ablation Time (min)	1.01	1.01-1.02	0.0011
Neuro Exam (Normal vs. Abnormal)	0.20	0.04-0.94	0.0416

* Analysis was based on 136 subjects with risk factors data available.

4.0 Discussion

The results generated in this clinical study establish that the irrigated NAVISTAR THERMOCOOL Catheter offers the clinical community a safe and effective technology for treating paroxysmal atrial fibrillation. The primary effectiveness hypothesis was met and the primary safety endpoint result represents an acceptable risk profile. Additionally, the results of the secondary safety hypothesis demonstrate a statistically significant difference between the THERMOCOOL group compared to the AAD (Control) group in favor of the THERMOCOOL group.

4.1 Effectiveness

The primary effectiveness endpoint for this study was met. Superiority for the THERMOCOOL group vs. AAD (Control) group was demonstrated in achieving freedom from documented, symptomatic AF recurrence throughout the effectiveness period.

Figure 3.6.3.1A demonstrates a statistically significant difference between the two randomization groups, showing a superior probability of chronic effectiveness success over time (p-value < 0.0001; log rank test). The difference in probability of treatment success was 48% in favor of the THERMOCOOL group (64% vs. 16%) at the end of the 9-month effectiveness evaluation period.

The posterior probability that the THERMOCOOL group is superior to the AAD (Control) group was essentially 1 (> 0.9999), in the primary, Bayesian analysis (June 2008) as shown in Figure 3.6.2.2C. This graphical representation of the posterior distributions for the probabilities of a subject being failure-free for the 9-month period clearly illustrates the superior result for the THERMOCOOL group.

The estimated mean probability of success for a subject in the THERMOCOOL group is 62.7%. For a subject in the AAD (Control) group, the posterior mean probability of success is 17.2%. 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, that is, a median 46% difference in probability of primary effectiveness success between the THERMOCOOL group and the AAD (Control) group.

4.1.1 Effectiveness Substantiated through Rigorous, Well Controlled TTM Data Collection and Analysis Process

The overall mean TTM compliance was 88.8%, with 88.5% and 89.2% overall mean compliance for the THERMOCOOL and AAD (Control) groups, respectively.

The TTM collection, analysis, and adjudication process was well controlled and highly compliant. A core lab was utilized for the objective evaluation of TTM and 24-hour Holter monitor for the evaluation of AF recurrence. Initial TTM evaluations were performed by two (2) certified cardiac technicians at the core lab trained in the evaluation of these tests according to the protocol definition for AF, and were subsequently reviewed by an independent board certified cardiologist who was blinded to the randomization assignment.

This 3-step review process for the TTMs further supports the due diligence approach to assessing chronic effectiveness in this study population.

To ensure TTM compliance with the protocol specified follow up, study subjects were provided a toll-free number to call the core lab in order to transmit the ECG data and provide symptomatic or asymptomatic classification. If a subject missed a scheduled transmission, the core lab would contact the subject, reminding them to call in for transmission. To add to the robustness of AF recurrence monitoring, if the site collected additional, non-protocol-required TTM data, this information was also collected and evaluated. All additional TTMs were reviewed by the core lab and independent cardiologist in the identical adjudication process to the per-protocol TTMs.

A total of 11,350 TTMs were collected and analyzed in this study, demonstrating a comprehensive and thorough assessment for AF episodes (symptomatic and asymptomatic) post-treatment. The 4,092 additional TTMs collected during the 9-month effectiveness period that were not required by the protocol (2,595 and 1,497 for THERMOCOOL and AAD (Control), respectively) helped to ensure the highest possible rigor for detection of AF recurrence.

4.1.2 Effectiveness Evaluation is Conservative

In this study, a rigorous protocol definition was used for the chronic effectiveness endpoint. To be adjudicated a chronic success required more than freedom from documented symptomatic AF recurrence, resulting in a conservative evaluation.

For the THERMOCOOL group, any of the following resulted in the subject being adjudicated as a chronic effectiveness failure, irrespective of symptomatic AF recurrence:

- AAD failure [The addition/increased dose of AAD post-blanking. AADs, per the protocol, include Class I, Class III, beta blockers (BB), calcium channel blockers (CCB), digitalis, angiotensin receptor blockers or angiotensin converting enzyme (ACE) inhibitors]
- Repeat ablation (>80 days)
- Acute failure
- Use of non- THERMOCOOL catheter for AF targets

Comparatively, in the AAD (Control) group, any of the following resulted in adjudication as chronic effectiveness failure, irrespective of AF recurrence:

- AAD failure [The addition/increased dose of AAD post-dosing. AADs, per the protocol, include Class I, Class III, beta blockers (BB), calcium channel blockers (CCB), digitalis, angiotensin receptor blockers or angiotensin converting enzyme (ACE) inhibitors],
- Safety failure requiring discontinuation of the assigned AAD

As shown in Figure 3.6.2.2D, two (2) THERMOCOOL subjects were adjudicated as chronic effectiveness failures for repeat ablation, even though they did not have documented symptomatic AF recurrence during the protocol-specified follow up period. Both subjects had a repeat ablation between days 80-90 post initial ablation, which constituted a chronic effectiveness failure according to the protocol, even though both subjects had no documented, symptomatic AF recurrence during the evaluation period. This reflects a conservative approach for analyzing the primary effectiveness endpoint in this clinical trial.

Additionally, ten (10) subjects randomized to the THERMOCOOL group, without symptomatic AF recurrence during the evaluation period, were deemed chronic effectiveness failures solely due to use of AADs (refer to Figure 3.6.2.2D). Three (3) of these subjects received either Class I or III drugs for AF during the protocol-

specified follow up period. However, seven (7) subjects without symptomatic AF recurrence were deemed chronic effectiveness failures only due to use of non-Class I or III drugs. Six (6) of these subjects were deemed chronic effectiveness failures solely due to use of beta-blocking agents post-ablation during the follow up period. One subject was adjudicated as a chronic effectiveness failure due to an ACE inhibitor prescribed for AF. The adjudications as chronic failures of these seven (7) subjects for treatment with either a beta-blocking agent or an ACE inhibitor is very conservative since there is neither expectation nor evidence that such drugs would be effective in preventing recurrence of AF.

The designation of 9% (9/103) of all THERMOCOOL subjects as chronic failures, due solely to either prescription of AV nodal blocking agents, ACE inhibitor use, or a late repeat ablation (days 80-90), in the absence of symptomatic AF recurrence during the effectiveness period, reflects a conservative approach for analyzing the primary effectiveness endpoint.

Control subjects in this trial were medically managed per the ACC/AHA/ESC Guidelines on the Management of Atrial Fibrillation (2001), with drug selection and dosage prescribed for each subject based on investigator judgment of their clinical needs within these guidelines. Site differences in the effectiveness of AAD therapy were noted, which may reflect in part drug-prescribing preferences as well as the individual subjects' responses. However, limiting the AAD therapy in this trial to the AADs recommended in the ACC/AHA/ESC Guidelines for medical management of AF offers sufficient guidance for medical management in this trial.

Seven (7) AAD (Control) group subjects were protocol adjudicated failures for safety and effectiveness without documented symptomatic recurrence of AF in their effectiveness evaluation period (refer to Figure 3.6.2.2E). All 7 subjects experienced intolerance to the assigned AAD, experiencing a Category 2 adverse event (refer to Appendix 21 for Subject Profiles). According to the study protocol, AAD (Control) subjects experiencing safety failure requiring discontinuation of the assigned AAD during days 0-285 post-treatment were deemed chronic failures. This is because a drug cannot effectively treat a patient who cannot tolerate it and therefore represents an effectiveness failure from an intention to treat point of view.

Interestingly, the majority of the protocol-specified AAD failures in the THERMOCOOL group occurred at the 3-month post-ablation visit and were due to beta-blocking agents. It is recognized that the use of beta- and calcium channel-blockers in patients with paroxysmal atrial fibrillation may have been underestimated during protocol development. While 10 THERMOCOOL subjects were adjudicated as effectiveness failures per the FDA approved protocol, it is important to understand how these drugs were being used in this clinical trial.

4.1.3 AAD Therapy Included AV Nodal Blocking Agents As Treatment for AF

AAD therapy is an important factor contributing to the site variations observed in this clinical trial since AV nodal blocking agents were formally considered anti-arrhythmic drugs when prescribed for AF. The protocol specified that AV nodal agents such as beta blockers and calcium channel blockers would be considered AADs, along with Class I and Class III antiarrhythmic drugs, when adjudicating subjects as chronic effectiveness successes or failures. For example, use of any of these drugs for AF after the end of the blanking period (beyond the pre-ablation maximum 24 hr dose) resulted in adjudication as a chronic effectiveness failure, irrespective of AF recurrence.

As summarized by the recent ACC/AHA/ESC Guidelines for the Management of Atrial Fibrillation, the principal role of beta-blockers and calcium channel blockers in the treatment of atrial fibrillation is to achieve ventricular rate control, and not for AF prevention. Beta blockers and/or calcium channel blockers are commonly used following ablation of atrial fibrillation because recurrence is common during the blanking period, probably due to the inflammation caused by the procedure itself.[1] Nevertheless, it is important to

control ventricular response rate should atrial fibrillation recur. In addition, some physicians choose to keep their patients on beta-blocker and/or calcium channel blocker therapy post-ablation because so many of these patients have hypertension. Thus, many patients may be continued on beta-blocker or calcium channel blocker therapy although AF had not recurred. Rather, it is because they are being treated for hypertension, or because their physicians are being conservative and want to be sure that should atrial fibrillation recur, the ventricular rate will not be too fast.

Variations in the AAD prescription practice patterns post-ablation were observed across sites (refer to Appendix 21, Subject Profiles). At some study sites (e.g. ---- ---- ---- beta-blocking agents were frequently prescribed post-ablation and continued, in some cases, into the effectiveness period. These subjects were adjudicated as chronic effectiveness failures. At other sites (e.g. ---- previously failed Class I or III drugs were administered post-ablation and continued into the effectiveness period. The latter approach was permissible under the protocol, provided that the dose was at or below the maximum baseline dose, and thus did not result in chronic failure adjudication.

4.1.4 Control Subjects Assigned to Previously Failed AAD

As shown in Table 3.6.1.2C, eleven (11) subjects in the AAD (Control) group were enrolled and placed on the same or higher dose of a previously failed drug, rather than the per protocol new antiarrhythmic drug. This occurred due to regional limitations in availability of protocol-specified AADs. These 11 subjects had a comparable failure rate as the remaining 45 AAD (Control) subjects prescribed a new (not previously failed) AAD (81.8% vs. 84.4% respectively, p= 1.0000). It is, therefore, unlikely that prescription of new antiarrhythmic drugs to these 11 subjects would have provided materially different results. Nonetheless, a sensitivity analysis was performed removing these 11 subjects from the AAD (Control) group (n=148). The resulting analysis is consistent with the primary analysis (n=159), that superiority of the THERMOCOOL group is demonstrated (p-value < 0.0001). In addition, Bayesian multiple imputation analysis was conducted for these 11 and 3 additional control subjects who had received less than the protocol-specified AAD dosage. The resulting posterior probability that THERMOCOOL AF ablation is superior to the AAD group was > 0.9999, thus further confirming the superiority of the THERMOCOOL group vs. control with respect to the primary effectiveness endpoint. The posterior mean probabilities of success for the AAD and THERMOCOOL Ablation groups were 0.159 (posterior standard deviation of 0.055) and 0.628 (posterior standard deviation of 0.048) respectively. The estimated advantage of THERMOCOOL AF ablation over AAD was 0.472 with a 95% credible interval of (0.316, 0.602) (refer to appendix 27).

4.1.5 Effectiveness Outcomes for High Enrolling Sites

Chronic effectiveness results revealed site variations in outcomes, modes of failures, and medical management. The chronic effectiveness results in this study population were further characterized by additional Kaplan-Meier Analyses. For example, it was noted that the highest enrolling sites (20 or more subjects enrolled) had better effectiveness outcomes. Figures 3.6.3.1D and Figure 3.6.3.1E show the time to chronic failure per the protocol definition for High Enrolling (i.e. ---- and ---- versus Low to Medium Enrolling sites for the two randomization groups.

The difference in the magnitudes of the treatment effects across these two strata may be influenced by investigator experience; both High Enrolling sites are located and had earlier access to the THERMOCOOL catheter, as discussed previously. The directio atment effect is consistent and corroborates the superiority of the THERMOCOOL catheter in the primary effectiveness analysis. Despite the site variations, the treatment effect of chronic success outcomes in favor of the THERMOCOOL group was consistent between High Enrolling and Low to Medium Enrolling sites [Odds ratio = 44.19; 95% Confidence Limits =

(10.45, 186.92)] and [Odds ratio = 4.19; 95% Confidence Limits = (1.02, 17.11)] respectively (refer to Table 3.7.3A).

4.1.6 Effectiveness Further Corroborated by Published Literature

Other randomized clinical trials corroborate the effectiveness results observed in this clinical trial. In a prospective, multicenter randomized clinical study involving 70 patients with paroxysmal AF, 88% (28/32) and 37% (13/35) had no AF recurrence at the one-year follow up visit for catheter ablation compared to AADs, respectively.[18] ----

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The single procedure success rate for catheter ablation of AF in the absence of post-procedure AAD therapy was 57% (95% Confidence Interval of 50%-64%). After multiple or uncertain number of RF ablation procedures, the success rate in the absence of post-procedure AAD therapy increased to 71% (95% Confidence Interval of 65%-77%). The ablation success rate was 77% (95% Confidence Interval of 73%-81%) after multiple or uncertain number of procedures in patients on AAD therapy and 72% after a single procedure on AAD therapy. The overall success rate (generally defined by authors as the disappearance of arrhythmia during the follow-up period) for all drug treatment groups was 46%.

Since the study protocols, monitoring regimes, subject demographics, etc. differed between the IDE study presented here and those cited from the literature, formal statistical comparison would be inappropriate. Nonetheless, it is reassuring to note that the 62.7% estimated mean probability of chronic effectiveness success for the THERMOCOOL group achieved in this study, with very conservative success criteria, extensive TTM monitoring, and an average of 1.__127/103) ablation procedures per subject, is consistent with the ranges of success reported in the literature.---

4.2 Safety Assessment

4.2.1 Primary Safety Analysis

The protocol-specified primary safety endpoint was the incidence of early-onset (within 7 days of ablation procedure) specified primary AEs for subjects undergoing an ablation procedure with the THERMOCOOL catheter. The safety endpoint specified in the protocol was 7.0% (upper confidence bound of 16.0%).

The Primary Safety Cohort (n=139) was comprised of THERMOCOOL group subjects (n=103) and AAD (Control) group subject undergoing an ablation procedure (n=36). The overall percentage of THERMOCOOL ablation subjects who experienced a serious primary AE was 10.8 % (15/139) with an upper confidence bound of 16.1%, thereby exceeding by 0.1% the upper confidence bound of the hypothesis.

It is important to note that no severe adverse events such as death, atrio-esophageal fistula, stroke, cerebrovascular accident, atrial perforation, myocardial infarction, thromboembolism, TIA, diaphragmatic paralysis, pneumothorax, heart block or severe pulmonary vein stenosis occurred within 7 days of the ablation

procedure. Thus, while the primary safety results slightly exceeded the protocol-established primary safety endpoint for this study, the nature and types of adverse events experienced in this trial nonetheless represent an acceptable risk profile.

Seven (7) subjects experienced primary AEs resulting in new or prolonged hospitalizations (5.0 % ; 7/139) within 7 days of the ablation procedure. Of the remaining 8 subjects, one (1) developed pericarditis followed by a late-onset tamponade with a pleural effusion at Day 17, one (1) developed a pericardial effusion, one (1) developed pulmonary edema, and 5 developed vascular access complications that required intervention or extended their hospital stay.

All 15 subjects observed with a primary AE experienced either improvement or complete resolution of the adverse event. One subject with pericarditis was improved at the time of hospital discharge. No primary AE was adjudicated as device-related.

One death (---- occurred 284 days post study ablation procedure and was not considered by definition a primary AE (see section 3.6.5.1.3 for details). The cause of death was attributable to acute myocardial infarction, ischemic cardiomyopathy, systemic arterial hypertension, and diabetes mellitus unrelated to the THERMOCOOL catheter.

No primary AE was classified as device-related by the investigator. One subject (0.7%; 1/139) experienced a primary AE that was classified as possibly device-related. The absence of device-related primary AEs and the excellent AE profile demonstrate the acute safety of AF ablation with the THERMOCOOL catheter.

4.2.2 Pulmonary Vein Stenosis

Pulmonary vein stenosis was defined in the study protocol as ≥70% reduction in the diameter of the pulmonary vein from baseline. This analysis cohort includes all subjects undergoing an ablation procedure, in either the THERMOCOOL group or AAD (Control) group. Based on the June 2008 dataset, 3-month and 12-month data were available for 84 and 29 subjects, respectively. No pulmonary vein stenosis, as defined in the protocol, has been reported to date.

4.2.3 Comparative Safety Assessment – THERMOCOOL Group vs. AAD (Control) Group

Additional safety analyses were performed to characterize the early-onset (≤ 90 days) adverse events by severity (Category 1 and Category 2 serious adverse events). These analyses were done on the overall safety cohort comparing the AAD (Control) group subjects (n=57) and THERMOCOOL group subjects (n=103). A serious adverse event was classified as Category 1 if the event resulted in permanent injury or impairment to the subject. An adverse event was classified as Category 2 if the event resulted in a temporary or reversible injury to the subject.

Because the types of adverse events in the AAD (Control) group were so different than the events in the THERMOCOOL group, as would be expected for such different treatment modalities, it is often challenging to compare these adverse events. Nevertheless, Table 3.6.5.2.1B presents a comparison of the number of early onset serious adverse events (SAEs) between the randomization groups. Early onset SAEs were defined as a combination of early onset (≤90 days post treatment) Category 1 and Category 2 adverse events. The number

of early onset SAEs was statistically different between the THERMOCOOL and AAD (Control) group with a favorable result observed in the THERMOCOOL group.

Overall, the primary and secondary safety analyses performed to date represent an excellent safety profile for THERMOCOOL catheter ablation in this AF population, with THERMOCOOL group subjects experiencing approximately one-half the serious adverse events of their AAD (Control) arm counterparts.

4.2.4 Safety Results Further Corroborated by Published Literature

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4.3 Quality of Life Assessment

THERMOCOOL subjects demonstrated roughly 50% improvement from baseline on average in symptom frequency and severity. This was seen beginning with the 3-month post-blanking visit (the start of the effectiveness evaluation period) and persisted through the final visit (refer to Figures 3.6.4.4C and 3.6.4.4D). In contrast, no improvement was demonstrated in symptom frequency or severity in the AAD (Control) group at the 3-month and 6-month visits; in fact, trends toward worsening symptom frequency and severity scores were noted at these time points. At the 9-month visit, the symptom severity in the AAD (Control) group did improve. However, we believe this finding to be biased by the fact that the majority of AAD (Control) group subjects had failed effectiveness and underwent an ablation procedure (64%, 36/56), presumably leaving only those who remained satisfied with their drug therapy in the AAD (Control) group analysis.

