# THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter

# Instructions for Use

**Symbol Definitions**

Following definitions are for reference only. Please refer to the product label for applicable usage.

Sterilized Using Ethylene Oxide


Do Not Re-Use


Caution


Consult Instructions for Use


Do not use if package is damaged.


Do not use if package is opened.


Keep Away from Sunlight


Keep Dry


Use-By Date

Batch Code

Catalog Number

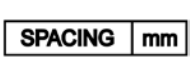
Contents: 1


Manufacturer


Date of Manufacture


Pin Connector

Electrodes



Spacing


Temperature Limit

Curve Type. Refer to label for colored circle containing applicable curve type.

THERMOCOOL SMARTTOUCH® SF Catheter

Navigational Catheter

Compatible with CARTO® 3 EP Navigation System

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

# THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter

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

- **STERILE. Sterilized using ethylene oxide.**
- **For single use only.**
- **Do not resterilize.**
- **Do not use if the package is open or damaged.**

## Device Description

The Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter is a multi-electrode 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 F ring electrodes. For ablation, the catheter is used in conjunction with an RF generator and a dispersive pad (indifferent electrode). The catheter has force-sensing technology that provides a real-time measurement of contact force between the catheter tip and the heart wall.

The catheter has a high-torque shaft with a uni-directional deflectable tip section containing an array of 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 noble metals. The catheter incorporates a thermocouple temperature sensor that is embedded in the 3.5 mm tip electrode. Tip deflection is controlled at the proximal end by a handle in which a piston slides; a thumb knob on the piston controls piston travel. When the thumb knob is pushed forward, the tip is deflected (curved). When the thumb knob is pulled back, the tip straightens. Three curve types designated “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 serves to permit the 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. A compatible irrigation pump is used to control the saline irrigation. The catheter interfaces with standard recording equipment and a compatible RF generator via accessory extension cables with the appropriate connectors.

This catheter features a location sensor embedded in the tip section that transmits location and contact force information to the CARTO® 3 Navigation System. An appropriate reference device is required for location reference position purposes.

The catheter is compatible with the following devices: SMARTABLATE® Generator, Stockert 70 Generator, SMARTABLATE® Pump, nGEN™ Pump, COOLFLOW® Pump, SMARTABLATE® Tubing, and COOLFLOW® Tubing. For description of the operation of the compatible devices refer to the directions for use for the devices.

## Indications for Use

The Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter and related accessory devices are indicated for catheter-based cardiac electrophysiological mapping (stimulating and recording) and, when used with a compatible RF generator, for the treatment of:

- Type I atrial flutter in patients age 18 or older.
- Drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three-dimensional electroanatomic mapping systems.
- Drug refractory recurrent symptomatic persistent atrial fibrillation (defined as continuous atrial fibrillation that is sustained beyond 7 days but less than 1 year), refractory or intolerant to at least one Class I or III antiarrhythmic medicine, when used with compatible three-dimensional electroanatomic mapping systems.

The Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter provides a real-time measurement of contact force between the catheter tip and heart wall, as well as location information when used with CARTO® 3 Navigation System.

## Contraindications

Do not use this catheter:

1. If the patient has had a ventriculotomy or atriotomy within the preceding eight weeks because the recent surgery may increase the risk of perforation.
2. In the patient with a myxoma or an intracardiac thrombus as the catheter could precipitate an embolus.
3. In patients with prosthetic valves as the catheter may damage the prosthesis.
4. In the coronary vasculature due to risk of damage to the coronary arteries.
5. In patients with an active systemic infection because this may increase the risk of cardiac infection.
6. Via the transseptal approach in a patient with an interatrial baffle or patch because the opening could persist and produce an iatrogenic atrial shunt.
7. Via the retrograde trans-aortic approach in patients who have had aortic valve replacement.
8. With a long sheath or short introducer < 8.5 F in order to avoid damage to the catheter shaft.

## Warnings and Precautions

1. Do not use excessive force to advance or withdraw the catheter when resistance is encountered during catheter manipulation through the sheath.
2. Do not manually pre-shape the distal shaft of the catheter by applying external forces intended to bend or affect the intended shape or curve of the catheter.
3. The catheter must be warmed up as specified prior to use. If the catheter has not reached a steady state condition, there is potential for a zero-offset drift to occur which could result in an inaccurate contact force reading.
4. Always zero the contact force reading following insertion into the patient or when moving the catheter from one chamber of the heart to another. Ensure the catheter is not in contact with heart tissue prior to zeroing. Refer to the User Manual for your CARTO® 3 System for instructions on how to zero the contact force reading.
5. The contact force reading might become inaccurate if the contact force sensor (located between the first and second ring electrode) comes into close proximity with a ferrous material, such as the braided shaft of another catheter. If extreme fluctuations in force are observed, ensure the catheter’s contact force sensor is not in close proximity with another catheter’s shaft,

check zero on the catheter and, if necessary, remove and inspect the catheter. The contact force reading is for information only and is not intended to replace standard handling precautions.

