FDA Executive Summary

Prepared for the
November 20, 2008 meeting of the
Circulatory System Devices Panel

P030031/S011
NaviStar ThermoCool RF Ablation Catheters
Biosense Webster, Inc.

Introduction

This is the FDA Executive Summary for the NaviStar ThermoCool RF ablation catheter system (P030031/S011). The device has been reviewed by the Division of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration.

The Executive Summary begins with a brief discussion of the regulatory history of this device, followed by a summary of FDA's review of the device description, preclinical, and clinical information. It concludes with an appendix that provides reference information on the application of Bayesian statistics.

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Regulatory History
A chronology of the key milestones with respect to this premarket approval application (PMA) application is provided below.

- **December 10, 2003 –** FDA approved an original investigational device exemption (IDE) for the NaviStar ThermoCool catheters for treatment of symptomatic paroxysmal atrial fibrillation (AF).
- **November 5, 2004** – FDA approved an original PMA for NaviStar and Celsius ThermoCool Diagnostic/Ablation Catheters for treatment of type I atrial flutter.
- **August 11, 2006** – FDA approved an original PMA for NaviStar ThermoCool Catheters for treatment of recurrent drug/device refractory sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction (MI) in adults.
- **October 10, 2007 –** Regarding the AF IDE application, sponsor notified FDA that it met interim analysis criteria to close enrollment.
- **August 13, 2008** – Sponsor submitted a Panel-Track PMA supplement (P030031/S011) requesting to add the indication of treatment of drug refractory symptomatic paroxysmal atrial fibrillation to the ThermoCool diagnostic/ablation catheter family.

This FDA review and Panel discussion focus on the data submitted in P030031/S011.

Proposed Indications for Use

The Biosense Webster NaviStar ThermoCool Diagnostic/Ablation Catheter is already 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; and

b) Recurrent drug/device refractory sustained monomorphic ventricular tachycardia (VT) due to prior myocardial infarction (MI) in adults.

The proposed new indication for use is the “treatment of drug refractory symptomatic paroxysmal atrial fibrillation”.

Device Description

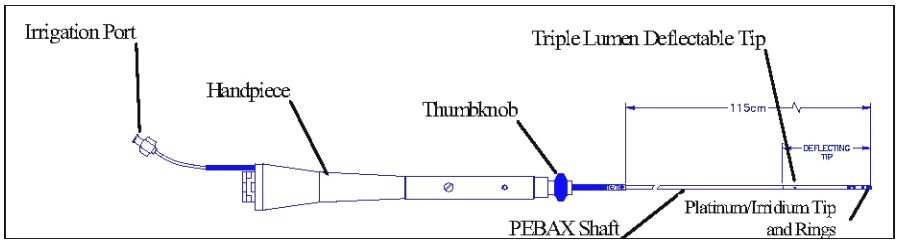
The Biosense Webster ThermoCool family of catheters consists of several different models of open-loop irrigated tip diagnostic/ablation catheters designed to be used with the Stockert 70 radiofrequency (RF) generator to deliver radiofrequency (RF) ablation energy to cardiac tissue.

The different catheter names and respective approved indications and key components are described in the table below:

Catheter Name	Indications	Location Sensor (CARTO)	Deflection Mechanism	Irrigated Tip
NaviStar Thermocool	Atrial Flutter, VT	Yes	Manual, Unidirectional	Yes
Celsius ThermoCool	Atrial Flutter	No	Manual, Unidirectional	Yes
NaviStar ThermoCool RMT	Atrial Flutter, VT	Yes	Computer-assisted Remote Magnetic	Yes
EZ Steer ThermoCool Nav	Atrial Flutter, VT	Yes	Manual, Bidirectional	Yes
EZ Steer ThermoCool	Atrial Flutter	No	Manual, Bidirectional	Yes

The family of catheters can be divided into manually deflectable catheters with (NaviStar ThermoCool, and EZ Steer ThermoCool navigational) and without (Celsius ThermoCool, and EZ Steer ThermoCool non-navigational) location sensors for use with the CARTO™ EP Navigation System, and magnetically steerable catheters for use with the Stereotaxis Niobe system (NaviStar RMT Thermocool). All devices have similar performance characteristics with regards to delivery of ablation energy to the heart, as verified by bench and animal testing. In addition all of the catheters have irrigated ThermoCool tips.

The NaviStar ThermoCool catheter shaft measures 7.5F with 8.0 F ring electrodes; the functional length is 115 cm.



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 radiofrequency current from the radiofrequency generator to the desired ablation site. The tip electrode and ring electrodes are made from platinum-iridium with 2-5-2 spacing of the ring electrodes. 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 thumb knob on the piston controls piston travel. At the proximal end of the catheter, a saline

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, normal saline is passed through the 0.027" diameter lumen of the catheter and through the tip electrode, to irrigate and cool the ablation site. This catheter has 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.

Comparison of NaviStar & Celsius Catheters

The NaviStar ThermoCool and the Celsius ThermoCool Catheters are similar; however, the NaviStar ThermoCool Catheters have the ability to interface with the CARTO EP Navigation System (due to the incorporation of the location sensor) to create electroanatomic maps, whereas the Celsius does not.

The sponsor has provided a discussion, supported by the peer reviewed literature, that localization is not necessary for performing an effective ablation with the ThermoCool family of catheters. The supporting literature is largely from experience outside the U.S. and in many instances includes electroanatomic localization using a non-CARTO system.

The Panel will be asked whether the study results support an indication for AF treatment in devices without electroanatomic location capabilities.

RMT Feature

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. Tip deflection is controlled by the interaction of magnets placed in the catheter tip and shaft, and the magnetic field created by the Stereotaxis MNS. The Stereotaxis MNS consists of computer-controlled magnets whose movement is reflected in the deflection of the catheter tip.

EZ Steer Feature

The EZ Steer ThermoCool Catheters (navigational and non-navigational) are essentially standard NaviStar and Celsius ThermoCool Catheters modified for bi-directional deflection. The "NAV" version has a sensor incorporated to allow localization using the CARTO system. The non-"NAV" version does not have the location sensor (and thus is not equipped to create electroanatomic maps with the CARTO EP Navigation System).

Key Definitions

AF episode – an episode of atrial fibrillation 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.

Blanking period – 90-day period between ablation procedure and the initiation of the 9-month follow up period during which up to two additional ablation procedures could be performed and patients could be prescribed previously ineffective antiarrhythmic drugs at a previously ineffective dose.

Censored Patient – a patient who had not completed follow up, and had not failed the effectiveness endpoint.

Chronic success - 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)]. Beta blockers (BB), calcium channel blockers (CCB), digitalis, angiotensin receptor blockers or angiotensin converting enzyme (ACE) inhibitors will be considered as AADs for purposes of determining efficacy of the ablation or AAD treatment.

Discontinued Subjects - subjects who met the following "discontinued criteria" for their corresponding randomization:

- ThermoCool Group – Subjects in whom the study catheter was 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 who 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).

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

Enrolled Subject - subjects who were eligible for enrollment, signed an informed consent document, and randomized to a treatment group.

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

Overall Safety Cohort - comprised of randomized subjects, in the ThermoCool group, in whom the study catheter was 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.

Primary Safety Cohort for ThermoCool - comprised of subjects who underwent an ablation procedure with the study catheter. This group includes subjects who 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.

Pulmonary Vein (PV) stenosis – greater than or equal to 70% diameter reduction of the PV from the baseline CT/MRA scan as interpreted by a core lab.