With the SF-36 instrument, THERMOCOOL subjects experienced approximately 8-10 unit increases in their mental component summary (MCS) and approximately 5-6 unit increases in their physical component summary (PCS) scores during the follow-up period. Subjects randomized to the AAD (Control) group reported little or no improvement in these scales (refer to Figures 3.6.4.4A and 3.6.4.4B). The average improvements in these scales for THERMOCOOL subjects therefore not only exceeded values generally considered clinically meaningful, but also were statistically significant compared with changes in the control group.[66]

Quality of life (QoL) changes of the magnitude seen for the THERMOCOOL group substantially exceed those typically observed with drug therapy for AF. In the AFFIRM trial, small improvements (<3 unit) in PCS and MCS scores were seen during the first year of follow-up but did not differ between the randomized rate control and rhythm control groups.[30] Likewise, in the Canadian Trial of Atrial Fibrillation, which randomized patients to amiodarone, sotalol, or propafenone, improvements in PCS and MCS at 3 months were only approximately 2

units for all groups combined.[8] Finally, analysis from the Sotalol Amiodarone Atrial Fibrillation Efficacy (SAFE-T) trial revealed that patients who maintained sinus rhythm improved to a greater extent than patients with recurrent AF on only 2 of the 8 SF-36 sub-scales at one year, and even then, the relative improvements for patients maintaining sinus rhythm were <5%.[7]

The Q--- findings from the THERMOCOOL study are [42] ---- ----

In summary, THERMOCOOL subjects demonstrated a significant improvement in average symptom frequency and severity. This contrasts with the absence of improvement in the AAD (Control) group at the 3-month and 6-month visits, though some improvement was observed at the 9-month visit. Clinically and statistically significant improvements were also measured with the SF-36 instrument for the THERMOCOOL subjects. These results together further substantiate the clinical benefit of THERMOCOOL catheter ablation for treatment of AF.

4.4 Robust Clinical Trial Design and Execution

This prospective, multicenter, randomized clinical trial represents a robust study design and provides valid scientific evidence regarding the safety and effectiveness of the THERMOCOOL Catheter for the treatment of atrial fibrillation. The protocol closely followed the recommendations stated in the FDA Guidance document, "Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation (January 2004)".[63] Additionally, the ACC 2001 Guidelines for Management of Subjects with Atrial Fibrillation was utilized for recommending the appropriate dosing for the AAD (Control) group, as they were the operative guidelines at the time of design and initiation of the trial.[64]

> The study was well-controlled and executed as evidenced by the successful FDA Bioresearch Monitoring Office of Compliance (BiMo) audits conducted in April, 2008, at the two highest enrolling sites (---- and ---- and of Biosense Webster as Sponsor in September, 2008. No 483 observations were cited. All study sites were frequently monitored by sponsor representatives for quality control and to provide rigorous oversight of the investigation. Additionally, Biosense Webster, Inc. contracted a third-party consulting firm as further due diligence for quality assurance. conducted additional audits to evaluate the compliance at the six highest enrolling inv the study, which contributed 72.5% (121/167) of the study subjects. Compliance at these sites was evaluated with Biosense Webster Inc.'s policies and procedures, applicable FDA regulations (21 CFR Parts 11, 50, 54, and 812) and the International Conference on Harmonization (ICH) GCP E6 guideline.

Rigorous source verification of all subject case report form data further demonstrated the robust, diligent approach to ensuring data integrity and appropriate compliance with the study protocol. Further, it is important to note that no adverse data integrity signal was observed for any of the sites in this study.

4.5 Clinical Trial Considerations

4.5.1 Statistical Plan Amendment

The statistical plan was amended mid-study as a result of an extremely slow enrollment rate. The Bayesian statistical method has been widely used for product approvals to enhance clinical trial efficiency, e.g., in orthopedics (PMA P060018; PRESTIGE® Cervical Disc System / Medtronic Sofamor Danek / Date of Panel Recommendation: September 19, 2006). This is further supported by FDA guidance including: "Modernizing Review of Innovative Devices" (May 2006), "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials- Draft Guidance for Industry and FDA Staff" (May 2006), and a presentation titled, "Bayesian Statistics at the Division of Biostatistics CDRH, FDA," given by Pablo Bonangelino, PhD, Biostatistician, FDA/CDRH/OSB (February 2007).

In this clinical study, Bayesian adaptive sample size (from ---- to 230 based on the result of the planned interim analysis) was approved by the agency on ---- At the request of FDA, an independent consulting group (---- Consultants) per nalysis per the IDE protocol. The interim analysis determined that there was sufficient statistical evidence for meeting the safety and effectiveness endpoints to stop enrollment at the current sample size and declare the trial an early success. Early stopping represented the spirit of a "least burdensome" approach.

While mid-trial protocol modifications are not ideal, the amended study design with a Bayesian adaptive sample size was prospective. It incorporated appropriate "statistical penalties" for interim analyses as evidenced by the study operating characteristics presented in the protocol, and was approved by FDA on ----. The predictive probability stopping criteria were set conservatively so as to control the e I error rate at less than .

Further, results from the interim analysis (October 2007) were comparable to the updated PMA dataset analysis (June 2008). The Bayesian design was based on early stopping of accrual (as opposed to the traditional "group sequential" stopping and making an immediate claim of efficacy). The prospective plan was to incorporate all available information and not just the results available at the interim analysis. There is always the formal possibility that the later results will be different from the earlier results and that the final comparison of test vs. control will be less compelling statistically than was predicted at the interim analysis. However, that was not the case. The probability of effectiveness derived from the June 2008 dataset was comparable or better than that predicted at the time accrual was stopped (October 2007).

4.5.2 Enrollment Challenges

Biosense Webster Inc. encountered unprecedented challenges to timely enrollment for completion of this study. In October 2004, the first subject was enrolled. After 1 year of enrollment, only 11 subjects were enrolled in the study. After 2 years of enrollment (October 2006) and screening over 2,100 patients, only 53 subjects were enrolled, representing an approximate 2.5% enrollment rate.

In early 2006, aggressive company-initiated U. S. patient recruitment efforts directed at both physicians and patients (compliant with HIPAA and all applicable patient privacy laws) generated a significant increase in study awareness and referrals, but resulted in only 3 subjects enrolled in the study. These extreme enrollment challenges were discussed in detail during the *FDA Circulatory System Device Panel: Clinical Trial Designs for Atrial Fibrillation Treatment Devices* held in September 2007.

As a result of disappointing results from U.S. recruitment efforts, 4 high volume AF ablation sites outside of the U.S. were added to the trial, resulting in increased enrollment. All non-U.S. clinical data were collected in accordance with the study protocol, Biosense Webster applicable Standard Operating Procedures (SOPs) and with 21CFR 812 and 21CFR 814.15 regulations. Interestingly, the enrollment at the non-US sites closely paralleled the US experience. Overall, three percent (3%) of screened patients were enrolled in this clinical study, approximately 5,500 patients screened and 167 subjects enrolled prior to meeting the early stopping criteria.

Additionally, Biosense Webster is initiating the Atrial Fibrillation Treatment Use Study protocol and is currently recruiting patients in this continued access study, following the same inclusion/exclusion and other protocol parameters as the IDE study population with the exception that this study is non-randomized (strictly THERMOCOOL group). This additional clinical trial will provide clinical data for similar paroxysmal AF patient population for consideration.

Thus, while the final sample size of 167 subjects may appear modest, the Bayesian approach provides a least burdensome, efficient and statistically valid approach. This approach demonstrated a posterior probability of essentially 1 that the THERMOCOOL group would have been found superior to the AAD (Control) group, had the original full sample size been enrolled. Therefore, it is a virtual certainty that the final posterior probability would have been larger than the ---- protocol-specified level needed for success had the full 230 subjects been enrolled.

4.5.3 Site Variations

Although stratification revealed site variations in the chronic effectiveness outcomes, there was a consistent treatment effect favoring the THERMOCOOL group. The treatment effect was also consistent in direction in the additional KM analyses that provided further characterization of the clinical study data. The observed site differences reflect "real world" practice patterns for treating AF.

The highest enrolling site (---- requires individual attention due to the exceptional effectiveness outcomes and large percentage of the subjects enrolled. The highest enrolling site (---- enrolled nearly 1/3 of the patients in this clinical trial and demonstrated an unusually high chronic success rate (100%) for the THERMOCOOL group. This substantially exceeds the primary effectiveness outcome for the Remaining Sites, as illustrated in Figure 4.5.3A.

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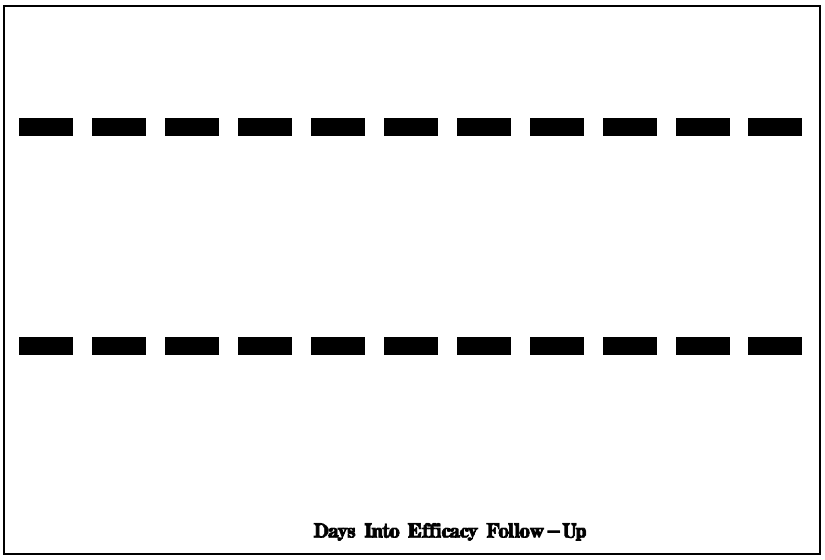
FIGURE 4.5.3A KM Curve of Time to Chronic Failures by ---- vs. Remaining Sites (Non- ----) - THERMOCOOL Group (n=103)



Note: Log rank test p-value < 0.0001; "Day 0" was defined as 90 days post-ablation procedures for Ablation Group.

The THERMOCOOL group at the Remaining Sites (Figure 4.5.3A) had a marked decrease in freedom from chronic failure during the first 30 days post-blanking period, and plateaus thereafter. This is attributed in part to the use of a new AAD during the effectiveness period as defined in the study protocol. The number of late chronic failures was relatively modest for subjects in this group. This graph shows the time to chronic failure for ---- vs. Remaining Sites showing a larger magnitude for the ---- site.

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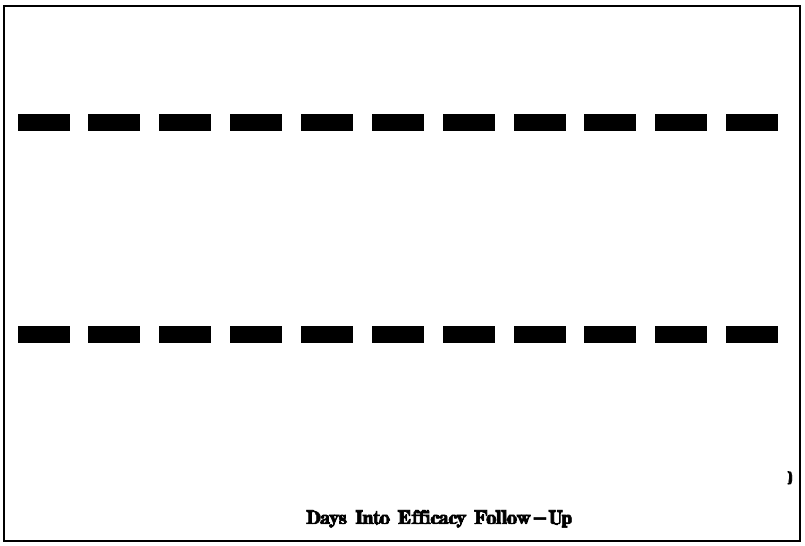
better chronic effectiveness outcomes as discussed in Section 3.6 (refer to Figures 3.6.3.1B and C) of this document. This is not surprising and corresponds with findings reported by Cappato and colleagues in which the overall success rate significantly increased (P<0.05) as the number of procedures performed per center increased.[62]

Other differences were observed regarding subjects enrolled at the ---- site. ---- subjects in both randomization groups had a statistically smaller left atrial mean dimensions and less hypertension compared to subjects at the other study sites (37.45 mm versus 41.34 mm, and 44% versus 51.3%, respectively). Additionally, prophylactic right-sided lines were placed in a higher proportion of ---- subjects (23/31) compared to non ---- subjects (1/72). While the ---- site investigator believed it was in the best interest of these subjects to minimize the risk of a repeat procedure, these additional ablation lines may have also contributed to the observed difference in effectiveness results.

For the AAD (Control) group, the main difference in the effectiveness outcomes between ---- and Remaining Sites is the relative time to event of the chronic effectiveness failures (cf. Figure 4.5.3B). It is possible that subtle differences in baseline covariates and medical management may have played a role. By the end of the effectiveness period, the magnitude of the difference was marginal (11% ---- vs.18% Remaining Sites).

FIGURE 4.5.3B KM Curve of Time to Chronic Failures by ---- vs. Remaining Sites (Non- ----) - AAD (Control) Group (n=56)



Note: Log rank test p-value = 0.1359; "Day 0" was defined as 14 days post initial treatment for AAD (Control) Group.

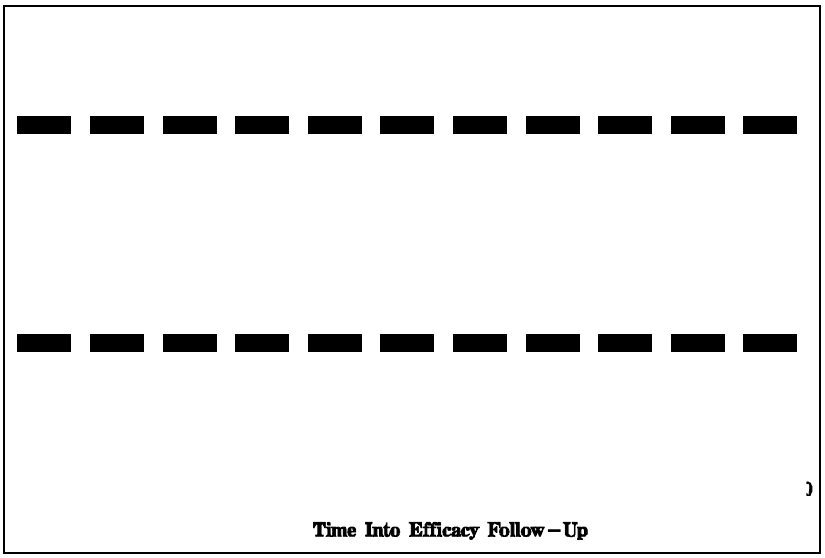
The effect of the ---- site and Non-US/Non- ---- results on the probability of superiority of the chronic effectiveness endpoint for the THERMOCOOL ablation group within the US sites was further evaluated. Various weighting schemes of sensitivity analyses involving Non-US and Non-US/Non- ---- primary effectiveness data were performed. Table 4.5.3A summarizes the probability of superiority for the US sites, borrowing (in a static fixed proportion way) from the ---- site and the Non-US/Non- ---- sites. So, this table reports the probability of superiority given the weighting of each "set of data". For example, if one borrows 20% (discounts by 80%) of Non-US/Non- ---- sites each, the probability of superiority is 0.991. The overall conclusion is that even if one heavily discounts ---- and Non-US sites, the result is still very compelling.

TABLE 4.5.3A: Sensitivity Analyses Varying Strengths of Borrowing of Non-US/ Non- ---- and ---- Site Data (June 2008 Dataset)

Probability of Superiority		---- Site										
		0	**0.10**	**0.20**	**0.30**	**0.40**	**0.50**	**0.60**	**0.70**	**0.80**	**0.90**	**1**
Non-US/ Non- ---- Sites	**0**	0.892	0.957	0.984	0.995	0.998	1	1	1	1	1	1
	0.10	0.915	0.966	0.988	0.996	0.999	1	1	1	1	1	1
	0.20	0.933	0.974	0.991	0.997	0.999	1	1	1	1	1	1
	0.30	0.947	0.980	0.993	0.998	0.999	1	1	1	1	1	1
	0.40	0.958	0.984	0.994	0.998	0.999	1	1	1	1	1	1
	0.50	0.967	0.987	0.996	0.998	1	1	1	1	1	1	1
	0.60	0.974	0.990	0.997	0.999	1	1	1	1	1	1	1
	0.70	0.980	0.992	0.997	0.999	1	1	1	1	1	1	1
	0.80	0.984	0.994	0.998	0.999	1	1	1	1	1	1	1
	0.90	0.987	0.995	0.998	0.999	1	1	1	1	1	1	1
	1	0.990	0.996	0.999	1	1	1	1	1	1	1	1

To further characterize the differences between the clinical outcomes experienced by ---- and Remaining Site subjects, additional KM analyses of time to any documented AF recurrence, symptomatic or asymptomatic, are presented below. Figure 4.5.3C presents the time to any documented recurrence for the THERMOCOOL group subjects stratified by these site groupings.

FIGURE 4.5.3C KM Curve of Time to Recurrence of Documented Symptomatic or Asymptomatic AF by ---- vs. Remaining Sites (Non- ----) - THERMOCOOL Group (n=103)

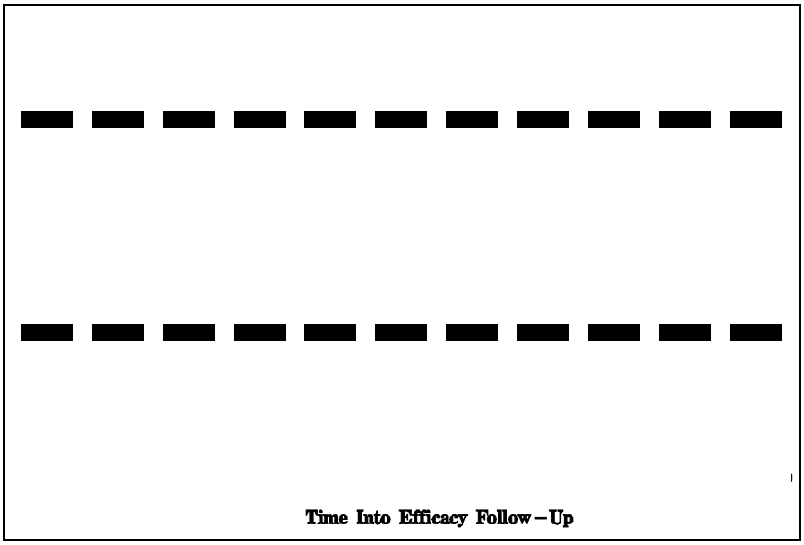


Note: Log rank test p-value = 0.0004. "Day 0" was defined as 90 days post-ablation procedures for THERMOCOOL Group.

The analysis of time to symptomatic or asymptomatic AF recurrence, when compared to the chronic effectiveness analysis, further confirms the treatment effect as it demonstrates that the subjects' arrhythmia was not simply rendered asymptomatic (cf. Figures 4.5.3A vs. C and B vs. D). Rather, a substantive decrease in AF disease burden was achieved. While TTM monitoring does not provide an absolute measure of burden, average

compliance with the TTM regimen was 93% at ---- . In fact, supplemental TTMs were provided on a near daily basis for all ---- subjects in accordance with the standard practice for patient management at this site.

FIGURE 4.5.3D KM Curve of Time to Recurrence of Documented Symptomatic or Asymptomatic AF by SRH vs. Remaining Sites (Non- ----) - AAD (Control) Group (n=56)



Note: Log rank test p-value =0.0187. "Day 0" was defined as 14 days post initial treatment for AAD (Control) Group.

Medical management of the ---- subjects conformed rigorously to the protocol yet differed in some regards from most other sites. THERMO OOL subjects at ---- were typically prescribed previously failed Class I or III AADs post-ablation and continued on the AAD until approximately 6 months post-ablation. The more typical practice at the Remaining Sites was to prescribe beta-blockers or calcium channel blockers post-ablation to THERMOCOOL subjects. The administration of a previously failed Class I or III AAD may have attributed to the better effectiveness result for the ---- site. As studied by Cappato and colleagues, an "additional 24% success rate (range among centers, 8.85 to 50.3%) was observed in the presence of AADs suggests that the changes in cardiac and PV tissue caused by ablation may, in some cases, be insufficient to eradicate the substrate for triggering and perpetuation of AF, but enough to enable control by formerly ineffective AADs."[62]

Rigorous conformance to the medical management and repeat ablation protocol requirements by the ---- investigational team also resulted in no (0/31) protocol-adjudicated (non-AF recurrence) chronic failures in the THERMOCOOL group. This contrasts with the remainder of the sites, from which 17% (12/72) of the THERMOCOOL group subjects were adjudicated as chronic failures without AF recurrence, for repeat ablation procedures between days 80 and 90 (n=2) or changes in AAD management outside the protocol specifications (n=10).