6. To ensure proper operation of the contact force sensor, all four electrodes located on the catheter tip must protrude from the distal tip of the guiding sheath.
7. When applying high lateral force during mapping and RF application, the user should monitor the contact force Dashboard and vector display on the CARTO® 3 screen to ensure that contact force measurements remain within the accurate range. Refer to the Error Messages and Alerts section of the CARTO® 3 System Instructions for Use for System-related alert messages and indications related to inaccurate force readings.
8. Do not use the temperature sensor to monitor tissue temperature or to guide power titration during ablation. The temperature sensor located within the tip section 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. Using tip temperature to guide ablation could result in deeper lesions and increased risk for collateral damage.
9. Power and contact force should both be reduced when creating RF lesions on the posterior wall of the left atrium.
10. Do not rely on electrode temperature rise to determine if tissue heating is occurring during RF energy delivery as bench, animal, and clinical studies showed no significant electrode temperature rise during RF ablations.
11. 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.
12. This catheter may damage the prosthetic tricuspid valve of a patient if the catheter is accidentally advanced through the valve.
13. The safety of discontinuing anticoagulation therapy following catheter ablation of atrial fibrillation has not been established; anticoagulation therapy in such patients should be administered in accordance with the AHA/ACC/HRS 2014 Guideline for the Management of Patients With Atrial Fibrillation (January CT, Wann LS, Alpert JS et al. AHA/ACC/HRS 2014 Guideline for the Management of the Patients With Atrial Fibrillation. Circulation 2014: 130:2071-2104).
14. The safety and effectiveness of radiofrequency ablation for the treatment of atrial fibrillation in patients with significant left ventricular dysfunction, advanced heart failure, substantial left atrial enlargement, and structural heart disease have not been established.
15. 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 the procedure, always identify the patient's risk of volume overload.
16. The catheter has not been shown to be safe at electrode temperatures above 40°C; verify that the CATHETER SELECTION KNOB on the compatible RF Generator is on the "T Cool SF" option to ensure that the maximum temperature is set at 40°C. If the RF generator does not have a "T Cool SF" option, contact Biosense Webster Technical Support immediately.
17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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 for the use of the catheter in pregnant women.
23. Do not expose the catheter to organic solvents such as alcohol.
24. Do not autoclave the catheter.
25. Do not immerse proximal handle or cable connector in fluids; electrical performance could be affected.
26. Do not scrub or twist the distal tip electrode during cleaning.
27. Inspect the irrigation saline for air bubbles prior to its use in the procedure. Air bubbles in the irrigation saline may cause emboli.
28. Purge the catheter and the irrigation tubing with heparinized normal saline.
29. Electrophysiology catheters and systems are intended for use only in X-ray shielded rooms due to electromagnetic compatibility requirements and other hospital safety guidelines.
30. Do not attempt to operate the Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter or the RF generator prior to completely reading and understanding the applicable instructions for use.
31. Cardiac ablation procedures should be performed by appropriately trained personnel in a fully equipped electrophysiology laboratory. Appropriate clinical instruction in use of the Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Catheter should also be completed.
32. 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.
33. To prevent thromboembolism, intravenous heparin (target ACT of ≥ 300 s) should be administered prior to or immediately following transseptal puncture during AF ablation procedures. The 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation recommends systemic

anticoagulation with warfarin or a novel oral anticoagulant for at least 2 months following an AF ablation procedure (Calkins H, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, Heart Rhythm (2017), doi:10.1016/j.hrthm.2017.05.012).

34. When using the Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Catheter with conventional systems (using fluoroscopy to determine catheter tip location), or with the CARTO® 3 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. The contact force reading is for information only and not intended to replace standard handling precautions.
35. Always pull the thumb knob back to straighten the catheter tip before insertion or withdrawal of the catheter.
36. Always maintain a constant heparinized normal saline infusion to prevent coagulation within the lumen of the catheter.
37. 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; twisting may damage the tip electrode bond and loosen the tip electrode, or may damage the contact force sensor. Make sure the irrigation holes are not plugged prior to re-insertion.
38. 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.
39. 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 (e.g. the 3M Model 1149F or Valley Lab Model 7505).
40. The Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter is indicated for use only with a compatible RF generator, compatible irrigation pump, CARTO® 3 Navigation System, Biosense Webster cables, and other appropriate interface cables and connectors. Use of a compatible irrigation pump is recommended to assure proper irrigation flow rate.
41. The Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter has been shown to create larger lesions than standard non-irrigated RF ablation catheters. Care should be taken when ablating near structures such as the sino-atrial and atrioventricular nodes.
42. The sterile packaging and catheter should be inspected prior to use. Do not use if the packaging or catheter appears damaged.
43. The catheter is sterilized with ethylene oxide gas and should be used by the "Use By" date on the catheter package. Do not use the catheter if past the "Use By" date.
44. The Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter is intended for single patient use only.
45. Do not resterilize and reuse.
46. Do not use near MRI equipment since movement or heating of the catheter may occur and the image on the display may become distorted.
47. Use both fluoroscopy and electrogram data to monitor catheter advancement and reduce risk of tissue injury.
48. The Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter is used in conjunction with a compatible RF generator 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 catheter. During energy delivery, the patient should not be allowed to come in contact with grounded metal surfaces.
49. 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.
50. Electromagnetic interference (EMI) produced by the Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter, when used in conjunction with a compatible RF generator during normal operation, may adversely affect the performance of other equipment.
51. 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.
52. 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.
53. The temperature measurement accuracy of the Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter, as with any temperature measurement electrophysiology catheter, is largely determined by the temperature accuracy specification of the RF generator used. Please consult the user manual for the RF generator to be used for the temperature accuracy specification.
54. Before use, check irrigation ports are patent by infusing of heparinized normal saline through the catheter and tubing.
55. Regularly inspect and test reusable cables and accessories.