Serious Adverse Event (SAE) - 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:

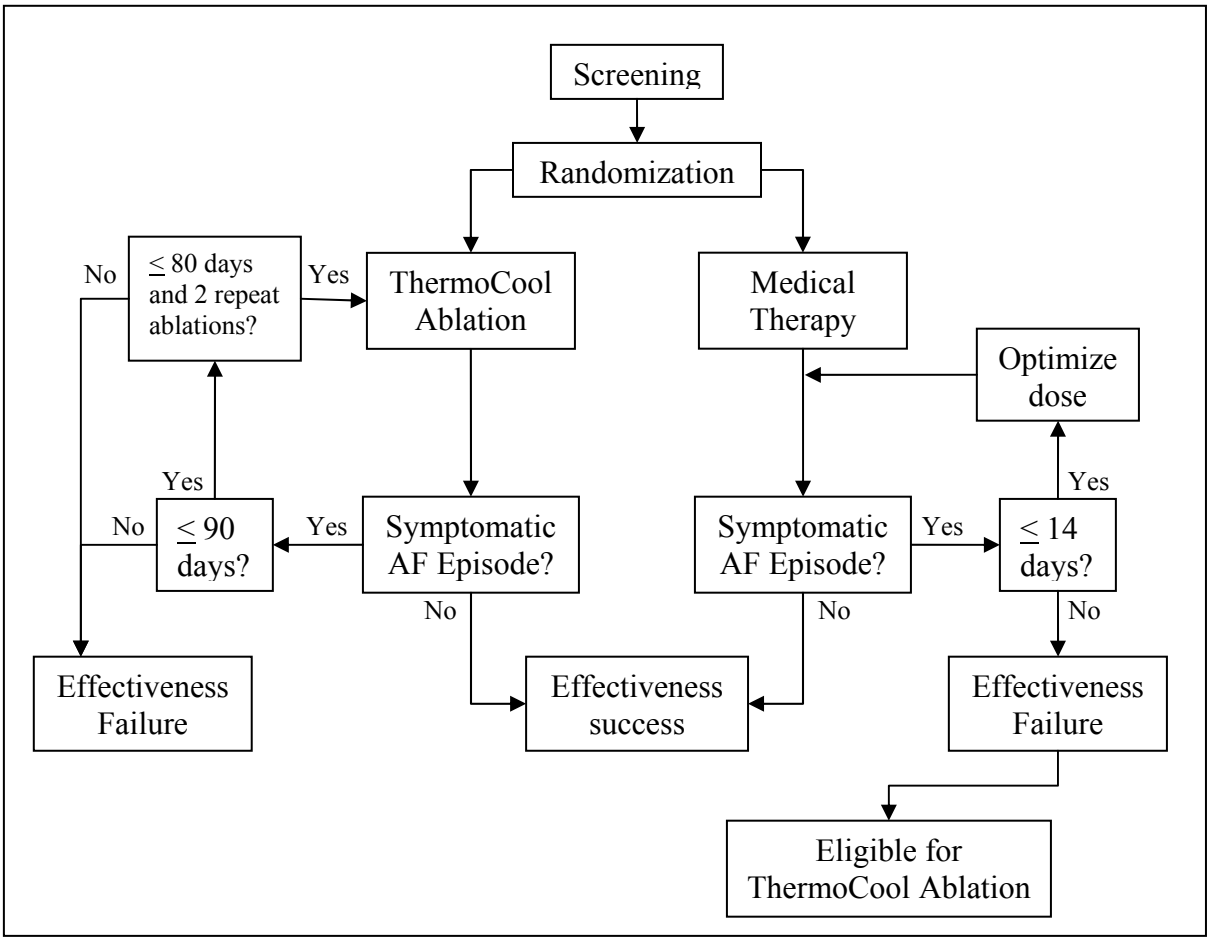
- Pacemaker implantation for nodal dysfunction rhythms (sick sinus syndrome, sinus bradycardia, sinus arrest or AV blocks) that resulted in symptomatic bradycardia (related to pre-existing disease states)

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, trans telephonic monitoring (TTM) and/or Holter monitor. Symptoms may have included palpitations, irregular pulse (i.e. rapid, racing, pounding, fluttering, bradycardic), dizziness, weakness, chest discomfort, and breathlessness.

Study Design

The study was a prospective, randomized, unblinded, multi-center pivotal clinical investigation involving 19 centers and 167 subjects with symptomatic paroxysmal atrial fibrillation (PAF) who were refractory or intolerant to antiarrhythmic drug (AAD) therapy. The randomization allocation ratio was 2:1, atrial fibrillation (AF) ablation treatment to medical therapy.

The following flow chart describes the general study design:



Subjects in the ThermoCool group could undergo up to 2 repeat ablation procedures within 80 days following the initial AF ablation procedure. Repeat ablation was allowed because experience has demonstrated that many patients require more than a single procedure to achieve success.

In the ablation group, during the 90 day blanking period 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 the dose of a previously ineffective AAD increased, 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 beta blockers (BBs) and/or calcium channel blockers (CCBs) during the blanking period, the subject was 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.

Subjects who 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.

Amiodarone use within six (6) months of enrollment was an exclusion criterion. The sponsor developed this approach in accordance with FDA's policy as described in the guidance document titled "Clinical Study Designs for Percutaneous Catheter Ablation for Treatment of Atrial Fibrillation" (http://www.fda.gov/cdrh/ode/guidance/1229.html). The guidance recommended amiodarone exclusion because the drug (at time of the issuance of the guidance in 2004 and as of today) is not approved for treatment of atrial fibrillation and also amiodarone's very long half-life makes assessment of catheter treatment effectiveness more difficult.

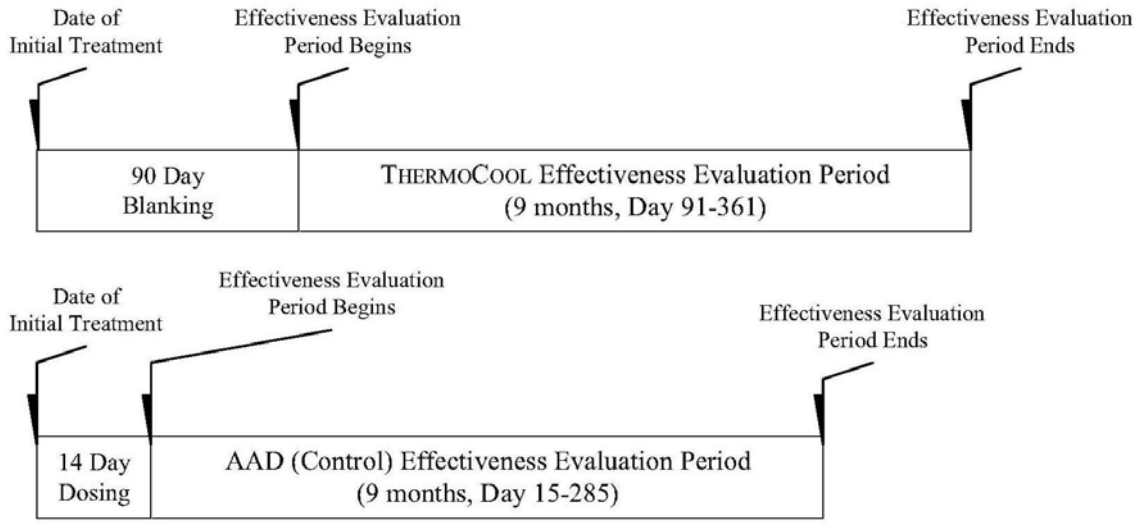
Acute success for the ablation of PAF was defined as the confirmation of entrance block into all targeted pulmonary veins (PVs).

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 BBs and CCBs] during nine months following treatment [Days 91-361 for the ThermoCool group and from Days 15-285 for the AAD (Control) group].

Transtelephonic transmissions (TTM) were to be provided 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.

The effectiveness evaluation windows for the device and drug arms are described in the figure below:

FIGURE 2.2.3.1A Effectiveness Evaluation Windows (270 days)



The analysis for the primary effectiveness endpoint uses Bayesian methodology (see Appendix 1). Thus, the success criterion is based on Bayesian posterior probability. Specifically, the primary effectiveness endpoint would be considered met if the posterior probability that ablation is superior to control in chronic success exceeds 0.98.

The primary safety endpoint was the proportion of subjects undergoing ablation who experienced early onset (within 7 days of ablation procedure) of primary adverse events. The primary safety endpoint would be considered met if the upper 95% confidence limit on the proportion of primary AEs does not exceed 16%.

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.

Interim Monitoring and Adaptive Design

The sponsor had difficulty enrolling patients due to various reasons including: subjects not meeting the protocol criteria for having sufficient AF episodes in the period prior to enrollment, subjects having a previous ablation for AF, and unwillingness to participate in a randomized study. To increase enrollment, the sponsor modified the inclusion criteria in the study protocol, allowing enrollment of patients that had failed only class II/IV AADs (i.e. rate-control therapy) and added high volume ablation centers outside the United States.