To characterize the effect of the ---- experience on overall safety, an additional analysis of the primary safety endpoint excluding ---- was performed. This analysis includes the remaining 93 subjects in the primary safety cohort. Thirteen (13) of the 93 (14%) non- ---- subjects who underwent ablation experienced a primary AE. Two subjects (2/46; 4.3%) at ---- who underwent an ablation procedure experienced a primary AE.

In conclusion, while site variations were observed in this trial as in many clinical studies, the primary justification for poolability across investigational sites remains on the basis of:

- The uniform study protocol with well-defined inclusion/exclusion criteria
- All sites were monitored to assure protocol compliance
- Data collection methods and instruments were identical across study sites.

Finally, the treatment effect is robust to all site stratifications, with a substantial difference in favor of THERMOCOOL catheter ablation effectiveness in every analysis.

4.5.4 Patients Failing AV Nodal Blocking Agents at Study Entry

There were 16% (26/167) patients in the trial that were enrolled due to failure of a rate control drug (AV nodal blocking agent), rather than a Class I or III drug. This was allowed in the FDA approved protocol. Failure of rate control usually means the patient is very symptomatic despite good rate control, or that the ventricular response rate during atrial fibrillation has not been adequately controlled, i.e., the rate control strategy was a clinical failure. Nonetheless, the same clinical decisions and considerations apply to such patients with regard to the use of beta-blockers and calcium channel blockers following catheter ablation for AF. There was no significant difference in chronic success results within either treatment arm between those failing Class I and III versus those failing only Class II and IV at baseline (refer to Table 3.6.4.2A).

5.0 Conclusions

Biosense Webster, Inc. has rigorously assessed both the effectiveness and safety parameters of the THERMOCOOL catheter for treating paroxysmal AF. The clinical trial data presented in this PMA supplement represent, in all likelihood, the most rigorously conducted and thoroughly vetted randomized controlled multicenter trial of catheter ablation for treatment of atrial fibrillation completed to date. The results of the prospectively planned analyses demonstrate that the NAVISTAR THERMOCOOL catheter met the protocol specified effectiveness endpoint with an acceptable safety profile.

Bayesian analysis methods have allowed Biosense Webster, Inc. to complete this study in an efficient, timely manner, while providing the valid scientific data from a randomized controlled trial to support PMA supplemental approval for Safety and Effectiveness.

In the U.S., the THERMOCOOL RF ablation catheter is currently market approved for the treatment of Type I atrial flutter (AFL) and for recurrent drug and device refractory sustained monomorphic Ventricular Tachycardia (VT) in post MI adults. The catheter is broadly used worldwide for both right- and left-sided ablation procedures.

The THERMOCOOL RF ablation catheter represents a major advancement in the field of ablation catheters. By maintaining low electrode tissue interface temperatures during RF application at high power (≤50 W) without an impedance rise, the catheter can produce larger lesions, thus reducing the time and the risk of tip charring that can lead to coagulum formation and the risk of thromboembolic events.[21,22]

The significant benefits associated with this technology have been thoroughly characterized in this clinical trial. These benefits include a superior chronic effectiveness outcome compared to conventional AAD therapy. Subjects randomized to THERMOCOOL catheter ablation were also twice as likely to be free from any documented AF recurrence, symptomatic or asymptomatic, at the end of the evaluation period than their counterparts randomized to AAD (Control) therapy. Further, significant improvement in Quality of Life, was shown in the THERMOCOOL group compared to the AAD (Control) group both clinically and statistically. From a safety standpoint, the THERMOCOOL group experienced only half the serious adverse event rate of the AAD (Control) group, an additional benefit compared to conventional AAD therapy.

Clinical Need

At present, effective treatment of atrial fibrillation (AF) represents a significant unmet clinical need. The effectiveness of AAD therapy for treating atrial fibrillation is quite variable, with the likelihood of AF recurrence in 6-12 months being at least 50% on most drugs.[30] Additionally, AAD therapy is associated with cumulative adverse effects over time.[1] Although AAD therapy remains first line therapy for the treatment of AF, its low success rates and intolerable drug adverse effects drive the search for a better treatment option for patients suffering from AF. Catheter ablation has accordingly become established second line therapy.[13,62]

Atrial fibrillation (AF) represents an important public health issue that is increasing each year. During the past decade, catheter ablation of atrial fibrillation has evolved rapidly from a highly experimental unproven procedure, to its current status as a commonly performed ablation procedure throughout the world.[13,62] Use of radiofrequency ablation of atrial fibrillation has grown so dramatically that it is now recognized as second line therapy and a standard of care in treatment guidelines, e.g., HRS/EHRA/ECAS Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation: Recommendations for Personnel, Policy, Procedures and Follow-up.[13] However, no ablation catheter has been market approved for treatment of AF in the U.S.

The benefits and risks associated with the NAVISTAR THERMOCOOL catheters have been well described in this clinical trial and reflected throughout the published literature. Public interest is best served by the timely review of the results of THERMOCOOL AF IDE study and rapid communication of AF ablation risks and benefits in FDA approved device labeling. Furthermore, an approved AF indication will permit company-sponsored training specific to AF treatment parameters to help assure that physicians use ablation catheters to treat AF in the most safe and effective manner.

Therefore, we conclude that the probable therapeutic benefits associated with the use of the NAVISTAR THERMOCOOL catheter for ablation therapy of paroxysmal AF outweigh the probable risks, when used in accordance with the proposed instructions for use.

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Appendix 9

Interim Analysis Report (---- Consultants) - Sept. 2007

Appendix 10

Clinical Report of First Interim Analysis

Report of the First Interim Analysis – September 2007 Dataset

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1.0 First Interim Analysis – September 24, 2007 Dataset

The FDA approved a Bayesian adaptive sample size on ---- (Protocol version). The protocol specified t ted when subject accrual reached sample sizes of ---- subjects. The interim analysis presented in this section is based on the September 24, 2007 dataset (N=160).

An independent consulting group (---- Consultants) performed the analysis and the findings are summarized in a report dated October 4, 2007 (Appendix 9). The results met the protocol's pre-specified effectiveness criteria for stopping enrollment and enrollment was stopped.

1.1 Subject Enrollment and Disposition

Study Period

The first study subject was enrolled on October 25, 2004 and the last subject, for this dataset, was enrolled on September 19, 2007. Effectiveness data in this section are based and derived from the analysis performed on October 4, 2007 by an independent consulting group, ---- Consulting, using the September 24, 2007 dataset. Follow-up data was collected through the 9-month follow-up period for subjects randomized to the AAD therapy and the 12-month follow-up period (including a 3-month blanking period) for subjects randomized to RF Ablation therapy with the THERMOCOOL catheter.

Subject Enrollment and Disposition

In this analysis, there were 160 enrolled subjects. Of these subjects, 101 were randomized to RF ablation with the THERMOCOOL catheter and 59 were randomized to AAD therapy. Table 1 shows the subject enrollment and accountability from the dataset obtained on September 24, 2007.

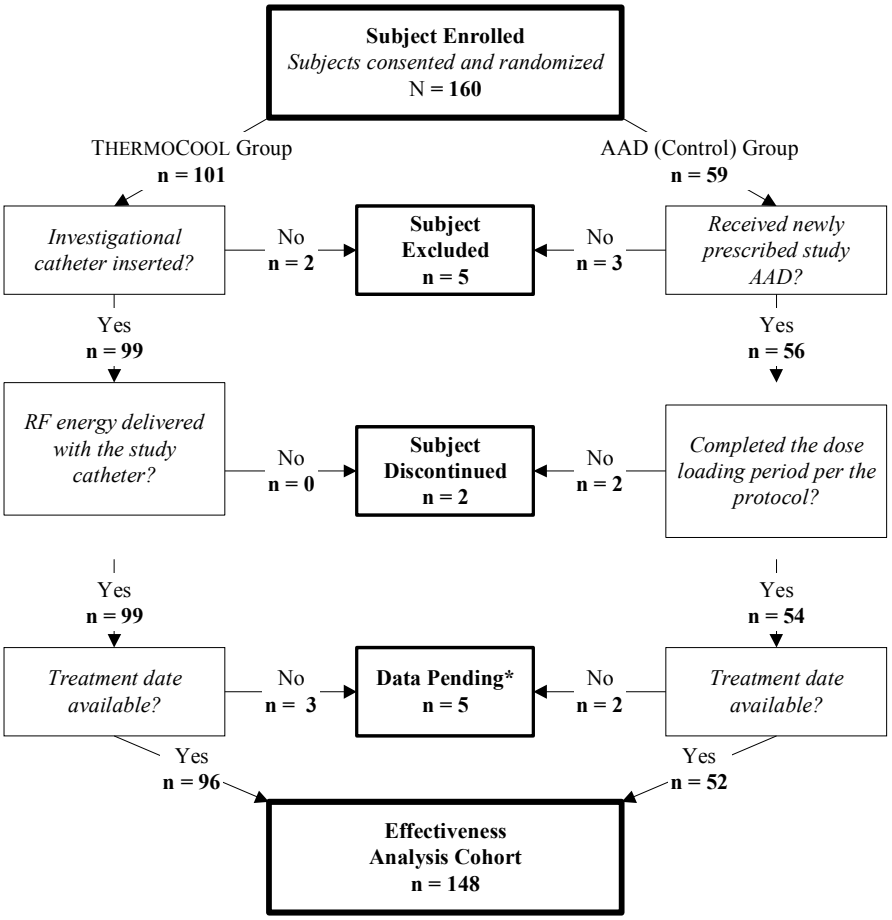
TABLE 1 Overall Subject Enrollment and Accountability (n=160)

Disposition	Treatment Group		Total
	THERMOCOOL	AAD (Control)	
Enrolled	**101**	**59**	**160**
Excluded	2	3	5
Discontinued	0	2	2
Data Pending*	3	2	5
Effectiveness Cohort	**96**	**52**	**148**

*Treatment date was unavailable at the time of the analysis.

Figure 1 illustrates how the enrolled subjects from the dataset were classified per the definitions in the study protocol.

FIGURE 1 Subject Enrollment and Accountability



*Treatment date was unavailable at the time of the analysis, precluding required time-to-event analyses.

Excluded Subjects

There were a total of 5 excluded subjects:

- Two (2) subjects were from the THERMOCOOL group
- Three (3) subjects were from the AAD (Control) group

Excluded subjects were not included in the Effectiveness Cohort since these subjects did not undergo ablation procedure. Reasons for exclusion by randomization assignment are explained in Table 2.

TABLE 2 Excluded Subjects (n = 5)

Subject ID	Description
THERMOCOOL Group Subjects	
----	Physician elected to withdraw the subject after randomization. No study catheter was inserted. Subject was diagnosed with persistent atrial fibrillation.
----	Insurance denied coverage for an RF ablation procedure with a study catheter and resulted in patient withdrawal.
AAD (Control) Group Subjects	
----	Subject withdrew consent after randomization to the AAD (Control) Group and elected to have a non-study RF ablation procedure.
----	Subject withdrew consent after randomization to the AAD (Control) Group. Subject refused hospitalization for dosing loading of the assigned study drug.
----	Subject withdrew consent after randomization. Subject had been prescribed a new AAD several weeks prior to enrollment. While on this new AAD, the subject was free of symptomatic atrial fibrillation and withdrew consent prior to capturing an episode.

Discontinued Subjects
There were a total of two discontinued subjects:

- No subjects in the THERMOCOOL group were discontinued from the study.
- Two from the AAD (Control) group.

The discontinued subjects were excluded from the Effectiveness Cohort since these subjects didn't undergo ablation procedure. Reasons for discontinuation by randomization assignment is explained in Table 3.

TABLE 3 Discontinued Subjects (n = 2)

Subject ID	Description
AAD (Control) Group Subjects	
----	Subject withdrew consent from the study. Subject was satisfied with results from the new AAD.
----	Subject withdrew consent after randomization and elected to have a non-study RF ablation procedure.

Table 4 presents summary demographics for the enrolled subjects at the time of this interim analysis. The majority of the enrolled subjects were male (65.6%; 105/160) and Caucasian (98.8%; 158/160). The mean age at time of enrollment was 56.2 ± 10.5 years and the age range was from 19 to 77 years. The two treatment groups are comparable in gender, ethnicity and age.

TABLE 4 Summary Demographics (Enrolled Subjects, N=160)

	Treatment Group		Total n/N (%)	P-value*
	THERMOCOOL n/N (%)	AAD (Control) n/N (%)		
Gender				0.3903
Female	32 / 101 (31.7)	23 / 59 (39.0)	55 / 160 (34.4)	
Male	69 / 101 (68.3)	36 / 59 (61.0)	105 / 160 (65.6)	
Ethnicity				1.0000
White	199 / 101 (98.0)	59 / 59 (100.0)	158 / 160 (98.8)	
Hispanic	1 / 101 (1.0)	0 / 59 (0.0)	1 / 160 (0.6)	
Other**	1 / 101 (1.0)	0 / 59 (0.0)	1 / 160 (0.6)	
Age (years)†				0.2764
N	101	59	160	
Mean	55.8	56.8	56.2	
Standard Deviation	9.28	12.38	10.50	
Median	57	59	58	
Minimum	32	19	19	
Maximum	76	77	77	

* P-value for comparing Ther ool Group vs. AAD (Control) Group
** Subject ---- was of ---- ethnicity.
†Age when informed consent signed.

1.2 Chronic Effectiveness

The primary effectiveness endpoint was the chronic success rate of the NAVISTAR THERMOCOOL catheter for the treatment of symptomatic PAF. It was expected that the THERMOCOOL group would be superior in chronic effectiveness outcome when compared to the AAD (Control) group.

A Bayesian adaptive sample size (from ---- to 2 lt of the planned interim analyses) was approved by the on ---- (protocol version 12.2). This approv

---

An interim analysis was performed in October 2007 per the IDE protocol by an independent consulting group (---- Consultants), and is summarized in a report dated October 4, 2007 (Appendix 9).

The results of the interim analysis met the pre-specified effectiveness criteria for stopping enrollment and therefore, enrollment was stopped.

One hundred and forty-eight (148) subjects were included for this interim effectiveness analysis. The predictive probability of success, based on full data available at the time of the interim analysis (including information on those patients with less than 9 months follow-up), was greater than 0.999. Since this was larger than the protocol specified cut-off of ---- , **subject accrual was stopped and the sample size at the time became the final le size**.

There were 85 subjects in the interim analysis that either had complete 9-month effectiven valuation follow-up information or were known failures. This number exceeded ---- of the 148 subjects that were enrolled at that time (85/148=57%), meeting the protocol criteria for an *early claim analysis* (---- complete effectiveness data).

Therefore, an *early claim analysis* was conducted and it was found that the predictive probability of superiority for the treatment group (posterior probability greater than ---- when the 148 subjects com follow-up) was >0.999. This was greater than the protocol specified cutoff of ---- and so the trial was **declared an early success**.

Details of the Interim Analysis

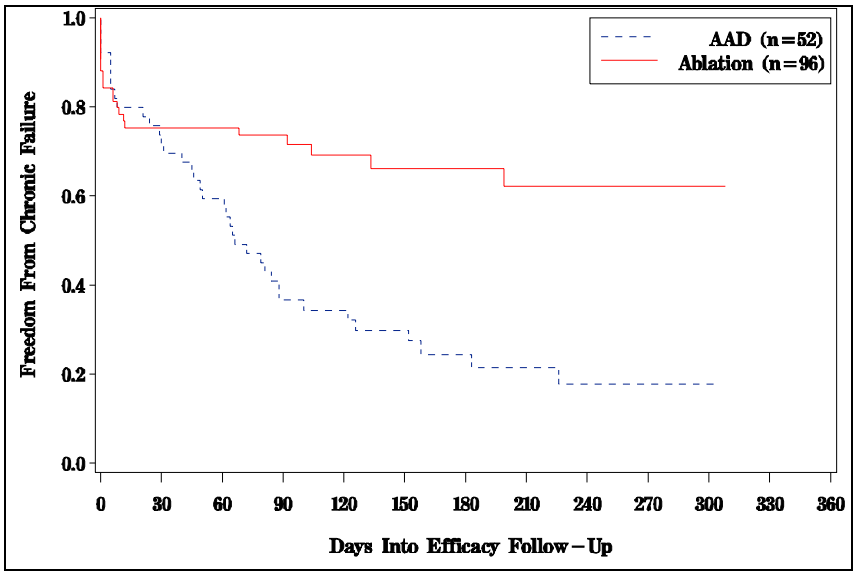
There were 148 subjects eligible for this interim analysis, 52 subjects in the AAD (Control) group and 96 subjects in the THERMOCOOL group. Table 5 is a breakdown of these subjects by exposure time (in months) and failures, for the three intervals in the time to event model.

TABLE 5 – Exposure Time (in Months) and Number of Failures Per Interval (n = 148)

Randomization Group	$0 < t \leq 0.5$		$0.5 < t \leq 2$		$2 < t \leq 9$	
	Expos	Failures	Expos	Failures	Expos	Failures
AAD (Control) (n = 52)	21.35	9	51.73	11	80.05	18
THERMOCOOL (n = 96)	28.87	20	70.75	0	164.34	5

Figure 2 shows the Kaplan-Meier survival curves for each of the treatment groups, based on the current data available. The solid line represents the THERMOCOOL group and the dashed line represents the AAD (Control) group.

FIGURE 2 A Kaplan-Meier Curve of Time to Chronic Failures By Randomization Group (Effectiveness Cohort, n=148)



* "Day 0" was defined 91 days post ablation procedures for ThermoCool Group and 15 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

Table 6 presents Kaplan-Meier life table of time to chronic failures by randomization group.

TABLE 6 Summary of InterimKaplan-Meier Analysis of Time to Chronic Failures By Randomization Group (Effectiveness Cohort, n=148)

Nominal Time Point [a]	THERMOCOOL Group (n=96)						AAD (Control) Group (n=52)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	96	17	9	0.9063	0.0297	(0.8479,0.9646)	52	3	3	0.9423	0.0323	(0.8789,1.0057)
Day 7	61	25	16	0.8130	0.0466	(0.7217,0.9043)	45	3	8	0.8399	0.0525	(0.7370,0.9428)
3-Weeks	48	29	20	0.7528	0.0546	(0.6458,0.8598)	39	3	10	0.7989	0.0574	(0.6865,0.9113)
1-Month	47	29	20	0.7528	0.0546	(0.6458,0.8598)	37	3	13	0.7375	0.0630	(0.6140,0.8609)
2-Months	47	29	20	0.7528	0.0546	(0.6458,0.8598)	29	3	20	0.5941	0.0703	(0.4563,0.7318)
3-Months	35	40	21	0.7364	0.0639	(0.6111,0.8617)	17	4	31	0.3657	0.0706	(0.2272,0.5041)
4-Months	24	49	23	0.6909	0.0784	(0.5372,0.8446)	15	5	32	0.3428	0.0718	(0.2022,0.4834)
5-Months	22	50	24	0.6609	0.0821	(0.5001,0.8217)	13	5	34	0.2971	0.0691	(0.1617,0.4325)
6-Months	19	53	24	0.6609	0.0883	(0.4878,0.8339)	8	8	36	0.2438	0.0749	(0.0969,0.3907)
7-Months	16	55	25	0.6220	0.0956	(0.4346,0.8094)	7	8	37	0.2133	0.0715	(0.0731,0.3534)
8-Months	16	55	25	0.6220	0.0956	(0.4346,0.8094)	5	9	38	0.1777	0.0721	(0.0365,0.3190)
9-Months	11	61	25	0.6220	0.1209	(0.3850,0.8590)	3	11	38	0.1777	0.0931	(0.0000,0.3601)
10-Months	4	67	25	0.6220	0.1912	(0.2472,0.9968)	1	13	38	0.1777	0.1612	(0.0000,0.3601)
11-Months	0	71	25	-	-	-	0	14	38	-	-	-
12-Months	0	71	25	-	-	-	0	14	38	-	-	-

a 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, 6 months = 183 days, 7 months = 213 days, 8 months = 244, 9 months = 274 days, 10 months = 305 days, 11 months = 335 days, 12 months = 365 days.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined as day-91 post initial ablation procedure for THERMOCOOL Group and day-15 post initial treatment for AAD (Control) Group. Events occurring prior to Day 0 were considered failures at Day 0.