## Adverse Events

**NOTE: The adverse events in the following summary were observed in clinical studies involving use of the THERMOCOOL SMARTTOUCH® SF Catheter, THERMOCOOL SMARTTOUCH® Catheter, and NAVISTAR® THERMOCOOL® Diagnostic/Ablation Catheter. The THERMOCOOL SMARTTOUCH® SF and THERMOCOOL SMARTTOUCH® Catheters are modified versions of the NAVISTAR® THERMOCOOL® Catheter with the added feature of a force sensor placed in the catheter tip used to measure the contact force between the catheter tip and endocardial tissue.**

**Clinical trial for the THERMOCOOL SMARTTOUCH® SF Catheter – PRECEPT Study**

Of the 348 patients in the Safety Population, 17 primary adverse events were reported in 16 subjects. See the "Summary of Clinical Studies Conducted for the THERMOCOOL SMARTTOUCH® SF Catheter" section below for a complete description of the AEs encountered during the study.

**Clinical trial for the THERMOCOOL SMARTTOUCH® SF Catheter – Safety Study**

Of the 159 patients in the Safety Cohort, 4 primary adverse events were reported in 4 subjects. See the "Summary of Clinical Studies Conducted for the

THERMOCOOL SMARTTOUCH® SF Catheter" section below for a complete description of the AEs encountered during the study.

**Clinical trial for the THERMOCOOL SMARTTOUCH® Catheter – Pivotal Study**
Of the 161 subjects in the Safety Analysis Cohort, 17 primary adverse events (AEs) were reported in 16 subjects. See the Pivotal Study in the "Summary of Clinical Studies Conducted for the THERMOCOOL SMARTTOUCH® Catheter" section below for a complete description of the AEs encountered during the study.

**Clinical trial for the THERMOCOOL SMARTTOUCH® Catheter – Continued Access Study**
Of the 143 subjects in the Safety Analysis Cohort, 27 primary adverse events (AEs) were reported in 25 subjects. See the Continued Access Study in the "Summary of Clinical Studies Conducted for the THERMOCOOL SMARTTOUCH® Catheter" section below for a complete description of the AEs encountered during the study.

**Clinical trials for atrial flutter indication**
Of the 190 subjects in the Safety Population in the pivotal study, 33 major adverse events were reported in 30 subjects. In the Post-Market Study, 4 cardiovascular specific adverse events were reported in 4 of the 291 enrolled subjects. See "Summary of Clinical Studies Conducted for Atrial Flutter Indication" below for a complete description of the adverse events encountered during the studies.

**Clinical trials for atrial fibrillation indication**
Of the 139 subjects in the Primary Safety Analysis Cohort, 15 serious catheter-related adverse events (CRAEs) were reported in 14 subjects. See "Summary of Clinical Studies Conducted for Atrial Fibrillation Indication" below for a complete description of the AEs encountered during the study.

## Summary of Clinical Studies – Pivotal Study

The clinical testing described below was performed with the THERMOCOOL SMARTTOUCH® SF Catheter, THERMOCOOL SMARTTOUCH® Catheter, and NAVISTAR® THERMOCOOL® Catheter. The THERMOCOOL SMARTTOUCH® SF Catheter meets the same performance specifications as the NAVISTAR® THERMOCOOL® and THERMOCOOL SMARTTOUCH® Catheters using reduced saline flow rates.

**SUMMARY OF CLINICAL STUDIES CONDUCTED FOR THE THERMOCOOL SMARTTOUCH® SF CATHETER**

**STUDY 1: PRECEPT Study**

**A. Objective**
The purpose of this study was to demonstrate the safety and effectiveness of the THERMOCOOL SMARTTOUCH® SF catheter in the treatment of drug refractory symptomatic persistent atrial fibrillation (PsAF) following standard electrophysiology mapping and RF ablation procedures.