In addition, on December 7, 2006, the sponsor proposed to change the study design to a (Bayesian) adaptive design that allowed for interim assessments of futility and effectiveness, as well as interim looks for stopping enrollment (up to a max of 230 patients). At the time the sponsor proposed the modification to an adaptive design, there were already 106 patients enrolled, with 18 patients known to have completed their 9-month follow-up. However, the sponsor was blinded to the chronic result for any patient.

The FDA review team believed it was problematic to introduce the Bayesian adaptive design after the trial had already begun and enrolled 106 subjects (almost 50% of the previously determined maximum). However, the sponsor emphasized that only 18 subjects had completed their nine-month evaluation period, and furthermore, that they were blinded to any chronic results. After several meetings with the sponsor, FDA agreed to the change in design, but recommended that the sponsor treat the first 106 patients as an interim look (but with zero chance of stopping), with appropriate alpha penalty. The sponsor agreed to this, and incorporated the 106-look into any simulations to determine operating characteristics of the statistical model. As a result, FDA believed that this issue was satisfactorily resolved.

Interim assessments were based on the Bayesian predictive probability of superiority (of ablation over control) at the end of the trial, for all enrolled subjects at the time of the calculation of the probability. Because the final outcomes of some enrolled subjects were not yet known at the time of the interim look, they were predicted, using information from the subjects with outcomes, as well as a statistical model for time-to-chronic-failure (described below). In addition, variability in the predicted (or, imputed) values was incorporated into the analysis by using multiple imputation from the posterior distribution of the unknown outcomes.

According to the adaptive design, when accrual reached sample sizes of 150, 175, and 200, an interim analysis would be performed. If the predictive probability of trial success including all enrolled patients so far, based on knowing only the information at the time of the interim look, was at least 0.90 at the 150-look or 0.80 at the 175- and 200-looks, then accrual would stop and the sample size would be the final sample size. Also, if the predictive probabilities of success for the current sample size and the maximum sample size (230) are less than 0.01 for the 150-, 175-, or 200-look then the trial would stop for futility. Otherwise, the sponsor would continue to enroll patients. After stopping accrual, according to the protocol, the sponsor would wait either 4.5 months or until 50% of enrolled patients had complete effectiveness outcomes (whichever comes first), in order to make an early claim of success. At such time, if the predictive probability of success exceeded 0.99, then the sponsor would make an early claim of success.

Predictive probability calculation

In order to get a predictive distribution for the unknown results, the sponsor needed to develop a model for patient response. The sponsor modeled the time at which an event took place as an exponential, with rate varying across time. There were 3 time periods (from 0 to 0.5 months, from 0.5 months to 2 months, and from 2 to 9 months). Each time period had a different rate. The rates were given identical prior gamma distributions, whose hyper-parameters were given exponential distributions with rate 1. Although the 3 rates (for the 3 time periods) are distinct across treatment groups, the prior distributions on the rates are the same for each treatment group.

Once all enrolled patients' predicted (or known) event times are obtained, one can compute the binary value of success or failure for each patient, as well as the primary effectiveness "statistic" (i.e. the posterior probability of superiority of ablation versus control).

The value of the posterior probability determines whether the trial is successful (if the posterior probability exceeds 0.98, then it is a successful trial). Because there is an entire distribution of predicted event times for each unknown patient, there will be a *distribution* of

statistic values, and a distribution (or probability) of trial success determinations. The proportion of successful determinations will be the predictive probability of trial success.

The choice of the hazard cut points is subjective. Assuming that the hazard rate changes at specific cut points (2 weeks, and then again at 2 months) could be open to discussion.

At the time of the updated analysis, in June 2008, however, there were 14 unknown (i.e., censored) outcomes, all from the ablation arm, considerably fewer than at the time of the interim analysis. Thus, 14 subjects' success/failure outcomes were imputed using the time-to-event model described by the sponsor. Imputed values were used to derive the predictive probability of superiority at the end of the trial (i.e., once all 159 subjects' outcomes are known). FDA tried a different imputation model, using only binary success/failure outcomes, and not modeling time-to-event information. The resulting predictive probability of study success at the end of the trial was virtually identical to the sponsor's result using the time-to-event model.

Cross-over Ablation Criteria

- 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 tab 7, 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 became eligible for an ablation procedure.
- Control subjects completing their 9-month observation window without experiencing a documented episode of symptomatic PAF became eligible 2 months after their 9-month visit.

Study Endpoints

The following were the pre-specified endpoints for the trial:

Acute safety:	The occurrence of early onset (within 7 days of the ablation procedure) of Primary adverse eventswhich included 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), and Heart block
Acute effectiveness:	Confirmation of entrance block into all targeted PVs.
Chronic effectiveness:	Freedom from symptomatic AF based upon electrocardiographic data and no changes in AAD regimen during nine months following treatment.

Additional Endpoints: 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

AF status evaluated by:

- 24-hour Holter data
- Transtelephonic monitor (TTM) data
- AF frequency/severity checklist
- Quality of Life (QOL) Scores

The acute safety endpoint was compared to a performance goal of 7.0% with an upper confidence bound of 16.0%.

Inclusion criteria

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.

Exclusion criteria

1. AF secondary to electrolyte imbalance, thyroid disease, or reversible or noncardiac 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.

Medical therapy – Control Group

Subjects randomized to the control arm of the study were to receive a "not previously administered" class I or class III anti-arrhythmic drug that was approved for the treatment of atrial fibrillation. Protocol-allowed AADs included dofetilide, flecainide, propafenone, sotalol and quinidine. Amiodarone was not allowed (see above, page 9)

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.

Required pre-ablation procedures

- 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.

Required during the investigational procedure

- 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 stenosis.
- 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.

Optional treatments during the investigational procedure

- Non-PV foci initiating AF in the left and/or right atrium were mapped and targeted.

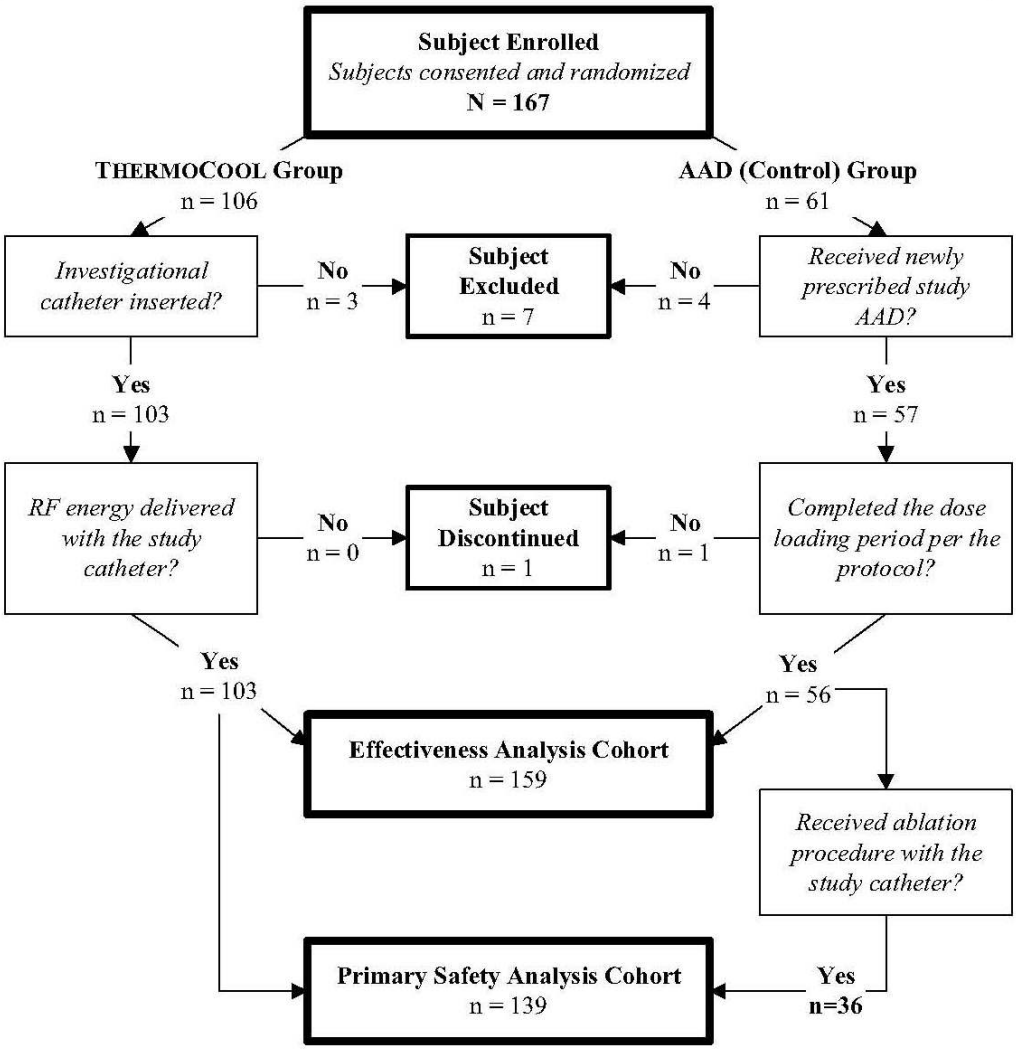
- Ablation along the mitral isthmus between the inferior portion of the left-sided circumferential lesion and the lateral mitral valve annulus was only allowed if left atrial flutter was induced during the ablation procedure.
- Ablation in the cavotricuspid isthmus for the ablation of right-sided, isthmus dependent flutter was only allowed if right atrial flutter was induced during the procedure.