[d] Based on Peto method

[e] Represents 95% pointwise confidence intervals using Peto standard error

The status of the 148 subjects in the Effectiveness Cohort is reported in Table 7. At the time of this analysis, subjects were classified as either a "Success," "Failure," or were "Censored." Subjects classified as "Censored" had not failed for effectiveness but were still in their 9-month effectiveness evaluation window.

TABLE 7 – Status of the Enrolled Subjects (Effectiveness Cohort, n=148)

Randomization Group	Success	Censored	Failure	n
THERMOCOOL (n = 96)	16	55	25	96
AAD (Control) (n = 52)	6	8	38	52

The posterior mean probability of success for the AAD (Control) group was 0.125, with a standard deviation of 0.047. In the THERMOCOOL group, the posterior mean probability of success was 0.568 with a standard deviation of 0.069. The posterior probability that the THERMOCOOL group would be superior to the AAD (Control) group was 1. The predictive probability, that the posterior probability of superiority for the THERMOCOOL group would be greater than 0.98 when all 148 subjects completed their 9-month follow-up, was 1.

Figure 3 shows the predictive distribution of the successful outcome for the 52 subjects randomized to AAD therapy. Figure 4 shows the predictive distribution for the 96 subjects randomized to RF ablation therapy with the THERMOCOOL catheter. The most likely outcome is 9/52 (17.31%) successes in the AAD (Control) group and 59/96 (61.46%) successes in the THERMOCOOL group.

FIGURE 3 Predictive Distribution of Success in the AAD (Control) Group (n=52)

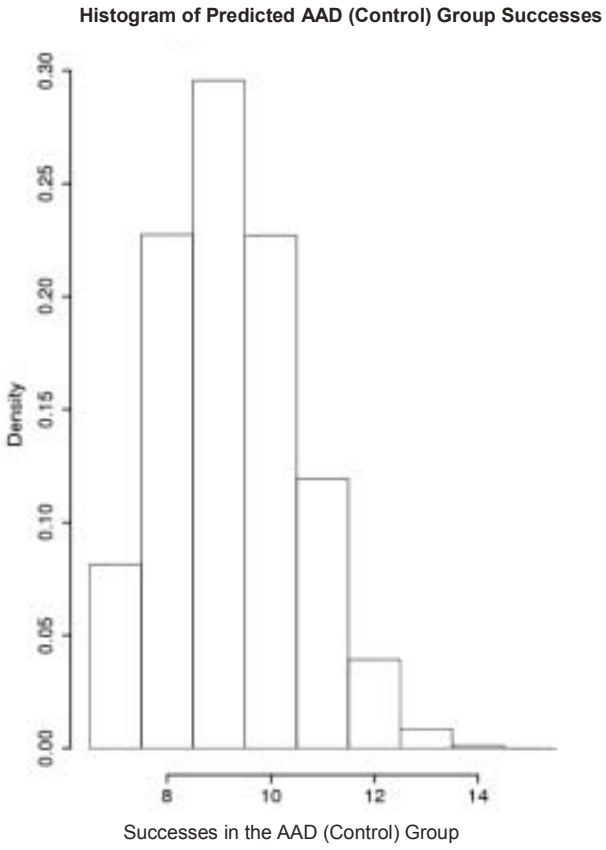
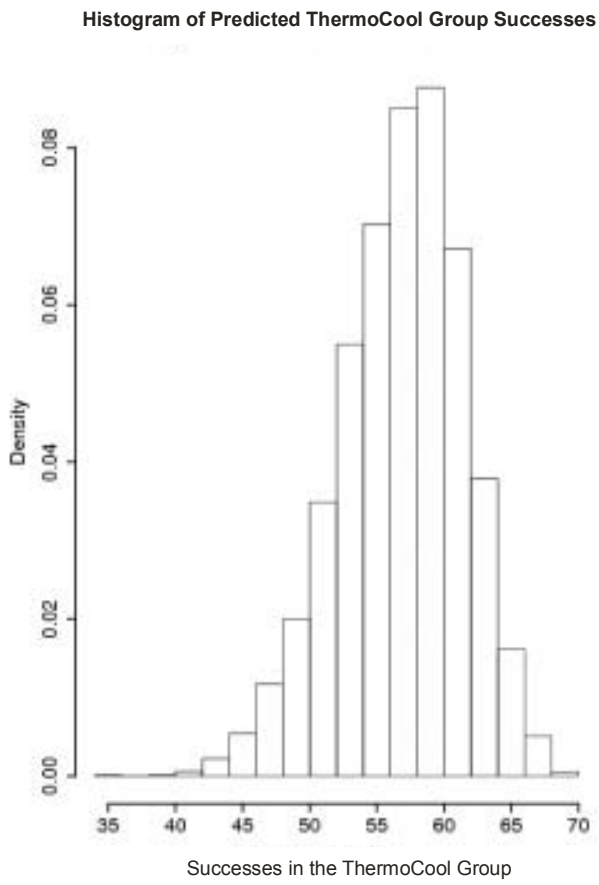


FIGURE 4 – Predictive Distribution of Success in the THERMOCOOL Group (n=96)



Various sensitivity analyses were done to check the sensitivity to the prior distribution and the predictive model. In each analysis, the predictive probability of trial success with the current 148 subjects was greater than 0.995, demonstrating the robustness of the interim analysis.

1.3 Safety Data

At the time of the interim analysis (September 2007 dataset), 160 subjects were enrolled and randomized to either the AAD (Control) group (n=59) or THERMOCOOL group (n=101). Of the 160 subjects, 7 subjects were either excluded or discontinued prior to receiving treatment, 5 subjects with data pending and 24 subjects not treated with study catheter, therefore, 124 subjects undergoing ablation are included in the Primary Safety Cohort.

The primary safety endpoint for this study was defined as the incidence of early onset (within 7 days of ablation procedure) specific adverse events, designated as primary adverse events for subjects undergoing a study ablation procedure.

TABLE R 8 Accountability for Primary Safety Cohort (n=124)

Disposition	THERMOCOOL	AAD (Control)	Total
Enrolled	101	59	160
Excluded / Discontinued	2	5	7
Data Pending*	3	2	5
Not Treated With Study Catheter	0	24	24
Primary Safety Cohort	96	28	124

* Treatment date was unavailable at the time of the analysis.

Deaths

There were no subject deaths at the time of this analysis.

Primary Safety Analyses

The primary safety endpoint is defined as the incidence of early onset (within 7 days of a study ablation procedure) primary AEs. There are 18 categories of primary AEs established in the study protocol and presented in Table R 3.6.5.1B of the clinical report (refer to clinical report section 2.2.8 for more details).

This analysis is based on the Primary Safety Cohort included all subjects undergoing an RF ablation procedure with the investigational catheter. As shown above, Table R 8 summarizes accountability of the Primary Safety Cohort (n = 124).

There were 124 subjects included in the Primary Safety Cohort. This cohort is composed of 96 subjects from the THERMOCOOL group and 28 subjects randomized to AAD (Control) group and who underwent a study ablation procedure after achieving the effectiveness outcome.

Table R 9 below presents the protocol-established endpoint and safety results based on the Primary Safety Cohort at the time of this interim analysis. The safety endpoint specified in the protocol was 7.0% (upper confidence bound of 16.0%). The percentage of subjects who experienced a primary AE was 7.3 % (9/124) with associated upper confidence bound of 12.3%.

The primary safety result met the protocol-established criteria for this study at the time of this interim analysis.

TABLE R 9 Primary Safety Endpoint Outcome – Primary Adverse Events (Primary Safety Cohort, n = 124)

	Protocol Established Endpoint	n
Number of Subjects in Safety Cohort		124
Number of Subjects with Primary AEs		9
% Primary AEs	7.0	7.3
One-sided 95% Confidence Bound*	16.0	12.3

* Exact binomial using a commercially available software package.

Table R 10 summarizes the early onset serious primary AEs. There were 10 reported serious primary AEs in 9 subjects. None of the primary AEs resulted in death, cardiovascular accident, stroke, tamponade, perforation, AV-fistula, myocardial infarction, thromboembolism, transient ischemic attack, pneumothorax, pericardial effusion, pericarditis, pulmonary vein stenosis, diaphragmatic paralysis, or heart block.

The majority of primary AEs were hospitalizations (70.0%; 7/10). One (1) of the primary AEs was pulmonary edema ( ). The remaining 2 primary AEs were post-procedure vascular access complications. Refer to primary AE summaries in Appendix 15 of the PMA for details.

TABLE R 10 Primary Safety Endpoint - Early Onset of Primary Adverse Events (Primary Safety Cohort, n=124)

Description	Total Number of Primary AEs n (%)	Subject ID
Total Primary AEs	**10**	
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 (10.0%)	----
Pericarditis	0	--
Hospitalization (initial and prolonged)	7(70.0%)	
Pericardial Effusion	0	--
Vascular Access Complication	2 (20.0%)	

* Subject ---- was hospitalized for pulmonary edema. The adverse event was classified as a hospitalization.
** Subject ---- was hospitalized on two occasions.
***Subject ---- remained in the hospital one extra day, post ablation procedure, because of pericardial effusion. The adverse event was classified as a hospitalization.

Table R 11 summarizes all primary AEs by causality (i.e. device-related, possibly device-related, procedure-related, possibly procedure-related, and unrelated to the device or procedure). The proportion of subjects who experienced a primary AE that were potentially attributable to the device was only 0.8 % (1/124); specifically, 0 were classified as device-related and one (1) as possibly device-related.

TABLE R 11 Primary AEs by Causality (Primary Safety Cohort, n=124)

Description	No. of AEs	Subject IDs
Primary AEs	**10**	**9***
Device-related	**0**	
Possibly Device-related	**1**	
Respiratory Disorder		
Pulmonary Edema	1	----
Procedure-related	**6**	
Cardiac Disorder		
Pericardial Effusion	1	----
Vascular Disorder		
AV Fistula	2	---- ----
Edema, SOB and lower extremity pain	1	----
Hematoma	1	----
Blood and Lymph System Disorder		
Decreased Hemoglobin	1	----
Possibly Procedure-related	**0**	
Unrelated to Device or Procedure	**3**	
Cardiac Disorder		
AF recurrence	3	---- ---- ----

* A Primary AE could be listed in more than one causality category.
** Subject ---- experienced 2 Primary AEs.

1.4 Poolability

The primary justification for poolability across investigational sites is made on a clinical basis (Meinert, 1986): that there was a uniform study protocol with well-defined inclusion/exclusion criteria and data collection methods and sites were monitored to verify protocol compliance across study sites. Participating sites included in this clinical report were in the [redacted] Typically, differences among site characteristics are considered to reflect variability in the overall subject population and clinical practice patterns. The poolability analyses were performed based on the September 2007 dataset.

1.4.1 Statistical Methods

Comparability across sites was assessed statistically. The baseline prognostic factors and co-morbid conditions that were included in these analyses consisted of:

- Demographics: Gender, age
- Medical History: SVT (AVNRT, accessory pathway, atrial tachycardia), atrial flutter, congenital heart disease, congestive heart failure, deep vein thrombus, diabetes, hypertension, hypertrophic cardiomyopathy, ischemic cardiomyopathy, left ventricular hypertrophy, non-ischemic dilated cardiomyopathy, pulmonary embolus, significant valve disease/replacement, cerebrovascular accident (cerebrovascular accident possibly secondary to thromboembolism & cerebrovascular accident not secondary to thromboembolism), transient ischemic attacks, ventricular fibrillation, ventricular tachycardia, NYHA heart failure class
- AF History: Number of symptomatic AF episodes within the past 6 months, any previous catheter ablation procedures for arrhythmias other than AF
- Liver Function: Baseline ALT, AST, ALP
- Cardiac Medical History: Antiarrhythmic and/or cardiac medications as follows:
  - Class I: Disopyramide, Flecainide, Propafenone, Quinidine
  - Class III: Amiodarone, Dofetilide, Sotalol
  - Beta-Blocker: Acebutolol, Atenolol, Metoprolol, Propranolol, other Beta-Blocker
  - Calcium Channel Blocker: Diltiazem, Verapamil, other Calcium Channel Blocker
  - Digoxin
- Neuro Exam: Baseline neurological exam outcome.
- TTE: Baseline left atrial dimension and left ventricular ejection fraction (LVEF)

A site term was included to evaluate if there are site differences. In order to allow for convergence of the logistic regression algorithm, sites were grouped as follows based on the Effectiveness Analysis Cohort:

- Group 1 (n=26): sites enrolling ≤ 5 subjects
- Group 2 (n=23): sites enrolling ≥ 6 to ≤10 subjects
- Group 3 (n=24): sites enrolling ≥ 11 to ≤15 subjects
- The remaining sites including site ---- (n=49) and ---- (N=26) were not grouped.

Additional grouping methods for sites were used and the site terms were included in the logistic regression analysis. These include:

(a) Including a "Non-US vs. US sites" term: A new site term, Non-US vs. US sites, was created. The Non-US sites include 93 subjects from ---- ---- ---- and ---- The US sites include 55 subjects from the remaining sites.

(b) Including a "High Enrolling vs. Low to Medium Enrolling Sites" term: According to section 7.2.3 in the study protocol (version 12.2), a site enrolled more than 20 subjects is considered as a high enrolling site and a site enrolled less than or equal to 20 subjects is considered as a low to medium enrolling site. The high enrolling sites include 75 subjects from ---- and ---- The low to medium enrolling sites include 73 subjects from the remaining sites.

(c) Including a " ---- vs. the remaining sites (Non- ---- sites)" term: Since ---- had the highest enrollment, a new site term, ---- vs. Non- ---- sites, was created. ---- site include 49 subjects and Non- ---- sites include 99 subjects.

COMPARISON AMONG SITES

All categorical covariates, such as gender (male/female) and SVT (yes/no), were compared among sites using Fisher's Exact test due to the discrete nature of the covariates. The Monte Carlo method was used, with 10,000 samples (the SAS default) because of the size of the tables. Comparisons among sites for all continuous covariates, such as age and LVEF, were performed using Kruskal-Wallis test due to the violation of normality assumption of the distribution.

LOGISTIC REGRESSION ANALYSIS OF CHRONIC SUCCESS OUTCOME

To further assess the comparability across sites and identify potential significant predictors of chronic success, a formal evaluation of baseline prognostic factors and co-morbid conditions was performed using logistic regression analysis. To screen these potential covariates, comparison analyses among sites and a univariate logistic regression analysis for each covariate with an adjustment of randomization group were performed separately and the summary is provided in Table 12.

An arbitrary cut-off of p-value < 0.20 was used for the purpose of screening covariates from comparison analyses among sites and univariate logistic regression analyses. Multivariate logistic regression analyses with an adjustment of randomization group were then conducted using those covariates that survived the initial screening process.

A forward selection algorithm was used for the covariates to enter into the multivariate logistic regression model starting with the lowest p-value from the univariate logistic regression analysis. A cut-off of p-value < 0.05 was used for the covariates to remain in the final model.

1.4.2 Comparison Analyses among sites & Univariate Logistic Regression

All enrolled subjects (n=160) were evaluated for the comparison among sites since the primary emphasis in these analyses was the baseline characteristics. The subjects in the Effectiveness Analysis Cohort (n=148), for whom their chronic efficacy outcome was determined, were included in the logistic regression for the prediction of chronic success. Due to the interim data, 63 subjects are still in the 9-month follow-up effectiveness

assessment period and have not met the chronic effectiveness endpoint at the time of data received. Therefore, these analyses were based on 85 subjects in which 41 subjects are from the RF Ablation Group and 44 subjects are from the AAD Group.

Table 12 shows the results of the comparison among sites and also summarizes the potential predictors of chronic success in the univariate logistic regression models. Based on the comparison analyses among sites, the p-value less than 0.05 indicates there were site differences on the corresponding covariate. These include age, SVT, NYHA heart failure class, symptomatic AF episodes, class I AAD usage, beta-blocker usage, calcium channel blocker usage, outcome of neurological exam, LA dimension, and LVEF.

Table 12. Comparison of Covariates Among Sites and Univariate Logistic Regression Model of Chronic Success Outcome

Covariate	Comparison of Covariate Among Sites (All Enrolled Subjects, n=160)		Covariate As a Univariate Predictor of Chronic Success Adjusting For Randomization Group (Efficacy Analysis Cohort, n=148)	
	Number of Subjects in the Analysis[a]	p-value [a]	Number of Subjects in the Analysis[a]	p-value
Age	160	0.0134*	85	0.7139
Gender	160	0.3795	85	0.9767
SVT	152	0.0027*	85	0.3901
AFL	147	0.1305*	80	0.9334
Congenital Heart Disease	153	0.8974	85	N/A[c]
Congestive Heart Failure	152	0.6863	84	0.6330
Deep Vein Thrombus	152	0.8309	84	N/A[c]
Diabetes	153	0.2982	85	0.1548*
Hypertension	153	0.8880	85	0.2407
Hypertrophic Cardiomyopathy	153	0.5482	85	N/A[c]
Ischemic Cardiomyopathy	153	0.8836	85	0.8922
Left Ventricular Hypertrophy	153	0.4028	85	N/A[c]
Non-Ischemic Dilated	153	N/A[b]	85	N/A[c]
Pulmonary Embolus	153	0.8974	85	N/A[c]
Significant Valve Disease	153	0.6105	85	N/A[c]
Cerebrovascular Accident	152	0.5098	85	0.6409
Transient Ischemic Attacks	153	0.5482	85	N/A[c]
Ventricular Fibrillation	153	N/A[b]	85	N/A[c]
Ventricular Tachycardia	153	0.8974	85	N/A[c]
NYHA Heart Failure Class	141	<0.0001*	77	0.6819
Symptomatic AF Episodes (6 Months prior to enrollment)	143	<0.0001*	80	0.1743*
Previous Catheter Ablation	153	0.0693*	85	0.9972
ALT Value Normal	135	0.1987*	73	N/A[c]
AST Value Normal	134	0.1056*	72	N/A[c]

ALP Value Normal	125	0.1813*	65	N/A[c]
Class I AAD Usage	160	<0.0001*	85	0.2935
Class III AAD Usage	160	0.0769*	85	0.9280
Beta Blocker Usage	160	<0.0001*	85	0.8095
Calcium Channel Blocker Usage	160	0.0115*	85	0.3454
Digoxin	160	0.2633	85	0.7290
Neurological Exam	120	0.0077*	66	0.8397
LA Dimension	137	0.0075*	77	0.7667
LVEF	138	<0.0001*	79	0.7277
Grouped Sites			85	0.7676
Non-US vs. US Sites			85	0.1835*
High Enrolling vs. Low to Medium Enrolling Sites			85	N/A[c]
---- vs. Non- ---- Sites			85	N/A[c]

[a] P-value based on Fisher's exact test for discrete covariates and Kruskal Wallis test for continuous covariates
[b] Analysis not performed due to no subjects with the specific medical condition
[c] Analysis not performed due to complete/quasicomplete data in the logistic regression analysis
* Denote p-value less than 0.20

1.4.3 Multivariate Logistic Regression analysis

The covariates with a p-value less than 0.20 either from comparison analyses among sites or univariate logistic regression (refer to Table 12) were considered as potential covariates for entering into the multivariate logistic regression model. The covariates that survived the screening process include: diabetes, symptomatic AF episodes, Non-US vs. US sites, class I AAD usage, calcium channel blocker, SVT, NYHA heart failure class, age, LVEF, left atrium dimension, beta-blocker usage, outcome of neurological exam, class III AAD usage, AFL, and previous catheter ablation. Three covariates (ALT value normal, AST value normal, and ALP value normal) were not included in the model building process due to a small number of subjects in some cells of the logistic regression model.