**B. Study Design**
The study was a prospective, multicenter, non-randomized clinical evaluation compared to a predetermined performance goal. The study was conducted at investigational sites in the US and Canada.

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

**Primary Effectiveness Endpoint** – freedom from documented atrial fibrillation, atrial flutter, and atrial tachycardia (AF/AFL/AT, atrial tachyarrhythmias) recurrence (episodes ≥ 30 sec on Holter recordings/TTM or continuously recorded on the standard 12-leads ECG) during the evaluation period (Day 181-450).

**Acute Success** – confirmation of entrance block in all pulmonary veins.

**Primary Safety Endpoint** – incidence primary adverse events (PAE) occurring within 7 days of the initial and repeat AF ablation procedures using the study catheter per protocol. Primary adverse events included the following conditions:

- Death
- Atrio-esophageal fistula[1]
- Cardiac Tamponade / Perforation
- Myocardial Infarction (MI)
- Stroke / Cerebrovascular accident (CVA)
- Thromboembolism
- Transient Ischemic Attack (TIA)
- Diaphragmatic paralysis
- Pneumothorax
- Heart block
- Pulmonary Vein (PV) stenosis[1]
- Pulmonary edema (Respiratory Insufficiency)
- Pericarditis
- Major vascular access complication / bleeding

[1] PV stenosis (PV) and atrio-esophageal fistula that occurs greater than one week (7 days) post-procedure shall be deemed Primary AEs.

***Secondary safety endpoints*** included:

- Occurrence of Early Onset (within 7 days of initial ablation) Serious Adverse Event
- Occurrence of Peri-Procedural (> 7 to 30 days) Serious Adverse Event
- Occurrence of Late Onset (> 30 days) Serious Adverse Event

B.2 – Pre-determined Performance Goal
The performance goal was prospectively established.

- Effectiveness: Performance Goal = 40.0% lower bound of the of the 95% CI around the primary effectiveness success rate
- Safety: Performance Goal = 16.0% upper bound of the 95% CI around the primary AE rate

B.3. – Subject Accountability

**Table 1 – Subject Accountability and Disposition**

| Disposition | N |
|---|---|
| **Enrolled Subjects** | **381** |
| Excluded Subjects | 33 |
| **Safety Population** | **348** |
| Not Meeting Eligibility Criteria | 14 |
| **mITT Population** | **334** |
| Undergone RF Ablation | 334 |

| | |
|---|---|
| Subjects Treated with Non-Study Catheter | 1 |
| **Per-Protocol Population** | **333** |

The following definitions were used to classify subjects:

**Safety Population** (n = 348) was comprised of all enrolled subjects who underwent insertion of the THERMOCOOL SMARTTOUCH® SF Catheter.

**Per-Protocol Population** (n = 333) consisted of subjects who satisfied the following criteria:

- Were enrolled and met all eligibility criteria
- Had undergone RF ablation
- Were treated with the study catheters, and had been treated for the study-related arrhythmia

B.4 – Subject Demographics and Baseline Characteristics

**Table 2 – Subject Demographics**
**(Enrolled Subjects, N = 381; Safety, N = 348; Per-Protocol, N = 333)**

| Demographics | Enrolled n/381 (%) | Safety n/348 (%) | Per-Protocol n/333 (%) |
|---|---|---|---|
| **Gender (%)** | | | |
| Male | 271 (71.1) | 246 (70.7) | 237 (71.2) |
| Female | 110 (28.9) | 102 (29.3) | 96 (28.8) |
| **Ethnicity – Hispanic or Latino (%)** | 7 (1.8) | 7 (2.0) | 6 (1.8) |
| **Race (%)** | | | |
| Asian | 3 (0.8) | 3 (0.9) | 3 (0.9) |
| Black or African American | 6 (1.6) | 6 (1.7) | 6 (1.8) |
| White | 349 (91.6) | 319 (91.7) | 307 (92.2) |
| Not reported | 23 (6.0) | 20 (5.7) | 17 (5.1) |
| **Age (years)** | 65.6 ± 8.72 | 65.4 ± 8.71 | 65.4 ± 8.79 |
| **AF History (months)** | 15.2 ± 29.2 | 15.5 ± 30.2 | 15.9 ± 30.8 |
| **LA Dimension (mm)** | 42.6 ± 5.20 | 42.4 ± 5.14 | 42.6 ± 5.06 |
| **LVEF (%)** | 56.0 ± 7.43 | 56.2 ± 7.23 | 56.2 ± 7.24 |