In summary, PV isolation was the required ablation procedure. Additional optional ablation procedures were allowed based on clinical findings after PV isolation was completed. Any non-PV foci identified in the left atrium (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.

Subject accountability

One hundred sixty-seven (167) subjects were enrolled at 19 investigational sites. Fifteen (15) of these sites were located in the US and 4 sites were located outside the US.

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



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.

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). Exclusions occurred in accordance with the protocol.

One subject was discontinued when consent was withdrawn; that subject was randomized to the Control arm.

There was one subject lost to follow-up in the ThermoCool group and no subjects in the AAD (Control) group. This subject 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.

Subject demographics

As seen below subject demographics and medical history were well matched between the treatment and control groups.

	Treatment Group		Total n=167 (%)
	ThermoCool n=106 (%)	Control n=61 (%)	
Gender			
Female	33(31.1)	23(37.7)	56 (33.5)
Male	73 (68.9)	38 (62.3)	111 (66.5)
Age			
Mean	55.5	56.1	55.7
Standard Deviation	9.34	12.84	10.72
Median	56	58	57
Range	32-76	19-77	19-77

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
NYHA class			
Class I	81/93 (87)	50/58 (86)	1.0000
Class II	12/93 (13)	8/58 (13)	
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; CCF-0003 and HUP-0001 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 one 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%.

Study Results

Interim Effectiveness Analysis

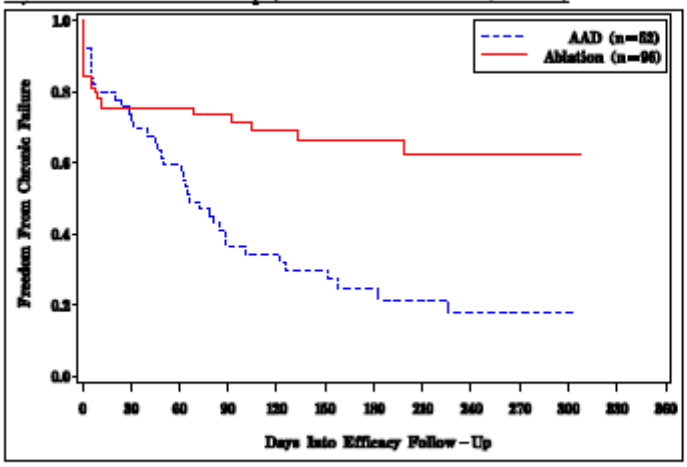
The sponsor performed the first interim analysis when 160 subjects had been enrolled. The predictive probability that the chronic success rate for the ablation group would be superior to the control group when all 160 subjects reached an event or 9 months of follow-up was calculated as > 0.999 With this result the sponsor could stop enrollment into the trial, according to the interim analysis plan. At the time this decision was made, 50% of enrollees had an effectiveness endpoint determination. So, the sponsor stopped the trial and concluded effectiveness, as per the interim analysis plan.

The following table and figure are from the sponsor's report. The interim status of the enrolled subjects, is noted when the sponsor decided to stop the trial.

Appendix 9, Table 2: A Summary of the Current Status for Each of the Enrolled Subjects

Group	Success	Censored	Fail	N
Control	6	8	38	52
Treatment	16	55	25	96

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.

Final Effectiveness Analysis

The Primary Effectiveness Analysis was based on a determination of chronic treatment success. Per the final approved protocol, chronic effectiveness at interim analyses was assessed using a Bayesian modeling approach. The final approved protocol allowed for a maximum of three interim analyses. The trial was stopped at the first interim analysis (September 2007) with a sample size of 160 subjects. Seven patients were subsequently enrolled during the period before the trial was officially discontinued, due to a time lag in completing the interim analysis. For the purposes of the PMA, the data were analyzed using a June 2008 dataset (sample size 167 subjects) to provide a more complete clinical report. With this dataset, only 14 (ThermoCool) subjects still have unknown outcomes. Thus, for

the predictive probability calculation, these 14 outcomes are imputed using the time-to-event imputation model developed by the sponsor.

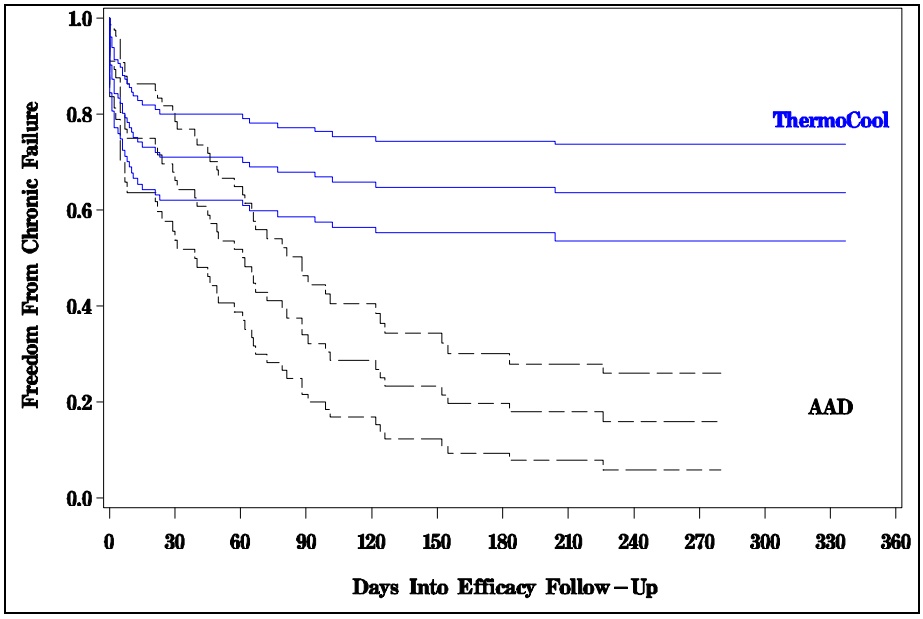
The primary effectiveness endpoint was freedom from recurrent symptomatic AF during the 9 month evaluation period, as documented by periodic event recordings and/or symptom-driven 12-lead ECGs. Overall compliance with event recordings (defined in the protocol as the percentage based on the number of event recording transmissions within an expected time-frame divided by the total number of expected event recording transmissions per subject) was 89%. At the time of the June 2008 analysis, 14 ThermoCool ablation group subjects had not yet fulfilled their contribution to the chronic effectiveness endpoint; therefore, the evaluable cohort was 89 subjects. There were 36 chronic effectiveness failures and 53 chronic effectiveness successes in the ThermoCool Group. At the time of the June 2008 analysis, all 56 Control group subjects had fulfilled their contribution to the chronic effectiveness endpoint. According to the sponsor, there were 47 chronic failures out of 56. The chronic success results (as presented by the sponsor) may be summarized as follows:

TABLE 3.6.2.2B A Summary of the Enrollment Status for Each of the Enrolled Subjects (June 2008 dataset, n = 159)

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

The sponsor also provided the updated Kaplan-Meier curves, which are provided below.