Table 13 presents the final multivariate logistic regression model includes randomization group

In conclusion, there was no site factor in the final multivariate model indicating no site difference on the chronic success outcome was observed. Therefore, the poolability among sites is statistically justified.

Table 13. Final Multivariate Logistic Regression Model of Chronic Success (Effectiveness Analysis Cohort, n=148*)

Covariate	**Odds Ratio**	**95% CL**	**p-value**
Randomization Group (RF Ablation Group vs. AAD Group)	4.05	1.40-11.76	0.0100

* 85 subjects with chronic outcome and covariate data available

Appendix 11

Updated Analysis Report (---- Consultants) - June 2008

Appendix 12

Kaplan-Meier Source Tables for Section 3.6.3

TABLE 1A Summary of KM Analysis of Time to Chronic Failures By Randomization Group (Effectiveness Analysis Cohort, n=159) – Reference to Figure 3.6.3.1A

Nominal Time Point [a]	THERMOCOOL Group (n=103)						AAD (Control) Group (n=56)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0[c]	103	3	8	0.9223	0.0264	(0.8706,0.9740)	56	0	4	0.9286	0.0344	(0.8611,0.9960)
Day 7	83	4	20	0.8020	0.0399	(0.7238,0.8802)	49	0	11	0.8036	0.0531	(0.6995,0.9076)
3-Weeks	71	5	27	0.7304	0.0450	(0.6422,0.8186)	42	0	14	0.7500	0.0579	(0.6366,0.8634)
1-Month	69	5	29	0.7098	0.0460	(0.6196,0.8001)	39	0	18	0.6786	0.0624	(0.5563,0.8009)
2-Months	69	5	29	0.7098	0.0460	(0.6196,0.8001)	29	0	27	0.5179	0.0668	(0.3870,0.6487)
3-Months	66	5	32	0.6790	0.0474	(0.5862,0.7718)	19	0	37	0.3393	0.0633	(0.2153,0.4633)
4-Months	63	6	34	0.6581	0.0485	(0.5631,0.7531)	16	0	40	0.2857	0.0604	(0.1674,0.4040)
5-Months	62	6	35	0.6476	0.0488	(0.5520,0.7433)	13	0	43	0.2321	0.0564	(0.1216,0.3427)
6-Months	61	8	35	0.6476	0.0496	(0.5504,0.7449)	11	0	45	0.1964	0.0531	(0.0924,0.3005)
7-Months	54	13	36	0.6363	0.0522	(0.5339,0.7386)	10	0	46	0.1786	0.0512	(0.0783,0.2789)
8-Months	52	16	36	0.6363	0.0537	(0.5310,0.7416)	7	2	47	0.1587	0.0550	(0.0509,0.2666)
9-Months	37	31	36	0.6363	0.0640	(0.5109,0.7616)	2	7	47	0.1587	0.1029	(0,0.3605)
10-Months	15	52	36	0.6363	0.0991	(0.4421,0.8305)	0	9	47	-	-	-
11-Months	3	64	36	0.6363	0.2215	(0.2021,1.0705)	0	9	47	-	-	-
12-Months	2	65	36	0.6363	0.2713	(0.1045,1.1681)	0	9	47	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 1B Summary of KM Analysis of Time to Chronic Failures - Non-US Sites (n=95) – Reference to Figure 3.6.3.1B

Nominal Time Point [a]	THERMOCOOL Group (n=60)						AAD (Control) Group (n=35)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0[c]	60	0	4	0.9333	0.0322	(0.8702,0.9965)	35	0	1	0.9714	0.0282	(0.9162,1.0266)
Day 7	54	0	8	0.8667	0.0439	(0.7807,0.9527)	33	0	6	0.8286	0.0637	(0.7037,0.9534)
3-Weeks	49	1	10	0.8330	0.0486	(0.7377,0.9283)	28	0	7	0.8000	0.0676	(0.6675,0.9325)
1-Month	49	1	10	0.8330	0.0486	(0.7377,0.9283)	26	0	10	0.7143	0.0764	(0.5646,0.8639)
2-Months	49	1	10	0.8330	0.0486	(0.7377,0.9283)	20	0	15	0.5714	0.0836	(0.4075,0.7354)
3-Months	47	1	12	0.7990	0.0523	(0.6966,0.9014)	11	0	24	0.3143	0.0785	(0.1605,0.4681)
4-Months	45	2	13	0.7816	0.0544	(0.6749,0.8883)	10	0	25	0.2857	0.0764	(0.1361,0.4354)
5-Months	45	2	13	0.7816	0.0544	(0.6749,0.8883)	7	0	28	0.2000	0.0676	(0.0675,0.3325)
6-Months	45	3	13	0.7816	0.0551	(0.6737,0.8896)	6	0	29	0.1714	0.0637	(0.0466,0.2963)
7-Months	41	5	14	0.7630	0.0580	(0.6493,0.8767)	5	0	30	0.1429	0.0591	(0.0269,0.2588)
8-Months	41	5	14	0.7630	0.0580	(0.6493,0.8767)	5	0	30	0.1429	0.0591	(0.0269,0.2588)
9-Months	31	16	14	0.7630	0.0678	(0.6301,0.8959)	0	5	30	-	-	-
10-Months	14	32	14	0.7630	0.0993	(0.5685,0.9576)	0	5	30	-	-	-
11-Months	3	43	14	0.7630	0.2145	(0.3427,1.1833)	0	5	30	-	-	-
12-Months	2	44	14	0.7630	0.2626	(0.2482,1.2778)	0	5	30	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 1C Summary of KM Analysis of Time to Chronic Failures - US Sites (n=64) – Reference to Figure 3.6.3.1C

Nominal Time Point [a]	THERMOCOOL Group (n=43)						AAD (Control) Group (n=21)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0[c]	43	3	4	0.9070	0.0443	(0.8202,0.9938)	21	0	3	0.8571	0.0764	(0.7075,1.0068)
Day 7	28	4	12	0.7054	0.0737	(0.5610,0.8498)	16	0	5	0.7619	0.0929	(0.5797,0.9441)
3-Weeks	22	4	17	0.5748	0.0799	(0.4182,0.7314)	14	0	7	0.6667	0.1029	(0.4650,0.8683)
1-Month	20	4	19	0.5225	0.0807	(0.3643,0.6808)	13	0	8	0.6190	0.1060	(0.4113,0.8267)
2-Months	20	4	19	0.5225	0.0807	(0.3643,0.6808)	9	0	12	0.4286	0.1080	(0.2169,0.6402)
3-Months	19	4	20	0.4964	0.0808	(0.3380,0.6548)	8	0	13	0.3810	0.1060	(0.1733,0.5887)
4-Months	18	4	21	0.4703	0.0807	(0.3122,0.6284)	6	0	15	0.2857	0.0986	(0.0925,0.4789)
5-Months	17	4	22	0.4442	0.0803	(0.2867,0.6016)	6	0	15	0.2857	0.0986	(0.0925,0.4789)
6-Months	16	5	22	0.4442	0.0828	(0.2819,0.6064)	5	0	16	0.2381	0.0929	(0.0559,0.4203)
7-Months	13	8	22	0.4442	0.0918	(0.2642,0.6242)	5	0	16	0.2381	0.0929	(0.0559,0.4203)
8-Months	11	11	22	0.4442	0.1047	(0.2389,0.6494)	2	2	17	0.1786	0.1144	(0,0.4029)
9-Months	6	15	22	0.4442	0.1352	(0.1792,0.7091)	2	2	17	0.1786	0.1144	(0,0.4029)
10-Months	1	20	22	0.4442	0.3311	(0,1.0932)	0	4	17	-	-	-
11-Months	0	21	22	-	-	-	0	4	17	-	-	-
12-Months	0	21	22	-	-	-	0	4	17	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 1D Summary of KM Analysis of Time to Chronic Failures - High Enrolling Sites (n=75) – Reference to Figure 3.6.3.1D

Nominal Time Point [a]	THERMOCOOL Group (n=48)						AAD (Control) Group (n=27)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0[c]	48	0	2	0.9583	0.0288	(0.9018,1.0149)	27	0	1	0.9630	0.0363	(0.8917,1.0342)
Day 7	45	0	3	0.9375	0.0349	(0.8690,1.0060)	26	0	5	0.8148	0.0748	(0.6683,0.9613)
3-Weeks	43	0	5	0.8958	0.0441	(0.8094,0.9823)	21	0	6	0.7778	0.0800	(0.6210,0.9346)
1-Month	43	0	5	0.8958	0.0441	(0.8094,0.9823)	19	0	9	0.6667	0.0907	(0.4889,0.8445)
2-Months	43	0	5	0.8958	0.0441	(0.8094,0.9823)	14	0	13	0.5185	0.0962	(0.3301,0.7070)
3-Months	43	0	5	0.8958	0.0441	(0.8094,0.9823)	7	0	20	0.2593	0.0843	(0.0940,0.4246)
4-Months	42	1	5	0.8958	0.0446	(0.8084,0.9833)	7	0	20	0.2593	0.0843	(0.0940,0.4246)
5-Months	42	1	5	0.8958	0.0446	(0.8084,0.9833)	5	0	22	0.1852	0.0748	(0.0387,0.3317)
6-Months	42	2	5	0.8958	0.0452	(0.8073,0.9843)	5	0	22	0.1852	0.0748	(0.0387,0.3317)
7-Months	39	3	6	0.8734	0.0498	(0.7759,0.9710)	4	0	23	0.1481	0.0684	(0.0142,0.2821)
8-Months	39	3	6	0.8734	0.0498	(0.7759,0.9710)	4	0	23	0.1481	0.0684	(0.0142,0.2821)
9-Months	30	13	6	0.8734	0.0577	(0.7603,0.9865)	0	4	23	-	-	-
10-Months	13	29	6	0.8734	0.0862	(0.7045,1.0423)	0	4	23	-	-	-
11-Months	3	39	6	0.8734	0.1794	(0.5218,1.2251)	0	4	23	-	-	-
12-Months	2	40	6	0.8734	0.2197	(0.4428,1.3041)	0	4	23	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 1E Summary of KM Analysis of Time to Chronic Failures - Low to Medium High Enrolling Sites (n=84) – Reference to Figure 3.6.3.1E

Nominal Time Point [a]	THERMOCOOL Group (n=55)						AAD (Control) Group (n=29)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0[c]	55	3	6	0.8909	0.0420	(0.8085,0.9733)	29	0	3	0.8966	0.0566	(0.7857,1.0074)
Day 7	38	4	17	0.6779	0.0650	(0.5504,0.8053)	23	0	6	0.7931	0.0752	(0.6457,0.9405)
3-Weeks	28	5	22	0.5763	0.0709	(0.4373,0.7152)	21	0	8	0.7241	0.0830	(0.5615,0.8868)
1-Month	26	5	24	0.5351	0.0716	(0.3948,0.6753)	20	0	9	0.6897	0.0859	(0.5213,0.8580)
2-Months	26	5	24	0.5351	0.0716	(0.3948,0.6753)	15	0	14	0.5172	0.0928	(0.3354,0.6991)
3-Months	23	5	27	0.4733	0.0716	(0.3330,0.6137)	12	0	17	0.4138	0.0915	(0.2345,0.5930)
4-Months	21	5	29	0.4322	0.0711	(0.2929,0.5715)	9	0	20	0.3103	0.0859	(0.1420,0.4787)
5-Months	20	5	30	0.4116	0.0706	(0.2732,0.5500)	8	0	21	0.2759	0.0830	(0.1132,0.4385)
6-Months	19	6	30	0.4116	0.0724	(0.2696,0.5536)	6	0	23	0.2069	0.0752	(0.0595,0.3543)
7-Months	15	10	30	0.4116	0.0815	(0.2518,0.5714)	6	0	23	0.2069	0.0752	(0.0595,0.3543)
8-Months	13	13	30	0.4116	0.0911	(0.2330,0.5902)	3	2	24	0.1655	0.0873	(0,0.3366)
9-Months	7	18	30	0.4116	0.1193	(0.1777,0.6455)	2	3	24	0.1655	0.1069	(0,0.3751)
10-Months	2	23	30	0.4116	0.2233	(0,0.8492)	0	5	24	-	-	-
11-Months	0	25	30	-	-	-	0	5	24	-	-	-
12-Months	0	25	30	-	-	-	0	5	24	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 1F Summary of KM Analysis of Time to Chronic Failures - [redacted] Site (n=49) – Reference to Figure 3.6.3.1F

Nominal Time Point [a]	THERMOCOOL Group (n=31)						AAD (Control) Group (n=18)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0[c]	31	0	0	1.0000	0.0000	(1.0000,1.0000)	18	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	31	0	0	1.0000	0.0000	(1.0000,1.0000)	18	0	4	0.7778	0.0980	(0.5857,0.9698)
3-Weeks	31	0	0	1.0000	0.0000	(1.0000,1.0000)	13	0	5	0.7222	0.1056	(0.5153,0.9291)
1-Month	31	0	0	1.0000	0.0000	(1.0000,1.0000)	11	0	8	0.5556	0.1171	(0.3260,0.7851)
2-Months	31	0	0	1.0000	0.0000	(1.0000,1.0000)	6	0	12	0.3333	0.1111	(0.1156,0.5511)
3-Months	31	0	0	1.0000	0.0000	(1.0000,1.0000)	3	0	15	0.1667	0.0878	(0,0.3388)
4-Months	30	1	0	1.0000	0.0000	(1.0000,1.0000)	3	0	15	0.1667	0.0878	(0,0.3388)
5-Months	30	1	0	1.0000	0.0000	(1.0000,1.0000)	2	0	16	0.1111	0.0741	(0,0.2563)
6-Months	29	2	0	1.0000	0.0000	(1.0000,1.0000)	2	0	16	0.1111	0.0741	(0,0.2563)
7-Months	28	3	0	1.0000	0.0000	(1.0000,1.0000)	2	0	16	0.1111	0.0741	(0,0.2563)
8-Months	28	3	0	1.0000	0.0000	(1.0000,1.0000)	2	0	16	0.1111	0.0741	(0,0.2563)
9-Months	21	10	0	1.0000	0.0000	(1.0000,1.0000)	0	2	16	-	-	-
10-Months	9	22	0	1.0000	0.0000	(1.0000,1.0000)	0	2	16	-	-	-
11-Months	2	29	0	1.0000	0.0000	(1.0000,1.0000)	0	2	16	-	-	-
12-Months	1	30	0	1.0000	0.0000	(1.0000,1.0000)	0	2	16	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 1G Summary of KM Analysis of Time to Chronic Failures – Remaining Sites (n=110) – Reference to Figure 3.6.3.1G

Nominal Time Point [a]	THERMOCOOL Group (n=72)						AAD (Control) Group (n=38)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0[c]	72	3	8	0.8889	0.0370	(0.8163,0.9615)	38	0	4	0.8947	0.0498	(0.7972,0.9923)
Day 7	52	4	20	0.7140	0.0545	(0.6071,0.8209)	31	0	7	0.8158	0.0629	(0.6925,0.9390)
3-Weeks	40	5	27	0.6085	0.0602	(0.4906,0.7265)	29	0	9	0.7632	0.0690	(0.6280,0.8983)
1-Month	38	5	29	0.5781	0.0609	(0.4587,0.6975)	28	0	10	0.7368	0.0714	(0.5968,0.8768)
2-Months	38	5	29	0.5781	0.0609	(0.4587,0.6975)	23	0	15	0.6053	0.0793	(0.4499,0.7607)
3-Months	35	5	32	0.5325	0.0615	(0.4119,0.6531)	16	0	22	0.4211	0.0801	(0.2641,0.5780)
4-Months	33	5	34	0.5020	0.0617	(0.3812,0.6229)	13	0	25	0.3421	0.0770	(0.1913,0.4929)
5-Months	32	5	35	0.4868	0.0617	(0.3660,0.6077)	11	0	27	0.2895	0.0736	(0.1453,0.4337)
6-Months	31	6	35	0.4868	0.0626	(0.3641,0.6096)	9	0	29	0.2368	0.0690	(0.1017,0.3720)
7-Months	26	10	36	0.4700	0.0671	(0.3385,0.6016)	8	0	30	0.2105	0.0661	(0.0809,0.3401)
8-Months	24	13	36	0.4700	0.0714	(0.3302,0.6099)	5	2	31	0.1805	0.0731	(0.0373,0.3236)
9-Months	16	21	36	0.4700	0.0884	(0.2969,0.6432)	2	5	31	0.1805	0.1155	(0,0.4069)
10-Months	6	30	36	0.4700	0.1397	(0.1962,0.7438)	0	7	31	-	-	-
11-Months	1	35	36	0.4700	0.3422	(0,1.1407)	0	7	31	-	-	-
12-Months	1	35	36	0.4700	0.3422	(0,1.1407)	0	7	31	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 2A Summary of KM Analysis of Time to Recurrence of Documented Symptomatic AF By Randomization Group (Effectiveness Analysis Cohort, n=159) – Reference to Figure 3.6.3.2.1A

Nominal Time Point [a]	THERMOCOOL Group (n=103)						AAD (Control) Group (n=56)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	103	3	0	1.0000	0.0000	(1.0000,1.0000)	56	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	97	4	3	0.9700	0.0171	(0.9364,1.0036)	49	1	7	0.8733	0.0449	(0.7854,0.9613)
3-Weeks	93	5	5	0.9497	0.0221	(0.9064,0.9930)	45	1	10	0.8187	0.0520	(0.7169,0.9206)
1-Month	91	5	7	0.9293	0.0259	(0.8785,0.9800)	43	1	13	0.7642	0.0573	(0.6519,0.8764)
2-Months	87	5	11	0.8884	0.0318	(0.8261,0.9508)	34	1	21	0.6186	0.0655	(0.4902,0.7470)
3-Months	82	5	16	0.8374	0.0373	(0.7643,0.9104)	23	2	31	0.4346	0.0681	(0.3010,0.5681)
4-Months	76	7	20	0.7957	0.0413	(0.7149,0.8766)	21	2	33	0.3968	0.0672	(0.2650,0.5286)
5-Months	75	7	21	0.7853	0.0420	(0.7029,0.8676)	17	2	37	0.3212	0.0642	(0.1954,0.4470)
6-Months	72	10	22	0.7747	0.0436	(0.6891,0.8602)	15	2	39	0.2834	0.0619	(0.1620,0.4048)
7-Months	62	17	24	0.7513	0.0476	(0.6580,0.8446)	15	2	39	0.2834	0.0619	(0.1620,0.4048)
8-Months	59	21	24	0.7513	0.0492	(0.6549,0.8477)	12	4	40	0.2632	0.0652	(0.1354,0.3910)
9-Months	43	37	24	0.7513	0.0578	(0.6380,0.8646)	4	10	42	0.2111	0.0937	(0.0273,0.3948)
10-Months	17	62	24	0.7513	0.0909	(0.5732,0.9294)	2	12	42	0.2111	0.1326	(0,0.4709)
11-Months	3	76	24	0.7513	0.2163	(0.3273,1.1753)	2	12	42	0.2111	0.1326	(0,0.4709)
12-Months	2	77	24	0.7513	0.2649	(0.2321,1.2706)	1	13	42	0.2111	0.1875	(0,0.5785)

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 2B Summary of KM Analysis of Time to Recurrence of Documented Symptomatic AF - Non-US Sites (n=95) – Reference to Figure 3.6.3.2.1B