**Table 3 – Baseline Characteristics**
**(Enrolled Subjects, N = 381; Safety, N = 348; Per-Protocol, N = 333)**

| Medical History | Enrolled n/381 (%) | Safety n/348 (%) | Per-Protocol n/333 (%) |
|---|---|---|---|
| **Hypertension** | 260 (68.2) | 238 (68.4) | 227 (68.2) |
| **Diabetes** | 69 (18.1) | 62 (17.8) | 61 (18.3) |
| **Obstructive sleep apnea** | 145 (38.1) | 134 (38.5) | 132 (39.6) |
| **AAD Failed** | | | |
| Class I & III | 1.3 ± 0.54 | 1.3 ± 0.55 | 1.3 ± 0.56 |
| **Heart Disease** | | | |
| Coronary artery disease | 86 (22.6) | 77 (22.1) | 74 (22.2) |
| Congestive heart failure | 61 (16.0) | 55 (15.8) | 52 (15.6) |
| Prior myocardial infarction | 23 (6.0) | 19 (5.5) | 19 (5.7) |
| Cardiomyopathy | 43 (11.3) | 42 (12.1) | 39 (11.7) |
| Cardiac surgical procedures | 41 (10.8) | 36 (10.3) | 34 (10.2) |
| **Thromboembolic Event** | 27 (7.1) | 25 (7.2) | 24 (7.2) |
| Transient ischemic attack | 10 (2.6) | 10 (2.9) | 9 (2.7) |
| Stroke | 8 (2.1) | 6 (1.7) | 6 (1.8) |
| CHA2DS2-VASc score | 2.3 ± 1.48 | 2.3 ± 1.48 | 2.3 ± 1.49 |
| **Other: Arrhythmia** | | | |
| Atrial flutter | 71 (18.6) | 68 (19.5) | 65 (19.5) |
| Atrial tachycardia | 7 (1.8) | 7 (2.0) | 7 (2.1) |

**C. Results**

C.1 – Procedural Data

Table 4 and Table 5 present the index procedural data. There were 348 procedures in 348 subjects. All subjects underwent one (1) study ablation procedure.

**Table 4 – Summary of Power, Temperature, and Impedance Data per Procedure (Safety Population, n = 348)**

| Description | Mean ± SD (n) |
|---|---|
| Mean Power (W) | 30.02 ± 7.83 (291) |
| Mean Temperature (°C) | 24.25 ± 2.49 (291) |
| Mean Impedance (ohms) | 117.72 ± 13.73 (277) |

**Table 5 – Summary of Ablation Procedure Parameters**
**(Safety Population, n = 348)**

| Procedure Parameters | Mean ± SD (n) |
|---|---|
| Total Procedure Time (min) | 178.0 ± 70.97 (348) |
| Ablation Procedure Time (min) | 107.7 ± 48.64 (348) |
| Total Fluoroscopy Time (min) | 15.29 ± 16.61 (348) |
| Fluid Input (ml) | 2115.9 ± 1016.54 (343) |
| Fluid via Catheter (ml) | 886.3 ± 391.19 (339) |

| | |
|---|---|
| Fluid via IV (ml) | 1247.2 ± 857.14 (341) |
| Fluid Output (ml) | 1044.2 ± 835.18 (189) |
| Balance (input - output) (ml) | 1493.6 ± 914.34 (187) |

All AF ablation procedures began with circumferential lesions targeting all pulmonary veins, with additional atrial ablation lines created as clinically required.

Table 6 summarizes the lesion sets applied to the subjects undergoing ablation during the index ablation procedures. Table 7 presents a summary of non-PV targets in the 186 procedures in the SP and 179 procedures in the PP that involved ablation beyond PVI.

**Table 6 – Outcomes by Ablation Targets per Procedure (Safety Population, n = 348; Per-Protocol, n = 333)**

| Ablation Targets | Safety n/348 (%) | Per-Protocol n/333 (%) |
|---|---|---|
| PVI only group | 193 (55.5) | 182 (54.7) |
| PVI+ CFAE group | 60 (17.2) | 59 (17.7) |
| PVI+ non-CFAE group | 95 (27.3) | 92 (27.6) |

**Table 7 – Ablation Targets per Procedure (Safety Population, n = 348; Per-Protocol, n = 333)**

| Ablation Target | Safety n/186 (%) | Per-Protocol n/179 (%) |
|---|---|---|
| Left Inferior PV Mitral | 14 (7.5) | 14 (7.8) |
| Roof Line | 90 (48.4) | 87 (48.6) |
| Other: Linear Lesion | 16 (8.6) | 16 (8.9) |
| SVC | 10 (5.4) | 10 (5.6) |
| CFAE | 60 (32.3) | 59 (33.0) |
| Other: AF Foci | 75 (40.3) | 72 (40.2) |
| Cavo-Tricuspid Isthmus | 67 (36.0) | 63 (35.2) |
| RAGP | 1 (0.5) | 1 (0.6) |

C.2 – Acute Procedural Success

Acute success was defined as the confirmation of entrance block into all PVs. Any use of non-study catheters was considered acute procedural failures.

Acute procedural success results are presented in Table 8.