FIGURE R3.6.2.2A Kaplan-Meier Failure-Free Curves For Each Treatment Group with 95% CI



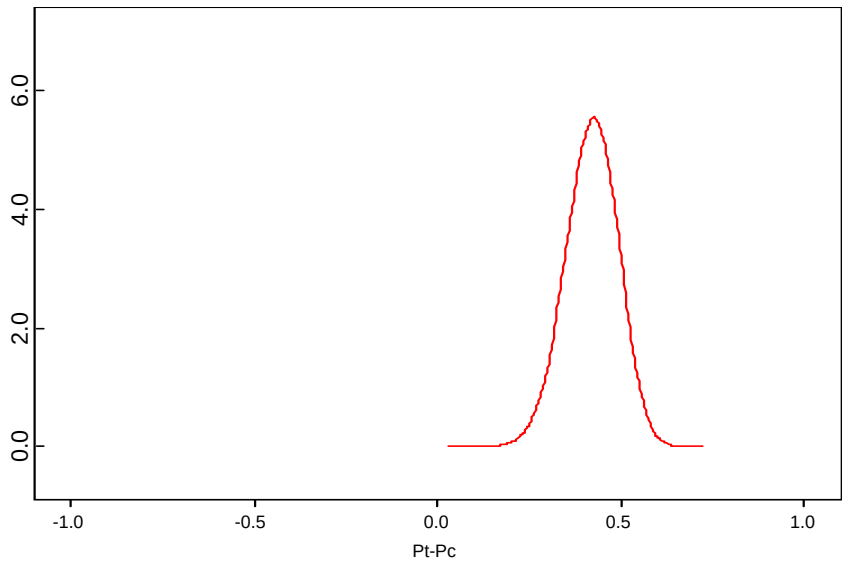
Number of Subjects at Risk

Time	0	30	60	90	120	150	180	210	240	270	300	330	360
ThermoCool	103	69	69	66	63	62	61	54	52	37	15	3	2
AAD	56	39	29	19	16	13	11	10	7	2	0	0	0

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 Control Group.

The posterior probability of superiority of ablation over control in terms of chronic success, given the data observed at the time of the final analysis, was greater than 0.999, which exceeded 0.98, the posterior criterion. Also, if accrual would have continued to 230 subjects, then the predictive probability that when all the 230 had complete information, that the posterior probability of superiority for the treatment group would be greater than 0.98 (the pre-specified criterion), is >0.9999.

To see this in graphical format, below is plotted the posterior distribution of Pt, the probability of chronic success for the ablation group, minus Pc, the probability of chronic success for the control group. Any unknown chronic outcomes out of the 230 total potential subjects were imputed from their predictive distributions. The fact that almost all of the density falls to the right of 0 is consistent with the predictive probability of superiority (i.e., Pt-Pc > 0) being greater than 0.9999.



The study included a "core lab" for the adjudication of the event recordings. FDA carefully re-reviewed all symptomatic event recordings provided by the sponsor. In general, the FDA review confirmed the core lab determinations.

Four (4) Control Group subjects were prescribed an AAD dose less than the minimum dose recommended by the protocol. Two (2) Control group subjects received less than the protocol specified minimum 24 hr dose and were classified as chronic treatment failures. The protocol deviation for one of these Control group subjects was clearly justified. A second Control group subject received less than the minimum protocol-specified dose of flecainide without a reported side-effect to justify the deviation and was classified as a chronic treatment failure. FDA is unclear as to why this Control subject received less than the minimum protocol-specified dose. Eleven (11) subjects in the Control group were prescribed a previously failed AAD, one of whom is included in the four (4) subjects above. Nine (9) of these subjects were classified as chronic treatment failures.

FDA requested that the sponsor perform a sensitivity analysis that, instead, imputes the chronic effectiveness result of each of the 11 control subjects, using multiple imputation (in

this case, the approach would use the same Bayesian predictive distribution for imputation as was used for the interim analysis). If these 11 control subjects had not been deviations, then assuming they are similar to other control subjects, their chronic effectiveness results might be predicted using results from the other control subjects. This sensitivity analysis found that the deviations had a negligible effect on overall trial conclusion about device effectiveness.

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.

Failed AAD at Baseline

	ThermoCool	Control	Total
Failed class II/IV only	19	7	26
Failed ≥ 1 class I/III	84	48	132
Total	103	55	158

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)		**Control (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)

*One AAD (Control) group subject was excluded from this analysis pending data query.

While the number of subjects who failed a class II/IV AAD is small, and the above table excludes the 14 ThermoCool subjects who have not yet completed their nine-month follow-up, the observed treatment difference in the Class II & IV group versus in the Class I & III group appears qualitatively different. A formal test of interaction between randomization group and failed AAD class is likely not powered to detect statistical significance and would be post-hoc. However, this perceived difference should be explored further.

The Panel will be asked to comment on the interpretation of the chronic effectiveness results when stratified by antiarrhythmic class.

At the time of the June 2008 dataset, 3 of the 36 Control subjects who underwent an ablation procedure with the study catheter were still in their effectiveness evaluation. Of the 33 remaining Control subjects in this group, 21 subjects had successful chronic effectiveness outcomes. The proportion of chronic successes in the Control group that crossed over to ablation therapy is similar to the proportion of chronic successes in the ThermoCool group.

Safety

For the primary safety endpoint, the study hypothesis was that the primary SAE incidence for ablated patients is less than 16%. The target of 16% was obtained from a literature review average of 7%, plus an added 9% "delta". The primary safety null hypothesis was that the primary AE rate was greater than or equal to 16% and the alternative hypothesis was that it

was less than 16%. Thus, if the 95% upper confidence limit is less than16%, the primary safety endpoint would be met.

The primary safety endpoint is defined as the incidence of early onset (within 7 days of a study ablation procedure) primary AEs. This analysis used the Primary Safety Cohort population and included all subjects undergoing an RF ablation procedure with the investigational catheter. There were 139 subjects included in the Primary Safety Cohort. This cohort is composed of 103 subjects from the ThermoCool group and 36 subjects randomized to AAD (Control) group and who subsequently underwent a study ablation procedure after having a chronic effectiveness endpoint determination. Ten (10) out of 103 subjects in the ThermoCool group and five (5) out of 36 subjects in the Control group (that crossed over to ablation) experienced a primary AE.

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 %. Therefore, the result did not meet the protocol-established 95% upper confidence of 16.0% for this study.

Revised TABLE 3.6.5.1A Primary Safety Endpoint Outcome – Primary Adverse Events (modified by FDA)

	Protocol Performance Goal	Number of subjects	% of subjects
Number of Subjects in Safety Cohort		139	
Number of Subjects with Primary AEs		15	
Observed Primary AEs			10.8
One-sided 95% UCB	16.0		16.1

The adverse events included in the Primary AE analysis are the following:

Description	**Number of Subjects with Primary AEs (%)**
Total Serious Primary AEs	**15 (10.8%, 95% UCB 16.1%)**
Hospitalization (initial and prolonged)	7 (5.0 %)
Vascular Access Complication	5 (3.6 %)
Pulmonary Edema	1 (0.7 %)
Pericarditis	1 (0.7 %)
Pericardial Effusion	1 (0.7 %)

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

The vascular access complications consisted of A-V fistulae (2), pseudoaneurysm (1), hematoma (1) and lower extremity pain (1).

The hospitalization complications consisted of AF recurrence (3), anemia (drop in hemoglobin), edema, pulmonary edema, hematuria, and pneumonia. FDA reviewed the clinical summaries for the subjects that experienced a primary adverse event. The nature and rate of the reported adverse events did not raise new safety questions for the review team.

An important secondary safety endpoint characterized serious adverse events (SAEs) that occurred within 90 days, comparing the ThermoCool ablation Group to the Control Group. 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. There were no category 1 SAEs that occurred ≤ 90 days of initial therapy. 19/103 (18.4%) of ThermoCool group subjects experienced a category 2 SAE. 20/57 (35%) of Control Group subjects experienced a category 2 SAE.