Nominal Time Point [a]	THERMOCOOL Group (n=60)						AAD (Control) Group (n=35)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	60	0	0	1.0000	0.0000	(1.0000,1.0000)	35	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	60	0	0	1.0000	0.0000	(1.0000,1.0000)	35	0	4	0.8857	0.0538	(0.7803,0.9911)
3-Weeks	58	1	1	0.9833	0.0167	(0.9507,1.0160)	30	0	5	0.8571	0.0591	(0.7412,0.9731)
1-Month	58	1	1	0.9833	0.0167	(0.9507,1.0160)	28	0	8	0.7714	0.0710	(0.6323,0.9105)
2-Months	57	1	2	0.9664	0.0235	(0.9204,1.0124)	21	0	14	0.6000	0.0828	(0.4377,0.7623)
3-Months	55	1	4	0.9325	0.0327	(0.8684,0.9965)	12	1	22	0.3657	0.0841	(0.2009,0.5305)
4-Months	52	2	6	0.8982	0.0397	(0.8204,0.9761)	11	1	23	0.3352	0.0824	(0.1737,0.4968)
5-Months	52	2	6	0.8982	0.0397	(0.8204,0.9761)	8	1	26	0.2438	0.0750	(0.0969,0.3907)
6-Months	50	4	7	0.8806	0.0435	(0.7954,0.9658)	7	1	27	0.2133	0.0715	(0.0732,0.3535)
7-Months	45	6	9	0.8435	0.0497	(0.7461,0.9410)	7	1	27	0.2133	0.0715	(0.0732,0.3535)
8-Months	45	6	9	0.8435	0.0497	(0.7461,0.9410)	7	1	27	0.2133	0.0715	(0.0732,0.3535)
9-Months	34	18	9	0.8435	0.0581	(0.7297,0.9574)	1	6	28	0.1600	0.1466	(0,0.4474)
10-Months	14	37	9	0.8435	0.0892	(0.6688,1.0183)	1	6	28	0.1600	0.1466	(0,0.4474)
11-Months	3	48	9	0.8435	0.1926	(0.4660,1.2211)	1	6	28	0.1600	0.1466	(0,0.4474)
12-Months	2	49	9	0.8435	0.2359	(0.3811,1.3060)	0	7	28	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 2C Summary of KM Analysis of Time to Recurrence of Documented Symptomatic AF - US Sites (n=64) – Reference to Figure 3.6.3.2.1C

Nominal Time Point [a]	THERMOCOOL Group (n=43)						AAD (Control) Group (n=21)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	43	3	0	1.0000	0.0000	(1.0000,1.0000)	21	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	37	4	3	0.9250	0.0422	(0.8422,1.0078)	17	1	3	0.8545	0.0791	(0.6996,1.0094)
3-Weeks	35	4	4	0.8993	0.0482	(0.8048,0.9938)	15	1	5	0.7540	0.0966	(0.5647,0.9432)
1-Month	33	4	6	0.8479	0.0576	(0.7351,0.9607)	15	1	5	0.7540	0.0966	(0.5647,0.9432)
2-Months	30	4	9	0.7708	0.0674	(0.6388,0.9029)	13	1	7	0.6534	0.1067	(0.4443,0.8625)
3-Months	27	4	12	0.6937	0.0739	(0.5489,0.8386)	11	1	9	0.5529	0.1115	(0.3344,0.7714)
4-Months	24	5	14	0.6404	0.0784	(0.4867,0.7940)	10	1	10	0.5026	0.1121	(0.2829,0.7224)
5-Months	23	5	15	0.6137	0.0795	(0.4578,0.7696)	9	1	11	0.4524	0.1116	(0.2337,0.6711)
6-Months	22	6	15	0.6137	0.0813	(0.4543,0.7731)	8	1	12	0.4021	0.1099	(0.1867,0.6176)
7-Months	17	11	15	0.6137	0.0925	(0.4324,0.7950)	8	1	12	0.4021	0.1099	(0.1867,0.6176)
8-Months	14	15	15	0.6137	0.1058	(0.4064,0.8210)	5	3	13	0.3447	0.1248	(0.1001,0.5892)
9-Months	9	19	15	0.6137	0.1271	(0.3645,0.8629)	3	4	14	0.2757	0.1355	(0.0102,0.5413)
10-Months	3	25	15	0.6137	0.2202	(0.1821,1.0453)	1	6	14	0.2757	0.2347	(0,0.7357)
11-Months	0	28	15	-	-	-	1	6	14	0.2757	0.2347	(0,0.7357)
12-Months	0	28	15	-	-	-	1	6	14	0.2757	0.2347	(0,0.7357)

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 2D Summary of KM Analysis of Time to Recurrence of Documented Symptomatic AF - High Enrolling Sites (n=75) – Reference to Figure 3.6.3.2.1D

Nominal Time Point [a]	THERMOCOOL Group (n=48)						AAD (Control) Group (n=27)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	48	0	0	1.0000	0.0000	(1.0000,1.0000)	27	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	48	0	0	1.0000	0.0000	(1.0000,1.0000)	27	0	4	0.8519	0.0684	(0.7179,0.9858)
3-Weeks	47	0	1	0.9792	0.0206	(0.9388,1.0196)	22	0	5	0.8148	0.0748	(0.6683,0.9613)
1-Month	47	0	1	0.9792	0.0206	(0.9388,1.0196)	20	0	8	0.7037	0.0879	(0.5315,0.8759)
2-Months	47	0	1	0.9792	0.0206	(0.9388,1.0196)	14	0	13	0.5185	0.0962	(0.3301,0.7070)
3-Months	47	0	1	0.9792	0.0206	(0.9388,1.0196)	7	1	19	0.2852	0.0911	(0.1066,0.4638)
4-Months	46	1	1	0.9792	0.0208	(0.9383,1.0200)	7	1	19	0.2852	0.0911	(0.1066,0.4638)
5-Months	46	1	1	0.9792	0.0208	(0.9383,1.0200)	5	1	21	0.2037	0.0813	(0.0444,0.3630)
6-Months	45	2	2	0.9579	0.0296	(0.8998,1.0160)	5	1	21	0.2037	0.0813	(0.0444,0.3630)
7-Months	41	3	4	0.9133	0.0420	(0.8310,0.9956)	5	1	21	0.2037	0.0813	(0.0444,0.3630)
8-Months	41	3	4	0.9133	0.0420	(0.8310,0.9956)	5	1	21	0.2037	0.0813	(0.0444,0.3630)
9-Months	32	13	4	0.9133	0.0483	(0.8187,1.0080)	0	5	22	-	-	-
10-Months	13	31	4	0.9133	0.0746	(0.7672,1.0595)	0	5	22	-	-	-
11-Months	3	41	4	0.9133	0.1552	(0.6091,1.2176)	0	5	22	-	-	-
12-Months	2	42	4	0.9133	0.1901	(0.5407,1.2860)	0	5	22	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 2E Summary of KM Analysis of Time to Recurrence of Documented Symptomatic AF - Low to Medium Enrolling Sites (n=84) – Reference to Figure 3.6.3.2.1E

Nominal Time Point [a]	THERMOCOOL Group (n=55)						AAD (Control) Group (n=29)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	55	3	0	1.0000	0.0000	(1.0000,1.0000)	29	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	49	4	3	0.9423	0.0327	(0.8783,1.0063)	25	1	3	0.8952	0.0580	(0.7816,1.0088)
3-Weeks	46	5	4	0.9223	0.0379	(0.8479,0.9966)	23	1	5	0.8236	0.0721	(0.6822,0.9650)
1-Month	44	5	6	0.8822	0.0457	(0.7927,0.9716)	23	1	5	0.8236	0.0721	(0.6822,0.9650)
2-Months	40	5	10	0.8020	0.0564	(0.6914,0.9126)	20	1	8	0.7162	0.0853	(0.5490,0.8834)
3-Months	35	5	15	0.7017	0.0648	(0.5748,0.8287)	16	1	12	0.5729	0.0936	(0.3895,0.7564)
4-Months	30	6	19	0.6197	0.0698	(0.4829,0.7565)	14	1	14	0.5013	0.0946	(0.3159,0.6868)
5-Months	29	6	20	0.5990	0.0704	(0.4610,0.7371)	12	1	16	0.4297	0.0937	(0.2461,0.6133)
6-Months	27	8	20	0.5990	0.0730	(0.4560,0.7421)	10	1	18	0.3581	0.0907	(0.1803,0.5359)
7-Months	21	14	20	0.5990	0.0828	(0.4368,0.7613)	10	1	18	0.3581	0.0907	(0.1803,0.5359)
8-Months	18	18	20	0.5990	0.0920	(0.4187,0.7794)	7	3	19	0.3183	0.0993	(0.1236,0.5130)
9-Months	11	24	20	0.5990	0.1144	(0.3749,0.8232)	4	5	20	0.2728	0.1163	(0.0448,0.5008)
10-Months	4	31	20	0.5990	0.1897	(0.2273,0.9708)	2	7	20	0.2728	0.1645	(0,0.5953)
11-Months	0	35	20	-	-	-	2	7	20	0.2728	0.1645	(0,0.5953)
12-Months	0	35	20	-	-	-	1	8	20	0.2728	0.2327	(0,0.7288)

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 2F Summary of KM Analysis of Time to Recurrence of Documented Symptomatic AF - [redacted] Site (n=49) – Reference to Figure 3.6.3.2.1F

Nominal Time Point [a]	THERMOCOOL Group (n=31)						AAD (Control) Group (n=18)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	31	0	0	1.0000	0.0000	(1.0000,1.0000)	18	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	31	0	0	1.0000	0.0000	(1.0000,1.0000)	18	0	4	0.7778	0.0980	(0.5857,0.9698)
3-Weeks	31	0	0	1.0000	0.0000	(1.0000,1.0000)	13	0	5	0.7222	0.1056	(0.5153,0.9291)
1-Month	31	0	0	1.0000	0.0000	(1.0000,1.0000)	11	0	8	0.5556	0.1171	(0.3260,0.7851)
2-Months	31	0	0	1.0000	0.0000	(1.0000,1.0000)	6	0	12	0.3333	0.1111	(0.1156,0.5511)
3-Months	31	0	0	1.0000	0.0000	(1.0000,1.0000)	3	0	15	0.1667	0.0878	(0,0.3388)
4-Months	30	1	0	1.0000	0.0000	(1.0000,1.0000)	3	0	15	0.1667	0.0878	(0,0.3388)
5-Months	30	1	0	1.0000	0.0000	(1.0000,1.0000)	2	0	16	0.1111	0.0741	(0,0.2563)
6-Months	30	2	0	1.0000	0.0000	(1.0000,1.0000)	2	0	16	0.1111	0.0741	(0,0.2563)
7-Months	28	3	0	1.0000	0.0000	(1.0000,1.0000)	2	0	16	0.1111	0.0741	(0,0.2563)
8-Months	28	3	0	1.0000	0.0000	(1.0000,1.0000)	2	0	16	0.1111	0.0741	(0,0.2563)
9-Months	21	10	0	1.0000	0.0000	(1.0000,1.0000)	0	2	16	-	-	-
10-Months	9	22	0	1.0000	0.0000	(1.0000,1.0000)	0	2	16	-	-	-
11-Months	2	29	0	1.0000	0.0000	(1.0000,1.0000)	0	2	16	-	-	-
12-Months	1	30	0	1.0000	0.0000	(1.0000,1.0000)	0	2	16	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 2G Summary of KM Analysis of Time to Recurrence of Documented Symptomatic AF – Remaining Sites (n=110) – Reference to Figure 3.6.3.2.1G

Nominal Time Point [a]	THERMOCOOL Group (n=72)						AAD (Control) Group (n=38)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	72	3	0	1.0000	0.0000	(1.0000,1.0000)	38	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	66	4	3	0.9565	0.0247	(0.9080,1.0050)	34	1	3	0.9203	0.0446	(0.8330,1.0076)
3-Weeks	62	5	5	0.9269	0.0318	(0.8645,0.9893)	32	1	5	0.8662	0.0560	(0.7564,0.9760)
1-Month	60	5	7	0.8970	0.0372	(0.8241,0.9698)	32	1	5	0.8662	0.0560	(0.7564,0.9760)
2-Months	56	5	11	0.8372	0.0451	(0.7487,0.9256)	28	1	9	0.7579	0.0705	(0.6198,0.8960)
3-Months	51	5	16	0.7624	0.0520	(0.6604,0.8644)	20	2	16	0.5660	0.0834	(0.4025,0.7294)
4-Months	46	6	20	0.7017	0.0565	(0.5910,0.8125)	18	2	18	0.5094	0.0841	(0.3445,0.6742)
5-Months	45	6	21	0.6864	0.0573	(0.5741,0.7988)	15	2	21	0.4245	0.0831	(0.2615,0.5874)
6-Months	42	8	22	0.6708	0.0594	(0.5544,0.7872)	13	2	23	0.3679	0.0811	(0.2089,0.5269)
7-Months	34	14	24	0.6358	0.0658	(0.5068,0.7648)	13	2	23	0.3679	0.0811	(0.2089,0.5269)
8-Months	31	18	24	0.6358	0.0701	(0.4985,0.7731)	10	4	24	0.3372	0.0868	(0.1671,0.5074)
9-Months	22	27	24	0.6358	0.0837	(0.4717,0.7999)	4	8	26	0.2601	0.1119	(0.0409,0.4794)
10-Months	8	40	24	0.6358	0.1357	(0.3699,0.9017)	2	10	26	0.2601	0.1582	(0,0.5702)
11-Months	1	47	24	0.6358	0.3837	(0,1.3878)	2	10	26	0.2601	0.1582	(0,0.5702)
12-Months	1	47	24	0.6358	0.3837	(0,1.3878)	1	11	26	0.2601	0.2238	(0,0.6987)

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 3A Summary of KM Analysis of Time to Recurrence of Documented Symptomatic or Asymptomatic AF By Randomization Group (Effectiveness Analysis Cohort, n=159) – Reference to Figure 3.6.3.2.2A

Nominal Time Point [a]	THERMOCOOL Group (n=103)						AAD (Control) Group (n=56)					
	Number of Subjects At Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	103	3	0	1.0000	0.0000	(1.0000,1.0000)	56	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	95	4	5	0.9500	0.0219	(0.9071,0.9929)	49	1	7	0.8733	0.0449	(0.7854,0.9613)
3-Weeks	91	5	7	0.9297	0.0258	(0.8790,0.9803)	44	1	11	0.8005	0.0539	(0.6949,0.9062)
1-Month	89	5	9	0.9092	0.0290	(0.8523,0.9662)	42	1	14	0.7460	0.0587	(0.6309,0.8610)
2-Months	86	5	12	0.8786	0.0330	(0.8139,0.9433)	31	1	24	0.5640	0.0669	(0.4329,0.6951)
3-Months	80	5	18	0.8173	0.0391	(0.7407,0.8939)	20	1	35	0.3639	0.0649	(0.2367,0.4911)
4-Months	74	7	22	0.7756	0.0427	(0.6919,0.8593)	18	1	37	0.3275	0.0633	(0.2034,0.4516)
5-Months	73	7	23	0.7652	0.0434	(0.6801,0.8502)	16	1	39	0.2911	0.0613	(0.1710,0.4112)
6-Months	71	10	23	0.7652	0.0443	(0.6783,0.8520)	14	1	41	0.2547	0.0588	(0.1395,0.3699)
7-Months	59	17	27	0.7183	0.0496	(0.6210,0.8156)	14	1	41	0.2547	0.0588	(0.1395,0.3699)
8-Months	56	21	27	0.7183	0.0514	(0.6175,0.8191)	11	3	42	0.2351	0.0620	(0.1136,0.3566)
9-Months	41	35	27	0.7183	0.0595	(0.6016,0.8350)	4	9	43	0.2137	0.0948	(0.0280,0.3995)
10-Months	16	60	27	0.7183	0.0953	(0.5315,0.9051)	2	11	43	0.2137	0.1340	(0,0.4764)
11-Months	2	74	27	0.7183	0.2696	(0.1899,1.2467)	2	11	43	0.2137	0.1340	(0,0.4764)
12-Months	2	74	27	0.7183	0.2696	(0.1899,1.2467)	1	12	43	0.2137	0.1895	(0,0.5852)

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 3B Summary of KM Analysis of Time to Recurrence of Documented Symptomatic or Asymptomatic AF - Non-US Sites (n=95) – Reference to Figure 3.6.3.2.2B

Nominal Time Point [a]	THERMOCOOL Group (n=60)						AAD (Control) Group (n=35)					
	Number of Subjects At Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	60	0	0	1.0000	0.0000	(1.0000,1.0000)	35	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	59	0	1	0.9833	0.0165	(0.9509,1.0157)	35	0	4	0.8857	0.0538	(0.7803,0.9911)
3-Weeks	57	1	2	0.9667	0.0234	(0.9208,1.0125)	29	0	6	0.8286	0.0637	(0.7037,0.9534)
1-Month	57	1	2	0.9667	0.0234	(0.9208,1.0125)	27	0	9	0.7429	0.0739	(0.5981,0.8877)
2-Months	56	1	3	0.9497	0.0285	(0.8939,1.0055)	19	0	16	0.5429	0.0842	(0.3778,0.7079)
3-Months	53	1	6	0.8988	0.0393	(0.8219,0.9758)	10	0	25	0.2857	0.0764	(0.1361,0.4354)
4-Months	50	2	8	0.8646	0.0450	(0.7764,0.9528)	9	0	26	0.2571	0.0739	(0.1123,0.4019)
5-Months	50	2	8	0.8646	0.0450	(0.7764,0.9528)	7	0	28	0.2000	0.0676	(0.0675,0.3325)
6-Months	49	4	8	0.8646	0.0459	(0.7746,0.9546)	6	0	29	0.1714	0.0637	(0.0466,0.2963)
7-Months	42	6	12	0.7902	0.0559	(0.6807,0.8996)	6	0	29	0.1714	0.0637	(0.0466,0.2963)
8-Months	42	6	12	0.7902	0.0559	(0.6807,0.8996)	6	0	29	0.1714	0.0637	(0.0466,0.2963)
9-Months	32	16	12	0.7902	0.0640	(0.6648,0.9156)	1	5	29	0.1714	0.1560	(0,0.4773)
10-Months	13	35	12	0.7902	0.1004	(0.5934,0.9869)	1	5	29	0.1714	0.1560	(0,0.4773)
11-Months	2	46	12	0.7902	0.2559	(0.2885,1.2918)	1	5	29	0.1714	0.1560	(0,0.4773)
12-Months	2	46	12	0.7902	0.2559	(0.2885,1.2918)	0	6	29	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 3C Summary of KM Analysis of Time to Recurrence of Documented Symptomatic or Asymptomatic AF - US Sites (n=64) – Reference to Figure 3.6.3.2.2C

Nominal Time Point [a]	THERMOCOOL Group (n=43)						AAD (Control) Group (n=21)					
	Number of Subjects At Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	43	3	0	1.0000	0.0000	(1.0000,1.0000)	21	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	36	4	4	0.9000	0.0481	(0.8057,0.9943)	17	1	3	0.8545	0.0791	(0.6996,1.0094)
3-Weeks	34	4	5	0.8743	0.0532	(0.7701,0.9785)	15	1	5	0.7540	0.0966	(0.5647,0.9432)
1-Month	32	4	7	0.8229	0.0612	(0.7029,0.9429)	15	1	5	0.7540	0.0966	(0.5647,0.9432)
2-Months	30	4	9	0.7714	0.0673	(0.6395,0.9034)	12	1	8	0.6032	0.1097	(0.3882,0.8182)
3-Months	27	4	12	0.6943	0.0739	(0.5495,0.8391)	10	1	10	0.5026	0.1121	(0.2829,0.7224)
4-Months	24	5	14	0.6409	0.0784	(0.4872,0.7945)	9	1	11	0.4524	0.1116	(0.2337,0.6711)
5-Months	23	5	15	0.6142	0.0795	(0.4583,0.7701)	9	1	11	0.4524	0.1116	(0.2337,0.6711)
6-Months	22	6	15	0.6142	0.0813	(0.4548,0.7736)	8	1	12	0.4021	0.1099	(0.1867,0.6176)
7-Months	17	11	15	0.6142	0.0925	(0.4328,0.7955)	8	1	12	0.4021	0.1099	(0.1867,0.6176)
8-Months	14	15	15	0.6142	0.1058	(0.4068,0.8216)	5	3	13	0.3447	0.1248	(0.1001,0.5892)
9-Months	9	19	15	0.6142	0.1272	(0.3649,0.8634)	3	4	14	0.2757	0.1355	(0.0102,0.5413)
10-Months	3	25	15	0.6142	0.2203	(0.1825,1.0459)	1	6	14	0.2757	0.2347	(0,0.7357)
11-Months	0	28	15	-	-	-	1	6	14	0.2757	0.2347	(0,0.7357)
12-Months	0	28	15	-	-	-	1	6	14	0.2757	0.2347	(0s,0.7357)