**Table 8 – Acute Effectiveness Summary (Per-Protocol Population, n = 333)**

| | Per Protocol |
|---|---|
| Number of Subjects with Success | 330 / 333 |
| Percentage of Subjects with Success | 99.1% |
| One-Sided Exact 97.5% Lower Confidence Bound | 97.4 |

C.3 – Contact Force Data

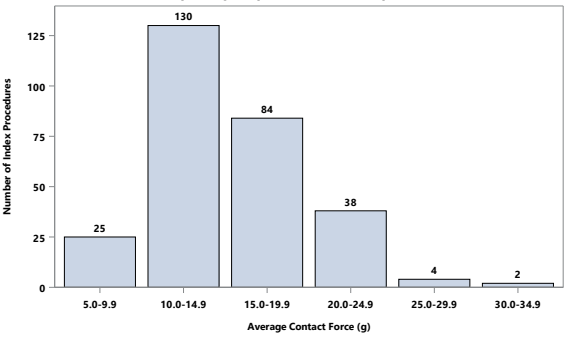
The graphical user interface (GUI) of the CARTO® 3 workstation displays the pressure applied to the endocardial surface of the heart by the THERMOCOOL SMARTTOUCH® SF in gram forces that the investigator can visualize during the procedure.

Table 9 presents the overall average contact force applied during the procedure for all subjects who underwent a study ablation procedure. As shown, the overall average CF applied during ablation procedures was 15.23 ± 4.41 grams. Figure 1 presents a distribution of average contact force in 5-gram increments. In the majority of procedures (239/283), the average contact force applied was less than 20 grams.

**Table 9 – Average Contact Force Measurements Overall per Ablation Procedure (Safety Population, n = 348)**

| | Average Contact Force (g) |
|---|---|
| n | 298 |
| Mean | 15.23 |
| Standard Deviation | 4.41 |
| Median | 14.40 |
| Q1 / Q3 | 12.10 / 18.13 |
| Min / Max | 6.6 / 33.7 |

**Figure 1 – Distribution of Average Contact Force per Ablation Procedure (Safety Population, n = 348)**




The real-time rolling graph display with the working ranges acts as a visual aid providing real-time feedback of the pressure being applied by the operator in relationship to their pre-selected CF values. In this study, the most frequently selected working range of contact force was 5 to 40 g (37.5%, 130/347), which accounted for 37.5% of the procedures (130/347).

The CARTO VISITAG™ Module of the CARTO® 3 System provides a marker for stability during an RF application. The CARTO® 3 System produces an auto tag on the screen at the site of RF application that is dependent on the user's pre-defined settings. The auto tag appears when the RF application reaches a

pre-determined time of application and the catheter has remained stable within a pre-determined range (mm) for the time. In this study the majority of operators chose a time to auto tag from 3-5 seconds with a stability of 1.5-3.0 mm.

**Figure 2 – Operator-Configured VISITAG™ Stability Time per VISITAG™ Point (Safety Population, N = 348)**

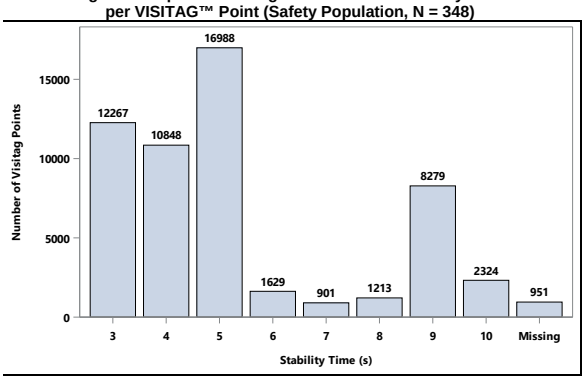
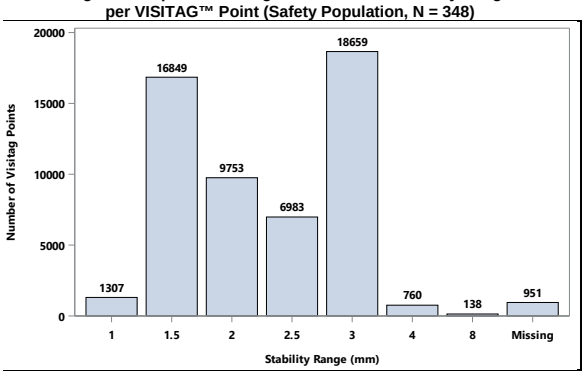



**Figure 3 – Operator-Configured VISITAG™ Stability Range per VISITAG™ Point (Safety Population, N = 348)**




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 Safety Population (N = 348) was comprised of all enrolled subjects who had the study catheter inserted.

**Primary Safety Endpoint** – Primary Adverse Events

Table 10 presents the protocol-specified endpoint and safety results. There were 17 primary AEs reported in 16 subjects. Among 17 primary AEs, sixteen (16) were considered definitely procedure-related, and one (1) was considered possibly procedure-related. One (1) was considered definitely device-related, thirteen (13) were considered possibly device-related, and three (3) were considered not device-related. The overall percentage of subjects in the Safety Population who experienced a serious primary AE was 4.7% (16/344) with upper confidence at 7.4%, which is significantly less than the specified performance goal of 16.0%. Therefore, the results met the pre-specified performance goal for the safety endpoint.