Group	**Subjects with Serious Adverse Event ≤ 90 days**			
	Category 1	**Category 2**	**Other***	**Total Subjects with SAEs**
ThermoCool (n=103)	0	19 (18.4%)	2 (1.9%)	21 (20%)
Control (n=57)	0	20 (35%)	1 (1.8%)	21 (37%)
Control Subjects undergoing ablation (n=36)	0	7 (19.4%)	4 (11%)	9 25(31%)

*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. Two subjects experienced more than one SAE.

In the ThermoCool Group, 21 subjects experienced 28 SAEs. The SAEs consisted of multiple episodes of AF recurrence and atrial flutter, and one each of pulmonary edema, pericardial effusion, anemia, vascular access complications, hematuria, edema, dysarthria/vertigo, pneumonia, urinary tract infection, hemoptysis, neoplasm, and Stevens-Johnson syndrome (a serious dermatologic condition).

In the Control Group, 21 subjects experienced 28 SAEs. The SAEs consisted largely of AF recurrence, exercise intolerance and fatigue. Several episodes of life-threatening arrhythmias occurred (3 adjudicated as treatment related, 1 adjudicated as not treatment related, and 1 was not adjudicated).

Assessments for pulmonary vein stenosis occurred pre-ablation, 3 months and 12 months and were based on a core lab interpretation of CT/MRA images. While most ablation subjects developed mild Pulmonary Vein (PV) stenosis (< 50% narrowing), only one subject developed moderate PV stenosis (50-70% narrowing). No ablation subject developed severe PV stenosis (>70% narrowing). No substantial progression in PV narrowing was observed over time, and no ablation subject developed symptoms attributed to PV stenosis.

There was only one death in the enrolled population. The subject died ~ 9 months after undergoing the ablation procedure after experiencing chest discomfort for which he failed to

seek medical attention. FDA has reviewed this case in detail and agrees with the sponsor's determination that the subject's death was unrelated to the investigational device and procedure.

The Panel will be asked to comment on the safety analysis.

Data Poolability

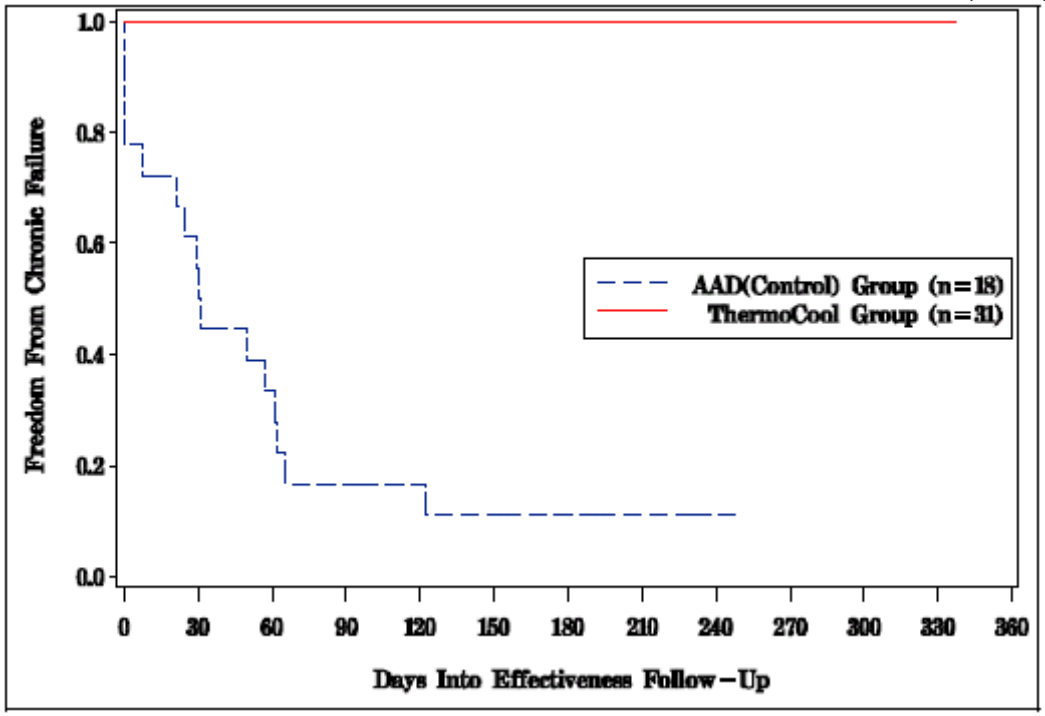
Site variation is observed for the treatment effect. It is primarily due to the better ablation and slightly worse control arm results achieved at one site located outside of the United States (OUS) which had the highest enrollment in the study. This site will be referred to as OUS-1. If we consider time to chronic failure, the ThermoCool group performed much better at the OUS-1 site than at the other sites combined (100% chronic success rate versus 47% chronic success rate at nine months evaluation), and the control group in the OUS-1 site performed slightly worse than at the other sites combined (11% chronic success rate versus 18% chronic success rate in other sites combined). If the difference in results is due to baseline differences in the OUS-1 site versus other sites, then there is a question of whether the same patient populations were recruited across sites in the US versus sites outside the US (in particular the OUS-1 site). However, any differences in subject demographics and baseline assessments were minor and did not impact study results.

Kaplan-Meier curves provided by the sponsor illustrate the better observed performance in the OUS-1 site (figure, page 26).

OUS-1 was the highest enrolling site (n = 50 subjects, 49 in effectiveness analysis), followed by the OUS-2 site with 27 subjects. An interaction test examining the effect of high versus low enrolling sites on chronic success (via logistic regression) demonstrated an interaction effect ($p = 0.02$), with an odds ratios of 44.19 in the high enrolling group (consisting of the OUS-1 and OUS-2 sites) versus 4.19 in the remaining sites combined.

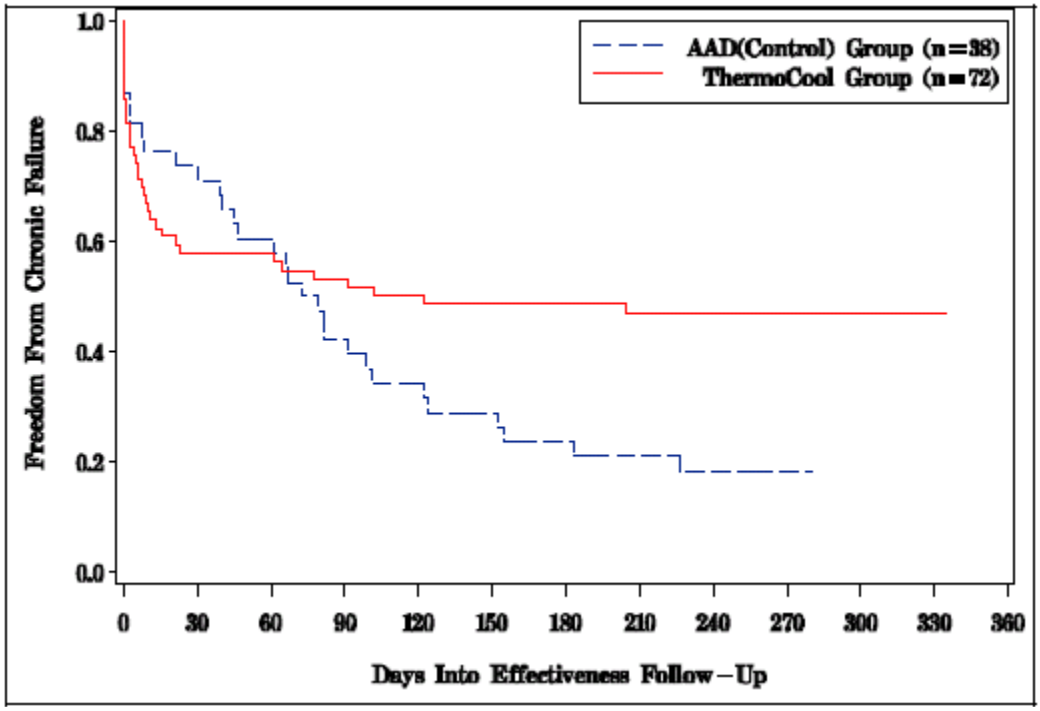
It is evident that the interaction is mostly due to the high performance of the ThermoCool group in the OUS-1 site. A test of the interaction between the OUS-1/remaining site grouping and treatment is not possible, however, using the maximum likelihood estimation of an interaction effect in a logistic regression model because the OUS-1 site had no failures in the ThermoCool randomization group. On the other hand, Bayesian estimation is possible using a vague Gaussian prior on the interaction coefficient. The resulting posterior means of the *log* odds ratios are 6.82 in the OUS-1 group (95% credible interval: 4.098, 10.32) and 1.31 in the remaining site group (95% credible interval: 0.385, 2.308). The posterior probability that the interaction coefficient in the logit model exceeded zero was 1.0 suggesting that interaction is present.