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 3D Summary of KM Analysis of Time to Recurrence of Documented Symptomatic or Asymptomatic AF - High Enrolling Sites (n=75) – Reference to Figure 3.6.3.2.2D

Nominal Time Point [a]	THERMOCOOL Group (n=48)						AAD (Control) Group (n=27)					
	Number of Subjects At Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	48	0	0	1.0000	0.0000	(1.0000,1.0000)	27	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	47	0	1	0.9792	0.0206	(0.9388,1.0196)	27	0	4	0.8519	0.0684	(0.7179,0.9858)
3-Weeks	46	0	2	0.9583	0.0288	(0.9018,1.0149)	21	0	6	0.7778	0.0800	(0.6210,0.9346)
1-Month	46	0	2	0.9583	0.0288	(0.9018,1.0149)	19	0	9	0.6667	0.0907	(0.4889,0.8445)
2-Months	46	0	2	0.9583	0.0288	(0.9018,1.0149)	12	0	15	0.4444	0.0956	(0.2570,0.6319)
3-Months	45	0	3	0.9375	0.0349	(0.8690,1.0060)	6	0	21	0.2222	0.0800	(0.0654,0.3790)
4-Months	44	1	3	0.9375	0.0353	(0.8682,1.0068)	6	0	21	0.2222	0.0800	(0.0654,0.3790)
5-Months	44	1	3	0.9375	0.0353	(0.8682,1.0068)	4	0	23	0.1481	0.0684	(0.0142,0.2821)
6-Months	44	2	3	0.9375	0.0357	(0.8674,1.0076)	4	0	23	0.1481	0.0684	(0.0142,0.2821)
7-Months	38	3	7	0.8482	0.0536	(0.7431,0.9533)	4	0	23	0.1481	0.0684	(0.0142,0.2821)
8-Months	38	3	7	0.8482	0.0536	(0.7431,0.9533)	4	0	23	0.1481	0.0684	(0.0142,0.2821)
9-Months	30	11	7	0.8482	0.0603	(0.7300,0.9665)	0	4	23	-	-	-
10-Months	12	29	7	0.8482	0.0954	(0.6612,1.0352)	0	4	23	-	-	-
11-Months	2	39	7	0.8482	0.2337	(0.3902,1.3062)	0	4	23	-	-	-
12-Months	2	39	7	0.8482	0.2337	(0.3902,1.3062)	0	4	23	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 3E Summary of KM Analysis of Time to Recurrence of Documented Symptomatic or Asymptomatic AF - Low to Medium Enrolling Sites (n=84) – Reference to Figure 3.6.3.2.2E

Nominal Time Point [a]	THERMOCOOL Group (n=55)						AAD (Control) Group (n=29)					
	Number of Subjects At Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	55	3	0	1.0000	0.0000	(1.0000,1.0000)	29	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	48	4	4	0.9231	0.0373	(0.8499,0.9963)	25	1	3	0.8952	0.0580	(0.7816,1.0088)
3-Weeks	45	5	5	0.9030	0.0419	(0.8208,0.9852)	23	1	5	0.8236	0.0721	(0.6822,0.9650)
1-Month	43	5	7	0.8629	0.0487	(0.7674,0.9584)	23	1	5	0.8236	0.0721	(0.6822,0.9650)
2-Months	40	5	10	0.8027	0.0564	(0.6922,0.9132)	19	1	9	0.6804	0.0882	(0.5074,0.8533)
3-Months	35	5	15	0.7023	0.0648	(0.5754,0.8293)	14	1	14	0.5013	0.0946	(0.3159,0.6868)
4-Months	30	6	19	0.6202	0.0698	(0.4835,0.7570)	12	1	16	0.4297	0.0937	(0.2461,0.6133)
5-Months	29	6	20	0.5996	0.0705	(0.4615,0.7377)	12	1	16	0.4297	0.0937	(0.2461,0.6133)
6-Months	27	8	20	0.5996	0.0730	(0.4565,0.7427)	10	1	18	0.3581	0.0907	(0.1803,0.5359)
7-Months	21	14	20	0.5996	0.0828	(0.4373,0.7618)	10	1	18	0.3581	0.0907	(0.1803,0.5359)
8-Months	18	18	20	0.5996	0.0920	(0.4192,0.7799)	7	3	19	0.3183	0.0993	(0.1236,0.5130)
9-Months	11	24	20	0.5996	0.1144	(0.3754,0.8238)	4	5	20	0.2728	0.1163	(0.0448,0.5008)
10-Months	4	31	20	0.5996	0.1897	(0.2278,0.9714)	2	7	20	0.2728	0.1645	(0,0.5953)
11-Months	0	35	20	-	-	-	2	7	20	0.2728	0.1645	(0,0.5953)
12-Months	0	35	20	-	-	-	1	8	20	0.2728	0.2327	(0,0.7288)

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 3F Summary of KM Analysis of Time to Recurrence of Documented Symptomatic or Asymptomatic AF - [redacted] Site (n=49) – Reference to Figure 3.6.3.2.2F

Nominal Time Point [a]	THERMOCOOL Group (n=31)						AAD (Control) Group (n=18)					
	Number of Subjects At Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	31	0	0	1.0000	0.0000	(1.0000,1.0000)	18	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	31	0	0	1.0000	0.0000	(1.0000,1.0000)	18	0	4	0.7778	0.0980	(0.5857,0.9698)
3-Weeks	31	0	0	1.0000	0.0000	(1.0000,1.0000)	13	0	5	0.7222	0.1056	(0.5153,0.9291)
1-Month	31	0	0	1.0000	0.0000	(1.0000,1.0000)	11	0	8	0.5556	0.1171	(0.3260,0.7851)
2-Months	31	0	0	1.0000	0.0000	(1.0000,1.0000)	6	0	12	0.3333	0.1111	(0.1156,0.5511)
3-Months	30	0	1	0.9677	0.0317	(0.9055,1.0299)	3	0	15	0.1667	0.0878	(0,0.3388)
4-Months	29	1	1	0.9677	0.0323	(0.9045,1.0310)	3	0	15	0.1667	0.0878	(00,0.3388)
5-Months	29	1	1	0.9677	0.0323	(0.9045,1.0310)	2	0	16	0.1111	0.0741	(0,0.2563)
6-Months	29	2	1	0.9677	0.0328	(0.9034,1.0321)	2	0	16	0.1111	0.0741	(0,0.2563)
7-Months	27	3	1	0.9677	0.0335	(0.9022,1.0333)	2	0	16	0.1111	0.0741	(0,0.2563)
8-Months	27	3	1	0.9677	0.0335	(0.9022,1.0333)	2	0	16	0.1111	0.0741	(0,0.2563)
9-Months	20	10	1	0.9677	0.0389	(0.8916,1.0439)	0	2	16	-	-	-
10-Months	8	22	1	0.9677	0.0615	(0.8473,1.0882)	0	2	16	-	-	-
11-Months	1	29	1	0.9677	0.1738	(0.6271,1.3084)	0	2	16	-	-	-
12-Months	1	29	1	0.9677	0.1738	(0.6271,1.3084)	0	2	16	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

TABLE 3G Summary of KM Analysis of Time to Recurrence of Documented Symptomatic or Asymptomatic AF - Remaining Sites (n=110) – Reference to Figure 3.6.3.2.2G

Nominal Time Point [a]	THERMOCOOL Group (n=72)						AAD (Control) Group (n=38)					
	Number of Subjects At Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	72	3	0	1.0000	0.0000	(1.0000,1.0000)	38	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	64	4	5	0.9275	0.0315	(0.8659,0.9892)	34	1	3	0.9203	0.0446	(0.8330,1.0076)
3-Weeks	60	5	7	0.8978	0.0370	(0.8252,0.9705)	31	1	6	0.8391	0.0605	(0.7206,0.9576)
1-Month	58	5	9	0.8679	0.0414	(0.7867,0.9491)	31	1	6	0.8391	0.0605	(0.7206,0.9576)
2-Months	55	5	12	0.8230	0.0467	(0.7315,0.9145)	25	1	12	0.6767	0.0770	(0.5259,0.8275)
3-Months	50	5	17	0.7482	0.0531	(0.6441,0.8523)	17	1	20	0.4602	0.0820	(0.2994,0.6209)
4-Months	45	6	21	0.6874	0.0573	(0.5751,0.7997)	15	1	22	0.4060	0.0808	(0.2477,0.5644)
5-Months	44	6	22	0.6721	0.0580	(0.5584,0.7859)	14	1	23	0.3789	0.0798	(0.2225,0.5354)
6-Months	42	8	22	0.6721	0.0594	(0.5557,0.7885)	12	1	25	0.3248	0.0770	(0.1738,0.4758)
7-Months	32	14	26	0.6017	0.0671	(0.4702,0.7333)	12	1	25	0.3248	0.0770	(0.1738,0.4758)
8-Months	29	18	26	0.6017	0.0718	(0.4611,0.7424)	9	3	26	0.2953	0.0826	(0.1333,0.4572)
9-Months	21	25	26	0.6017	0.0829	(0.4393,0.7642)	4	7	27	0.2625	0.1127	(0.0416,0.4834)
10-Months	8	38	26	0.6017	0.1343	(0.3386,0.8649)	2	9	27	0.2625	0.1594	(0,0.5749)
11-Months	1	45	26	0.6017	0.3797	(0,1.3460)	2	9	27	0.2625	0.1594	(0,0.5749)
12-Months	1	45	26	0.6017	0.3797	(0,1.3460)	1	10	27	0.2625	0.2254	(0,0.7043)

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365.

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined 90 days post ablation procedures for THERMOCOOL Group and 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method.

[e] Represents 95% pointwise confidence intervals using Peto standard error.

Appendix 13

Kaplan Meier Source Tables for Section 4.0

TABLE 1 Summary of KM Analysis of Time to Chronic Failures by [redacted] vs. Remaining Sites (Non-[redacted]- THERMOCOOL Group (n=103) – Reference to Figure 4.5.3A

Nominal Time Point [a]	[redacted] Site (n=31)						Remaining Sites (n=72)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	31	0	0	1.0000	0.0000	(1.0000,1.0000)	72	3	8	0.8889	0.0370	(0.8163,0.9615)
Day 7	31	0	0	1.0000	0.0000	(1.0000,1.0000)	52	4	20	0.7140	0.0545	(0.6071,0.8209)
3-Weeks	31	0	0	1.0000	0.0000	(1.0000,1.0000)	40	5	27	0.6085	0.0602	(0.4906,0.7265)
1-Month	31	0	0	1.0000	0.0000	(1.0000,1.0000)	38	5	29	0.5781	0.0609	(0.4587,0.6975)
2-Months	31	0	0	1.0000	0.0000	(1.0000,1.0000)	38	5	29	0.5781	0.0609	(0.4587,0.6975)
3-Months	31	0	0	1.0000	0.0000	(1.0000,1.0000)	35	5	32	0.5325	0.0615	(0.4119,0.6531)
4-Months	30	1	0	1.0000	0.0000	(1.0000,1.0000)	33	5	34	0.5020	0.0617	(0.3812,0.6229)
5-Months	30	1	0	1.0000	0.0000	(1.0000,1.0000)	32	5	35	0.4868	0.0617	(0.3660,0.6077)
6-Months	30	2	0	1.0000	0.0000	(1.0000,1.0000)	31	6	35	0.4868	0.0626	(0.3641,0.6096)
7-Months	28	3	0	1.0000	0.0000	(1.0000,1.0000)	26	10	36	0.4700	0.0671	(0.3385,0.6016)
8-Months	28	3	0	1.0000	0.0000	(1.0000,1.0000)	24	13	36	0.4700	0.0714	(0.3302,0.6099)
9-Months	21	10	0	1.0000	0.0000	(1.0000,1.0000)	16	21	36	0.4700	0.0884	(0.2969,0.6432)
10-Months	9	22	0	1.0000	0.0000	(1.0000,1.0000)	6	30	36	0.4700	0.1397	(0.1962,0.7438)
11-Months	2	29	0	1.0000	0.0000	(1.0000,1.0000)	1	35	36	0.4700	0.3422	(0,1.1407)
12-Months	1	30	0	1.0000	0.0000	(1.0000,1.0000)	1	35	36	0.4700	0.3422	(0,1.1407)

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method

[e] Represents 95% pointwise confidence intervals using Peto standard error

TABLE 2 Summary of KM Analysis of Time to Chronic Failures by [redacted] vs. Remaining Sites (Non-[redacted] - AAD (Control)_ Group (n=56) – Reference to Figure 4.5.3B

Nominal Time Point [a]	[redacted] Site (n=18)						Remaining Sites (n=38)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From Chronic Failure		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	18	0	0	1.0000	0.0000	(1.0000,1.0000)	38	0	4	0.8947	0.0498	(0.7972,0.9923)
Day 7	18	0	4	0.7778	0.0980	(0.5857,0.9698)	31	0	7	0.8158	0.0629	(0.6925,0.9390)
3-Weeks	13	0	5	0.7222	0.1056	(0.5153,0.9291)	29	0	9	0.7632	0.0690	(0.6280,0.8983)
1-Month	11	0	8	0.5556	0.1171	(0.3260,0.7851)	28	0	10	0.7368	0.0714	(0.5968,0.8768)
2-Months	6	0	12	0.3333	0.1111	(0.1156,0.5511)	23	0	15	0.6053	0.0793	(0.4499,0.7607)
3-Months	3	0	15	0.1667	0.0878	(0,0.3388)	16	0	22	0.4211	0.0801	(0.2641,0.5780)
4-Months	3	0	15	0.1667	0.0878	(0,0.3388)	13	0	25	0.3421	0.0770	(0.1913,0.4929)
5-Months	2	0	16	0.1111	0.0741	(0,0.2563)	11	0	27	0.2895	0.0736	(0.1453,0.4337)
6-Months	2	0	16	0.1111	0.0741	(0,0.2563)	9	0	29	0.2368	0.0690	(0.1017,0.3720)
7-Months	2	0	16	0.1111	0.0741	(0,0.2563)	8	0	30	0.2105	0.0661	(0.0809,0.3401)
8-Months	2	0	16	0.1111	0.0741	(0,0.2563)	5	2	31	0.1805	0.0731	(0.0373,0.3236)
9-Months	0	2	16	-	-	-	2	5	31	0.1805	0.1155	(0,0.4069)
10-Months	0	2	16	-	-	-	0	7	31	-	-	-
11-Months	0	2	16	-	-	-	0	7	31	-	-	-
12-Months	0	2	16	-	-	-	0	7	31	-	-	-

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined as 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method

[e] Represents 95% pointwise confidence intervals using Peto standard error

TABLE 3 Summary of KM Analysis of Time to Recurrence of Documented Symptomatic or Asymptomatic AF by [redacted] vs. Remaining Sites (Non-[redacted] - THERMOCOOL Group (n=103) – Reference to Figure 4.5.3C

Nominal Time Point [a]	[redacted] Site (n=31)						Remaining Sites (n=72)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	31	0	0	1.0000	0.0000	(1.0000,1.0000)	72	3	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	31	0	0	1.0000	0.0000	(1.0000,1.0000)	64	4	5	0.9275	0.0315	(0.8659,0.9892)
3-Weeks	31	0	0	1.0000	0.0000	(1.0000,1.0000)	60	5	7	0.8978	0.0370	(0.8252,0.9705)
1-Month	31	0	0	1.0000	0.0000	(1.0000,1.0000)	58	5	9	0.8679	0.0414	(0.7867,0.9491)
2-Months	31	0	0	1.0000	0.0000	(1.0000,1.0000)	55	5	12	0.8230	0.0467	(0.7315,0.9145)
3-Months	30	0	1	0.9677	0.0317	(0.9055,1.0299)	50	5	17	0.7482	0.0531	(0.6441,0.8523)
4-Months	29	1	1	0.9677	0.0323	(0.9045,1.0310)	45	6	21	0.6874	0.0573	(0.5751,0.7997)
5-Months	29	1	1	0.9677	0.0323	(0.9045,1.0310)	44	6	22	0.6721	0.0580	(0.5584,0.7859)
6-Months	29	2	1	0.9677	0.0328	(0.9034,1.0321)	42	8	22	0.6721	0.0594	(0.5557,0.7885)
7-Months	27	3	1	0.9677	0.0335	(0.9022,1.0333)	32	14	26	0.6017	0.0671	(0.4702,0.7333)
8-Months	27	3	1	0.9677	0.0335	(0.9022,1.0333)	29	18	26	0.6017	0.0718	(0.4611,0.7424)
9-Months	20	10	1	0.9677	0.0389	(0.8916,1.0439)	21	25	26	0.6017	0.0829	(0.4393,0.7642)
10-Months	8	22	1	0.9677	0.0615	(0.8473,1.0882)	8	38	26	0.6017	0.1343	(0.3386,0.8649)
11-Months	1	29	1	0.9677	0.1738	(0.6271,1.3084)	1	45	26	0.6017	0.3797	(0,1.3460)
12-Months	1	29	1	0.9677	0.1738	(0.6271,1.3084)	1	45	26	0.6017	0.3797	(0,1.3460)

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined as 90 days post ablation procedures for THERMOCOOL Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method

[e] Represents 95% pointwise confidence intervals using Peto standard error

TABLE 4 Summary of KM Analysis of Time to Recurrence of Documented Symptomatic or Asymptomatic AF by [redacted] vs. Remaining Sites - AAD (Control) Group (n=56) – Reference to Figure 4.5.3D

Nominal Time Point [a]	[redacted] Site (n=18)						Remaining Sites (n=38)					
	Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence			Number of Subjects at Risk [b]	Cumulative		Probability of Freedom From AF Recurrence		
		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]		Number of Subjects Censored	Number of Events	Point Estimate	Standard Error [d]	95% Confidence Interval [e]
Day 0 [c]	18	0	0	1.0000	0.0000	(1.0000,1.0000)	38	0	0	1.0000	0.0000	(1.0000,1.0000)
Day 7	18	0	4	0.7778	0.0980	(0.5857,0.9698)	34	1	3	0.9203	0.0446	(0.8330,1.0076)
3-Weeks	13	0	5	0.7222	0.1056	(0.5153,0.9291)	31	1	6	0.8391	0.0605	(0.7206,0.9576)
1-Month	11	0	8	0.5556	0.1171	(0.3260,0.7851)	31	1	6	0.8391	0.0605	(0.7206,0.9576)
2-Months	6	0	12	0.3333	0.1111	(0.1156,0.5511)	25	1	12	0.6767	0.0770	(0.5259,0.8275)
3-Months	3	0	15	0.1667	0.0878	(0,0.3388)	17	1	20	0.4602	0.0820	(0.2994,0.6209)
4-Months	3	0	15	0.1667	0.0878	(0,0.3388)	15	1	22	0.4060	0.0808	(0.2477,0.5644)
5-Months	2	0	16	0.1111	0.0741	(0,0.2563)	14	1	23	0.3789	0.0798	(0.2225,0.5354)
6-Months	2	0	16	0.1111	0.0741	(0,0.2563)	12	1	25	0.3248	0.0770	(0.1738,0.4758)
7-Months	2	0	16	0.1111	0.0741	(0,0.2563)	12	1	25	0.3248	0.0770	(0.1738,0.4758)
8-Months	2	0	16	0.1111	0.0741	(0,0.2563)	9	3	26	0.2953	0.0826	(0.1333,0.4572)
9-Months	0	2	16	-	-	-	4	7	27	0.2625	0.1127	(0.0416,0.4834)
10-Months	0	2	16	-	-	-	2	9	27	0.2625	0.1594	(0,0.5749)
11-Months	0	2	16	-	-	-	2	9	27	0.2625	0.1594	(0,0.5749)
12-Months	0	2	16	-	-	-	1	10	27	0.2625	0.2254	(0,0.7043)

[a] 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, 6 months = 183 days, 7 months = 213, 8 months = 244, 9 months = 274, 10 months = 305, 11 months = 335, 12 months = 365

[b] The number of subjects at risk is the number who did not have events or censoring before the exact time-point. If there are no censors and events on the exact time-point, the total number of subjects in the analysis equals the number at risk + the cumulative number censored + the cumulative number of events.