**Table 10 – Primary Safety Endpoint Outcome – Primary Adverse Events (Safety Population, n = 348)**

| Variable | Number of Subjects with Event | Number of Events | Event Rate n/N (%) | One-sided Exact 97.5% Upper Confidence Bound |
|---|---|---|---|---|
| **Primary Adverse Event** | 16 | 17 | 16 / 344 (4.7) | 7.4% |
| Death | 0 | 0 | 0 / 344 (0.0) | |
| Atrio-esophageal Fistula | 0 | 0 | 0 / 344 (0.0) | |
| Cardiac Tamponade | 5 | 5 | 5 / 344 (1.5) | |
| Myocardial Infarction | 0 | 0 | 0 / 344 (0.0) | |
| Cerebrovascular Accident (CVA) / Stroke | 1 | 1 | 1 / 344 (0.3) | |
| Thromboembolism | 0 | 0 | 0 / 344 (0.0) | |
| Transient Ischemic Attack | 0 | 0 | 0 / 344 (0.0) | |
| Diaphragmatic Paralysis | 1 | 1 | 1 / 344 (0.3) | |
| Pneumothorax | 0 | 0 | 0 / 344 (0.0) | |
| Heart Block | 0 | 0 | 0 / 344 (0.0) | |
| Pulmonary Vein Stenosis | 0 | 0 | 0 / 344 (0.0) | |
| Pulmonary Edema (Respiratory Insufficiency) | 5 | 5 | 5 / 344 (1.5) | |
| Pericarditis | 2 | 2 | 2 / 344 (0.6) | |
| Major Vascular Access Complication / Bleeding | 3 | 3 | 3 / 344 (0.9) | |

Table 11 summarizes the SAEs (by causality and body system) occurring within 30 days of a study ablation procedure that were not classified as Primary AEs by protocol definition.

**Table 11 – Non Primary SAEs Occurring within 30 Days of the Ablation Procedure by Causality and Body System (Safety Population, n = 348)**

| Relationship to the Device/Procedure by Body System | Number of Subjects with Event | Number of Events |
|---|---|---|
| **Occurring 0-7 Days Post Ablation Procedure** | | |
| **Overall** | 20 | 20 |
| **Definitely device related** | 1 | 1 |
| Esophageal ulcer | 1 | 1 |
| **Possibly device related** | 1 | 1 |
| Hypotension | 1 | 1 |
| **Not device related** | 18 | 18 |
| Atrial fibrillation | 2 | 2 |
| Hypotension | 1 | 1 |
| Complication associated with urinary catheter | 3 | 3 |
| Diplopia | 1 | 1 |
| Dyspnea | 1 | 1 |
| Fluid overload | 2 | 2 |
| Hypertensive crisis | 1 | 1 |
| Hypoxia | 1 | 1 |
| Pyrexia | 1 | 1 |
| Renal failure | 1 | 1 |
| Sepsis | 1 | 1 |
| Tachycardia | 1 | 1 |
| Torsade de pointes | 1 | 1 |
| Urinary tract infection | 1 | 1 |
| **Definitely procedure related** | 9 | 9 |
| Complication associated with urinary catheter | 2 | 2 |
| Hypotension | 2 | 2 |
| Fluid overload | 2 | 2 |
| Esophageal ulcer | 1 | 1 |
| Sepsis | 1 | 1 |
| Torsade de pointes | 1 | 1 |
| **Possibly procedure related** | 6 | 6 |
| Complication associated with urinary catheter | 1 | 1 |
| Diplopia | 1 | 1 |
| Dyspnea | 1 | 1 |
| Hypoxia | 1 | 1 |
| Renal failure | 1 | 1 |
| Urinary tract infection | 1 | 1 |
| **Not procedure related** | 5 | 5 |
| Atrial fibrillation | 2 | 2 |
| Hypertensive crisis | 1 | 1 |
| Pyrexia | 1 | 1 |
| Tachycardia | 1 | 1 |
| **Occurring 8-30 Days Post Ablation Procedure** | | |
| **Overall** | 6 | 7 |
| **Not device related** | 6 | 7 |
| Atrial flutter | 1 | 1 |
| Complication associated with device | 1 | 1 |
| Pleural effusion | 1 | 1 |
| Presyncope | 1 | 1 |
| Pulmonary embolism | 1 | 1 |
| Tachycardia | 1 | 1 |
| Tuberculosis | 1 | 1 |
| **Definitely procedure related** | 1 | 1 |
| Complication associated with urinary catheter | 1 | 1 |
| **Possibly procedure related** | 2 | 2 |
| Pleural effusion | 1 | 1 |
| Pulmonary embolism | 1 | 1 |
| **Not procedure related** | 4 | 4 |
| Atrial flutter | 1 | 1 |
| Presyncope | 1 | 1 |
| Tachycardia | 1 | 1 |
| Tuberculosis | 1 | 1 |