FIGURE 3.6.3.1F KM Curve of Time to Chronic Failure – OUS-1 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 dayspost initial treatment for AAD (Control) Group.

Reasons given by the sponsor for the difference in results between the OUS-1 and remaining sites were:

1. There were no ThermoCool subjects prescribed a new AAD during the effectiveness period. Thus, no ThermoCool subjects at the OUS-1 site failed due to AAD change. However, only 10 of the 36 ThermoCool failures in the remaining sites are due to AAD failure.
2. The control group appeared to perform worse in the OUS-1 site than the remaining sites. The reasons for this difference are not clear to FDA; however, FDA has assurance that the clinical protocol was followed and follow-up on enrolled patients was complete.
3. The ThermoCool ablation catheter has been legally marketed in Europe longer than it has been legally marketed in the U.S. European sites (of which OUS-1 was one) may have more experience with the catheter which may have impacted the success rates.
4. The lead investigator at OUS-1 has more than a decade of RF catheter ablation experience for treating AF, and OUS-1 is one of the highest volume AF ablation centers worldwide.

Of interest, the OUS-1 site performed prophylactic right atrial cavotricuspid isthmus ablation on most of their ablation subjects (23 out of 31), whereas the procedure was performed on a much lower proportion of subjects at other sites (1/72). However, it is not clear to what extent this particular procedure might have influenced the success rate reported from the OUS-1 site.

When the primary safety and effectiveness analyses were repeated by the sponsor, excluding the OUS-1 site, the posterior probability for ablation demonstrating superior effectiveness was 0.999. The upper confidence limit on the safety rate (21.3%) exceeded the pre-specified threshold of 16%. For the primary safety endpoint, the OUS-1 site had 2 subjects with a primary AE out of 46 initial and 4 repeat ablations. The OUS-2 site with 19 initial and 4 repeat ablations had 3 subjects with primary AEs. Remaining sites had 9 or fewer ablations, many with zero or 1 primary AE.

Post-Approval Study Considerations

Should FDA approve this PMA, several questions remain unanswered which might be addressed in an appropriate post-approval study (PAS).

1. The PMA trial included centers with a long history of doing AF ablations. The generalizability of these safety and effectiveness results to less experienced centers is of interest. The PMA data represent experiences at several recognized centers of excellence in ablation for the treatment of paroxysmal AF.
2. The data from the PMA study provide important information on acute and mid-term outcomes. Longer term data to assess durability of effect and the possible effect of ablation on mortality and stroke might be beneficial.
3. The impact of adjunctive right atrial cavotricuspid isthmus ablation on the overall effectiveness of the AF ablation procedure remains unclear at this point. The incorporation of a right atrial ablation procedure may partially explain, for example, the better results noted at the OUS-1 site.

The sponsor proposed a PAS designed to provide additional corroborative long term safety and effectiveness data for the ThermoCool catheter in the treatment of symptomatic paroxysmal atrial fibrillation. The sponsor proposed to follow the subjects for 5-years after the procedure. The hypothesis of the study is that the proportion of PAS patients with a primary AE, at 7 days, is no worse than the RFA treated patients (primary AE rate=11%) in the pivotal trial with a region of indifference of 9%. The study population would consist of 145 ablation PAS subjects and 139 historical control subjects. The ablation PAS group consists of subjects who will be treated with approved ThermoCool catheters in the PAS, while the controls are subjects who were treated with NaviStar ThermoCool catheter in the pivotal study. The secondary safety analysis proposed by the sponsor is a descriptive analysis of the occurrence of serious adverse events at 5 years. The effectiveness analyses include a descriptive analysis of the recurrence of symptomatic AF at 5 years, and descriptive evaluation of the effectiveness outcome in subjects in whom cavo-tricuspid ablation lines are placed in addition to the PV isolation.

FDA is continuing to work with the sponsor on PAS protocols for: (a) the extended follow-up of the premarket cohort (b) evaluation of device performance in general conditions of use, and (c) the evaluation of prophylactic placement of a right sided ablation line on chronic effectiveness

The Panel will be asked to comment on potential PAS study plans, including hypotheses, controls, and length and type of follow-up.

Conclusions

The data presented in the PMA characterize the acute and mid- term safety and effectiveness of the Biosense Webster NaviStar ThermoCool Diagnostic/ablation catheter when used to treat drug refractory recurrent symptomatic atrial fibrillation. The Advisory Panel will be asked to fully assess the significance of these results and comment on the utility of the NaviStar ThermoCool System for the treatment of atrial fibrillation.

Appendix – What is Bayesian Statistics?

Bayesian statistics is an approach for learning from evidence as it accumulates. The Bayesian approach uses Bayes' Theorem to combine prior information with current information on a quantity of interest. The Bayesian idea is to consider the prior information and the trial results as part of a continual data stream, in which inferences are being updated each time new data become available.

When good prior information on clinical use of a device exists, the Bayesian approach may enable this information to be incorporated into the statistical analysis of a trial. However, the Bayesian approach is useful even in the absence of prior information. For example, the approach can accommodate adaptive trials (e.g., interim analyses or change to sample size) and even some unplanned, but necessary trial modifications. Other potential uses include adjustment for missing data, sensitivity analysis, multiple comparisons, and optimal decision making.

The prior distribution

As an illustration, suppose that the Greek letter **θ** represents a parameter in a clinical trial. The initial knowledge about **θ** prior to data collection is represented by the prior distribution for **θ**, which we denote in symbols as P(**θ**). Suppose **θ** is the rate of a serious adverse event. Its possible values lie between 0 and 1. The prior distribution might give preference to lower values of **θ** (see Figure 1). The probability that **θ** takes on any particular set of values is determined by the area under the curve for those values. So the prior probability that the adverse event rate **θ** is greater than 0.4 (the shaded area) is about 0.38.

An *informative* prior distribution gives preferences to some values of the quantity of interest as being more likely than others (See Figure 1). Lack of preference among the values or lack of information can be represented through a *non-informative* prior distribution (e.g., a uniform prior which indicates no preference for any value of **θ**).

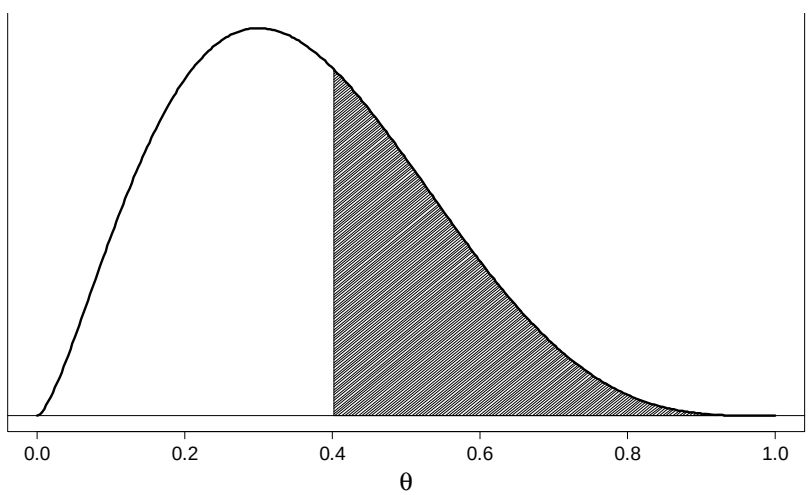


Figure 1. Example of a unimodal, right-skewed prior distribution for a serious adverse event rate, denoted by θ. The prior probability that θ is greater than 0.4 (the shaded area) is about 0.38.