[c] "Day 0" was defined as 14 days post initial treatment for AAD (Control) Group. Events occurred prior to Day 0 were considered as failures at Day 0.

[d] Based on Peto method

[e] Represents 95% pointwise confidence intervals using Peto standard error.

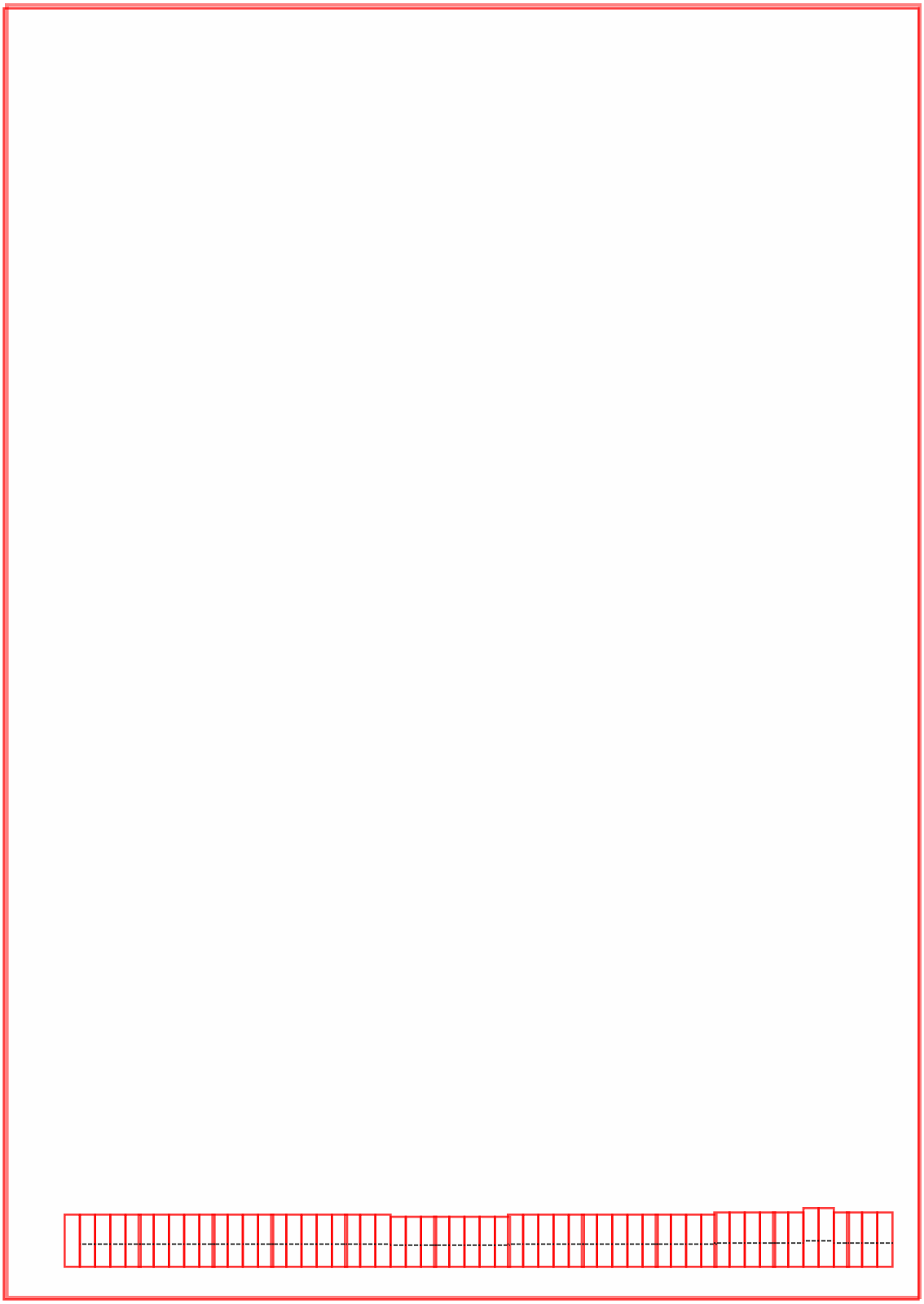
Appendix 14

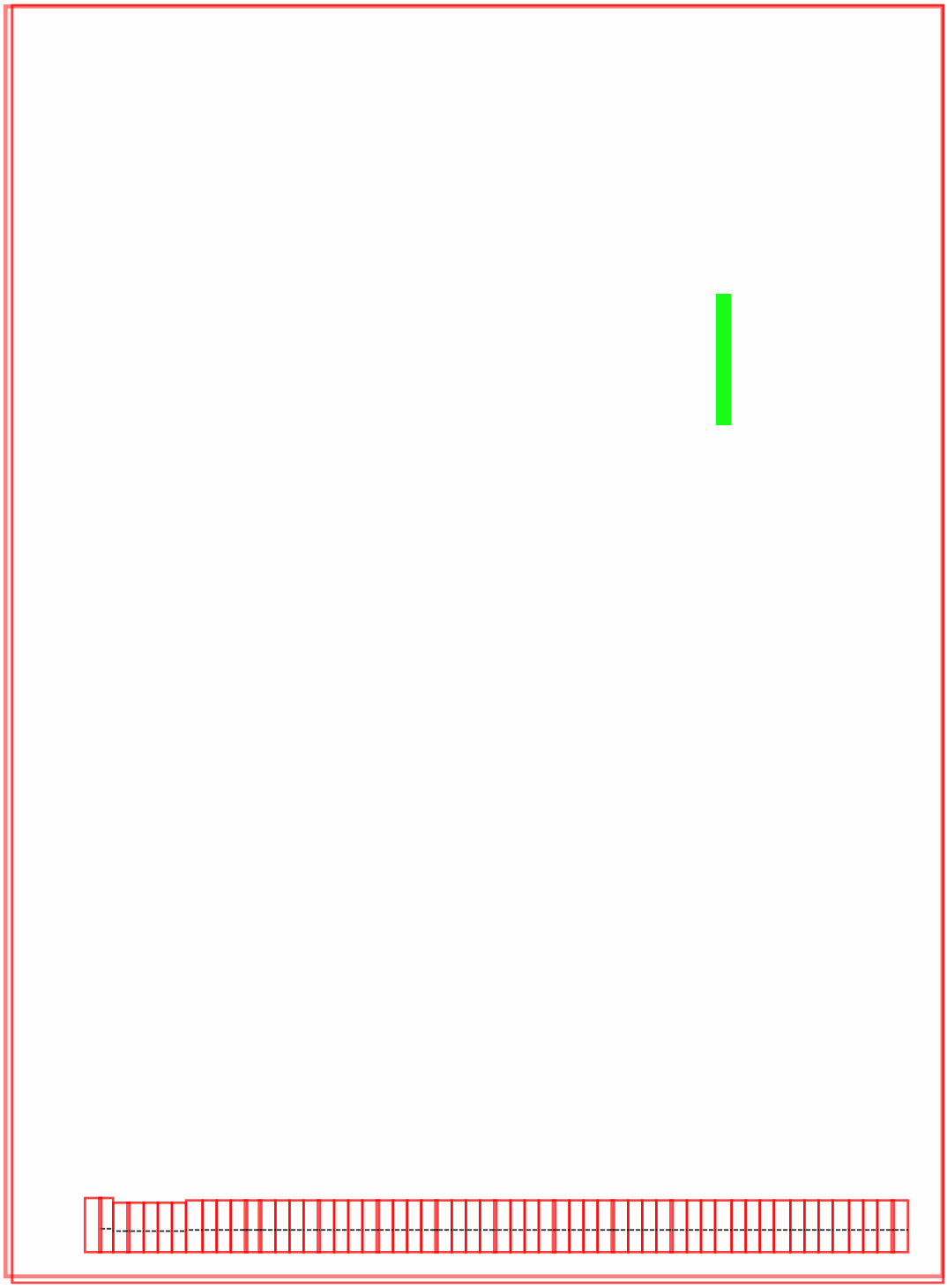
TTM Compliance By Subject

BIOSENSE WEBSTER IDE #
CONFIDENTIAL DB LOCK
= 13JUN2008

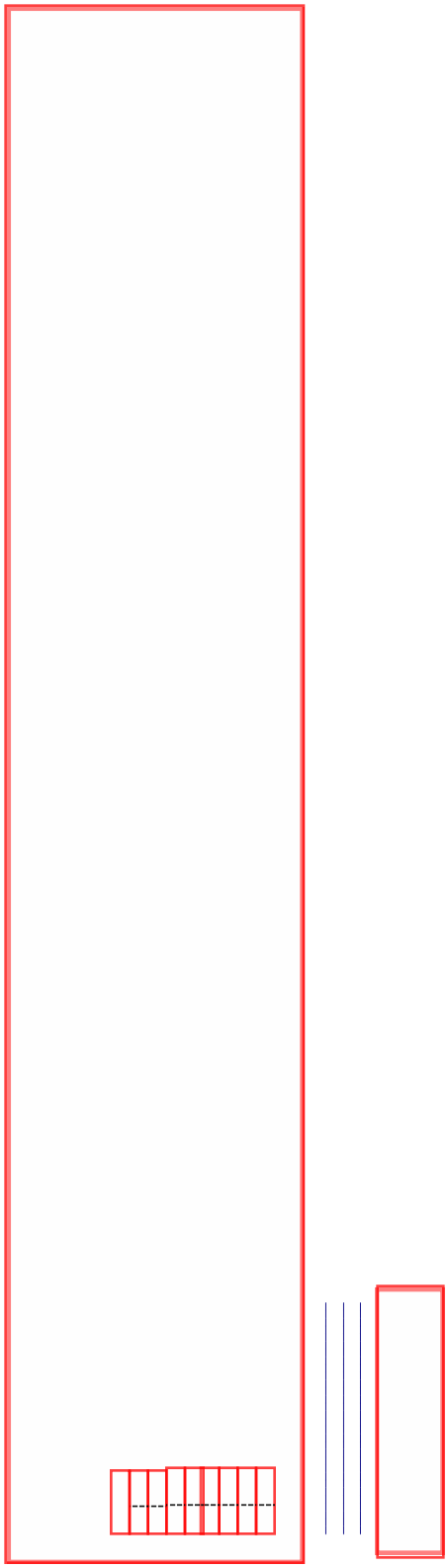
ThermoCool Atrial Fibrillation
IDE

Transtelephonic (TTM) Compliance -
Patient Summary





ThermoCool Catheter - Atrial Fibrillation Indication
Panel Pack
PMA Supplement P030031/S11



Appendix 15

Primary Safety Endpoint - Primary AE Summaries

Subject Summaries of Primary AEs Occurring Within 7 Days Post-procedure (Primary Safety Cohort, n = 139)

Subject Identification	AE Description	Body System	Causality	Intervention	Impairment of a Body Function or Damage to a Body Structure	Outcome
	Vascular Access Complication – AV Fistula	Vascular Disorders	Procedure Related	Surgical Repair	Moderate	Resolved
	Hospitalization – AF recurrence	Cardiac Disorders	Unrelated to Device or Procedure	None	None	Resolved
	Hospitalization – Decreased Hemaglobin	Blood and Lymphatic System Disorders	Procedure Related	Blood Transfusion	None	Resolved
	Hospitalization – Edema	Vascular Disorders	Procedure Related	Lovenox Therapy for Low INR	Mild	Resolved
	Vascular Access Complication – hematoma	Skin and Subcutaneous Tissue Disorders	Procedure Related	Reduced Anticoagulation Therapy	Mild	Resolved
	Pulmonary Edema	Respiratory Disorder	Possibly Device Related and Possibly Procedure Related	Diuresed	Severe	Resolved
	Vascular Access Complication – AV Fistula	Vascular Disorders	Procedure Related	local compression	None	Resolved
	Vascular Access Complication – Pseudoaneurysm	Vascular Disorders	Procedure Related	Thrombin Injection	None	Resolved
	Hospitalization - Hematuria	Renal and Urinary Disorders	Procedure Related	None	None	Resolved
	Hospitalization – AF Recurrence	Cardiac Disorders	Unrelated to Device or Procedure	Chemical Cardioversion	None	Resolved
	Pericarditis	Infections and Infestations	Procedure Related	Levofloxacin & Anxiolytic Therapy, Pericardiocentesis, and Thoracentesis	None	Improved
	Hospitalization – AF Recurrence	Cardiac Disorders	Unrelated to Device or Procedure	DC Cardioversion or Spontaneous Conversion	None	Resolved
	Vascular Access Complication	Vascular Disorders	Procedure Related	Femstop Applied	None	Resolved
	Hospitalization – Pneumonia	Respiratory, Thoracic and Mediastinal Disorders	Unrelated to Device or Procedure	Antibiotics, Oxygen, and Bronchodilator Therapy	None	Resolved

Subject Summaries of Primary AEs Occurring Within 7 Days Post-procedure (Primary Safety Cohort, n = 139)

Subject Identification	AE Description	Body System	Causality	Intervention	Impairment of a Body Function or Damage to a Body Structure	Outcome
	Hospitalization – Atrial Flutter Recurrence	Cardiac Disorders	Unrelated to Device or Procedure	DC Cardioversion	None	Resolved
	Pericardial Effusion	Cardiac Disorders	Procedure Related	None	None	Resolved

Note: Some subjects experienced more than one AE.

Primary Safety Endpoint – Primary AE Summaries

Case Histories of All Subjects with primary AEs (n = 15)

Primary AE Summaries for subjects undergoing an ablation procedure (THERMOCOOL group subjects and AAD (Control) group subjects undergoing an ablation procedure).

THERMOCOOL Group:

The investigator considered this event serious and unanticipated. The causality of the event was assessed as not related to device-treatment and not related to the ablation procedure.

---**– Hospitalization (x2); Decreased Hemoglobin Levels; Edema/Cough/Shortness of Breath/Pain in Lower Extremities Requiring Hospitalization**

considered the event serious and anticipated. The causality was assessed as not related to the device and related to the ablation procedure.

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the ablation procedure.

---- **– Hospitalization; Pulmonary Edema**

The investigator considered this event serious and anticipated. The adverse event is assessed as possibly related to device-treatment and possibly related to the ablation procedure.

The investigator considered these events non-serious and unanticipated. The causality of the adverse event was assessed as not related to device treatment, and related to the ablation procedure.

The investigator considered this event serious and anticipated. The causality was assessed as not related to device-treatment and not related to ablation procedure.

The investigator considered this event as serious and unanticipated. The causality was assessed as not related to device-treatment and not related to ablation procedure.

The investigator considered this event serious and unanticipated. The causality of the event was assessed as not related to device-treatment and related to the ablation procedure.

The investigator considered this event serious and unanticipated. The causality of the adverse event was assessed as not related to device treatment and not related to the ablation procedure.

The investigator considered this event serious and anticipated. The causality of the event was assessed as not related to device-treatment and related to the ablation procedure.

The investigator considered this event serious and anticipated. The causality of the event was assessed as not related to device-treatment and related to the ablation procedure.

AAD (Control) Group:

--- **– Vascular Access Complication; AV Fistula (AAD (Control) Subject**

The investigator considered this event serious and anticipated. The causality of the event was assessed as not related to device-treatment and related to the ablation procedure.

– Hospitalization; Hematoma (AAD Undergoing an Ablation Procedure)

The investigator considered this event serious and anticipated. The causality of the event was assessed as not related to device-treatment and related to the ablation procedure.

---- **– Vascular Access Complication; Dyspnea; Pericardial Effusion (AAD Undergoing an Ablation Procedure)**

The investigator considered this event serious and anticipated. The adverse event is assessed as not related to device-treatment and related to the ablation procedure.

---- **– Vascular Access Complication (AAD (Control) Subject Undergoing an**

The investigator considered this adverse event serious and unanticipated. The causality of the adverse event was assessed as not related to device-treatment but related to the ablation procedure.

– Emergency Department Visit; Pericarditis/Epistaxia (AAD (Control)

The investigator considered this event serious and anticipated. The causality was assessed as not related to device-treatment and related to ablation procedure.

The investigator considered this event non-serious and unanticipated. The causality was assessed as not related to device-treatment and not related to ablation procedure.

The investigator considered this event serious and anticipated. The causality was assessed as not related to device-treatment and possibly related to ablation procedure.

The investigator considered this event non-serious and anticipated. The causality was assessed as not related to device-treatment and possibly related to ablation procedure.

Appendix 16

Narratives - Serious Non-Primary AEs </= 7 days

Subject Summaries of Serious Non-Primary AEs Occurring Within 7 Days Post-procedure (Primary Safety Cohort, n = 139)

Subject Identification	AE Description	Body System	Causality	Intervention	Impairment of a Body Function or Damage to a Body Structure	Outcome
SAE Non-CR						
	Disruption and Tearing of Atrial Septum of Thrombus	Cardiac Disorders	Procedure Related	None	Moderate	Unchanged
	Urinary Tract Infection	Infections and Infestations	Procedure Related	Antibiotics	None	Resolved
	Nodule on Left Kidney	Renal and Urinary Disorders	Unrelated to Device or Procedure	Surgical Resection	None	Resolved
	Tumor between Right Kidney and Right Hepatic Lobe	Neoplasms Benign, Malignant and Unspecified	Unrelated to Device or Procedure	Surgical Resection	None	Unchanged
	Hemoptysis	Respiratory, Thoracic and Mediastinal Disorders	Possibly Procedure Related	None	None	Resolved
	Hematuria – Traumatic Foley Placement	Renal and Urinary Disorders	Unrelated to Device or Procedure	None	Mild	Resolved
	Emergency Department Visit-Cat 2 – AF Recurrence	Cardiac Disorders	Unrelated to Device or Procedure	Chemical Cardioversion	None	Resolved

Note: Some subjects experienced more than one AE.

Case Histories of All Subjects with Serious Non-Primary AEs (n = 5)

Serious non-primary AEs summaries for subjects undergoing an ablation procedure (THERMOCOOL group subjects and AAD (Control) group subjects undergoing an ablation procedure).

THERMOCOOL Group:

The investigator considered these events serious and unanticipated. The causality of both adverse events were assessed as not related to device treatment and not related to the ablation procedure.

The investigator considered these events serious and unanticipated. The causality of the adverse event was assessed as not related to device treatment and possibly related to the ablation procedure.

The investigator considered this event serious and anticipated. The causality of the adverse event was assessed as not related to device treatment and not related to the ablation procedure.

AAD (Control) Group:

---**– Other: Disruption and Tearing of Atrial Septum or Thrombus (AAD**

The investigator considered these events serious and unanticipated. The causality of the adverse event was assessed as not related to device treatment and related to the ablation procedure.

---**– Other: Hematuria (AAD Undergoing an Ablation Procedure)**

The investigator considered this event serious and unanticipated. The causality was assessed as not related to device-treatment, and not related to ablation procedure.

Appendix 26

Bayesian Analysis Excluding ----

Appendix 27

Bayesian Analysis Imputation of AAD Subjects

Tab 8

Proposed Post-Approval Study

Biosense Webster
a Johnson & Johnson company

MEMORANDUM

Prepared By:	BWI AF PMA Team
Subject:	Clinical Study Outline / Clinical Strategy for Condition of Approval Atrial Fibrillation Study
Date:	September 24, 2008
CC:	

Clinical Study Outline

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Tab 9

Publications Disc