The likelihood of the observed data

Now suppose outcomes have been obtained from a clinical trial. The likelihood function is a mathematical representation of the relationships between observed outcomes and the parameter **θ**. The likelihood function can be expressed in symbols by P(data |**θ**), which is the conditional probability of observing the data given a specific value of the parameter **θ**, for each possible value of **θ**.

The posterior distribution

The final objective is to obtain the posterior distribution, the probabilities of the possible values of the parameter **θ** conditional on the observed data, which can be denoted in symbols as P(**θ**| data). Bayes' theorem is used to update the prior distribution for **θ,** P(**θ**), via the likelihood, P(data|**θ**), to obtain the posterior distribution for **θ**, P(**θ**|data). At the conclusion of the trial, the information about **θ** is summarized by this posterior distribution, and Bayesian inferences are based on it.

As an example, Figure 2 shows the posterior distribution that would be obtained if we started with the prior shown in Figure 1 and observed data with 1 adverse event in 10 patients. Since the adverse event rate observed in these patients is 0.10, the distribution has shifted further to the left (that is, it now favors even lower values for **θ**). The posterior probability that **θ** is greater than 0.4 (the shaded area) is about 0.04. The probability that the adverse event rate is greater than 0.4 has been reduced from about 0.38 (the prior probability) to about 0.04 (the posterior probability) by the favorable trial results.

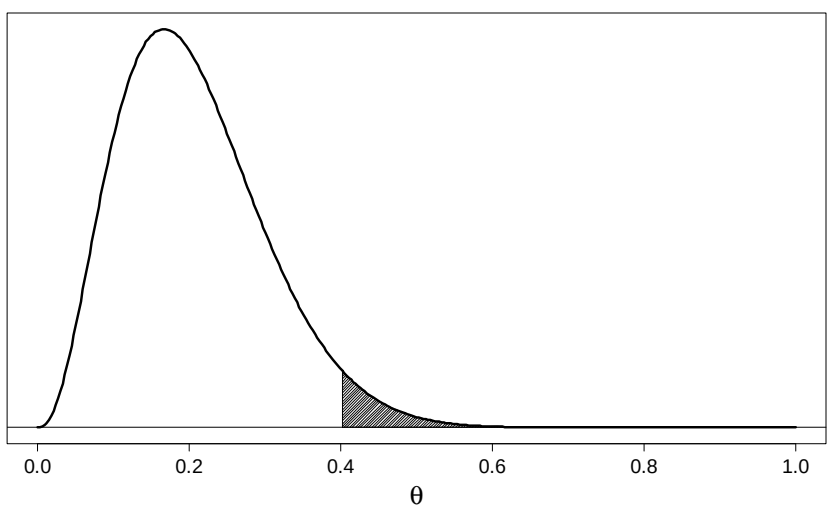


Figure 2. Example of a unimodal, right-skewed posterior distribution for a serious adverse event rate, denoted by θ, after observing one adverse event in 10 patients and updating the prior probability in Figure 1. The posterior probability that θ is greater than 0.4 (the shaded area) is about 0.04.

The posterior distribution that has been obtained today may serve as a prior distribution when more data are gathered. The more information that is accrued, the less uncertainty there may be about the posterior distribution for **θ**. If enough data are collected, the relative importance of the prior distribution will be negligible compared to the likelihood.

Bayesian inferences are based on the posterior distribution. For example, a Bayesian decision procedure might rule out a set of parameter values if the posterior probability of the parameter values (given the observed data) is small.

A pre-specified decision rule is used to demonstrate hypotheses that define safety and effectiveness with reasonable assurance. For Bayesian trials, one common type of decision rule considers that a hypothesis has been demonstrated (with reasonable assurance) if its posterior probability is large enough (e.g., 95 or 99 percent).

The predictive distribution

The Bayesian approach allows for the derivation of a special type of posterior probability; namely, the probability of unobserved outcomes (future or missing) given what has already been observed. This probability is called the *predictive probability*. Collectively, the probabilities for all possible values of the unobserved outcome are called the predictive distribution. Predictive distributions have many uses, including determining when to stop a trial (based on predicting outcomes for patients not yet observed) or adjusting trial results for missing data (imputation).

These uses are discussed in more detail below in **Analyzing a Bayesian Clinical Trial**.

Exchangeability

Exchangeability is a fundamental concept underlying statistical inference. It can be of particular importance in Bayesian trials. Formally, we would say that units (patients or trials) are considered *exchangeable* if the probability of observing any particular set of observations on those units is invariant to any re-ordering of the units.

Exchangeability of patients

In a clinical trial, patients within the trial are usually assumed to be exchangeable. Under exchangeability, patient outcomes are not expected to depend on the order in which the patients were enrolled, the order in which the outcomes are observed, or any other re-indexing or re-numbering of the patients.

If patients in the trial are exchangeable with patients in the population from which they were sampled (e.g., the intended use population), then inferences can be made about the population on the basis of data observed on the trial patients. Thus, the concept of a *representative sample* can be expressed in terms of exchangeability.

Exchangeability of trials

For a Bayesian clinical trial, another level of exchangeability might be assumed. Namely, the trial can be assumed to be exchangeable with other previous trials when the previous trials are considered to be good prior information. The assumption of trial exchangeability enables the current trial to “borrow strength” from the previous trials, while acknowledging that the trials are not identical in all respects. Thus, exchangeability is important in the development of realistic models for combining trial data with prior information.

Bayesian Adaptive Designs

Adaptive designs use accumulating data to decide how to modify certain aspects of a trial according to a pre-specified plan without undermining the validity and integrity of the trial. Adaptive trial designs have the potential to provide optimal statistical inference and to improve quality, speed and efficiency of decision making.

An adaptive Bayesian clinical trial can involve interim looks to adapt the sample size (to stop or to continue patient accrual) or interim looks for the purpose of possibly stopping the trial early either for success, futility, or harm.

A purely Bayesian approach would allow for continuous design adaptation as the trial take place. However, in order to maintain the integrity of the trial while minimizing operational biases, the Bayesian adaptive trial should be adaptive *by design*.

Analyzing a Bayesian Clinical Trial

The results, conclusions, and interpretation of a Bayesian analysis all rely on the posterior distribution. Consequently, results and conclusions for a Bayesian trial are based only on the posterior distribution.

Hypothesis testing

For Bayesian hypothesis testing, one can use the posterior distribution to calculate the probability that a particular hypothesis is true, given the observed data.

Interval estimation

Bayesian interval estimates are based on the posterior distribution and are called *credible intervals*. If the posterior probability that an endpoint lies in an interval is 0.95, then this interval is called a 95 percent *credible interval*.

Predictive probabilities

Uses of predictive probabilities include the following:

Deciding when to stop a trial

One can use a predictive probability at an interim point as the rule for stopping the trial. If the predictive probability that the trial will be successful is sufficiently high (based on results at the interim point), the trial may be stopped and declared successful.

Exchangeability is a key issue here: these predictions are reasonable only if you can assume the patients who have not been observed are exchangeable with the patients who have. This assumption is difficult to formally evaluate but may be more plausible in some instances (e.g., administrative censoring) than others (e.g., high patient drop-out).

Predicting outcomes for future patients

One may also calculate the predictive probability of the outcome of a future patient, given the observed outcomes of the patients in a clinical trial, provided the current patient is exchangeable with the patients in the trial.

Predicting (imputing) missing data

One may use predictive probabilities to predict (or *impute*) missing data, and trial results can be adjusted accordingly. The adjustment depends on the assumption that patients with missing outcomes follow the same statistical model as patients with observed outcomes. This means the missing patients are exchangeable with the non-missing patients, or that data are *missing at random*.

Predicting a clinical outcome from earlier measurements

If patients have measurements of the same outcome at earlier and later follow-up visits, one can make predictions for the later follow-up visit (even before the follow-up time has elapsed).

Interim analyses

Bayesian interim analyses typically involve the following applications:

Applying posterior probability

One method stops the trial early if the posterior probability of a hypothesis at the interim look is large enough. In other words, the same Bayesian hypothesis test is repeated during the course of the trial.

Applying predictive distribution

Another method calculates at interim stages the probability that the hypothesis test will be successful at the end of accrual and follow-up. This method uses the Bayesian predictive distribution for patients yet to be measured. If the predictive probability of success is sufficiently high, the trial may stop early. If the predictive probability is very low, the trial may stop early for futility.