There were 2 deaths during the study. Two subjects died during the study. Neither death was reported to be device or procedure-related. No deaths occurred within 3 months following the study procedure. An 80-year-old woman with known coronary artery disease, type II DM, and hypertension underwent uncomplicated study procedure for the treatment of persistent AF. The subject developed dyspnea and was hospitalized and treated for pneumonia and

congestive heart failure at 452 days following the study procedure. She was discharged with home oxygen and died shortly after on day 464 following the index ablation. The second death occurred in an 83-year-old man who was hospitalized on day 164 for management of non-ST-elevation myocardial infarction, atrial fibrillation, and COPD exacerbation. The hospital course was complicated by respiratory decompensation and multifactorial neurologic dysfunction requiring intubation and mechanical ventilation support. The family subsequently withdrew care, and the patient died on day 166 following the index ablation.

Table 12 summarizes the primary safety outcome for the safety population by sex. There were no statistically significant differences in the Primary AE rates between males and females (nominal p > 0.15).

**Table 12 – Primary Safety Endpoint by Sex (Safety Population, N = 348)**

| Primary Safety Endpoint | Male | Female | p-value[1] |
|---|---|---|---|
| Primary AE | | | 1.000 |
| n/N | 12 / 244 | 4 / 100 | |
| % | 4.9% | 4.0% | |
| One-sided Exact 97.5% Upper Confidence Bound | 8.4% | 9.9% | |

[1] Fisher's exact test

C.4.1 – Average CF and Primary AEs

Figure 4 compares the average CF during procedures in subjects experiencing Primary AEs with those who did not. Average contact force was recorded for three (3) subjects with tamponade. These are marked with solid dots in the box plot of average contact force for all subjects in the safety population. Average contact force of these 3 subjects were above the Q3 (75th percentile) of overall average contact force.

**Figure 4 – Comparison of Average Contact Force in Subjects with Tamponade vs Safety Population (Safety Population, n = 348)**


C.5 – Primary Effectiveness Endpoint - Freedom from Atrial Tachyarrhythmias

**Primary Effectiveness Analysis**

The primary effectiveness endpoint was defined as freedom from documented symptomatic and asymptomatic AF/AFL/AT ("atrial tachyarrhythmias") based on electrocardiographic data and freedom from failure modes during the effectiveness evaluation period (day 181-450).

Approximately sixty percent (59.3%, 176/297) of the Per-Protocol population were free from documented atrial tachyarrhythmias and additional failure modes during their effectiveness evaluation period. The lower bound of the one-sided exact 97.5% lower confidence interval of the primary effectiveness rate was 53.4%, significantly higher than the pre-determined performance goal of 40%.

Primary effectiveness results are described in Table 13.

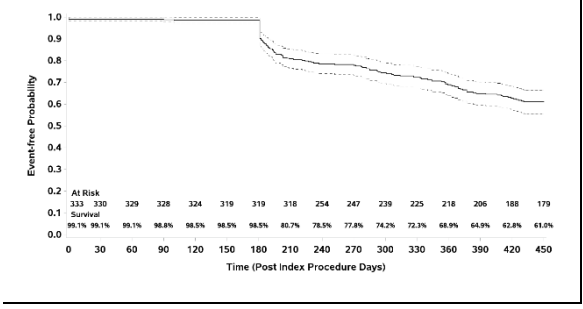
**Table 13 – Primary Effectiveness Endpoint through 15 Month Follow-Up Visit (Per-Protocol Population, n = 333)**

| Variable | Number of Subjects | Event Rate n/N (%)[1] | One-sided Exact 97.5% Lower Confidence Bound |
|---|---|---|---|
| Success | 176 | 176/297 (59.3%) | 53.4% |
| Failures[2] | 121 | 121/297 (40.7%) | |
| Missing[3] | 36 | | |

[1] N is the number of subjects with non-missing primary effectiveness endpoint.
[2] First failures: if a subject has more than one failure event, only the earliest failure event is considered.
[3] Missing primary effectiveness endpoint: the endpoint is missing if a subject (1) did not experience any failure, (2) did not finish the 15-month follow-up, and (3) had no ECG, TTM, HM or Post Procedural Arrhythmia data beyond 422 days after index procedure.

Figure 5 shows the Kaplan-Meier survival curves for the per protocol population. The probability of freedom from primary effectiveness endpoint failure at 15 months post-blanking was 61.0%. The lower bound of the one-sided 97.5% CI for this KM graph (55.5%, as indicated by the lower dotted line) is greater than 40% of the pre-determined performance criterion. The primary effectiveness performance goal was met.

**Figure 5 – Kaplan-Meier Analysis – Probability of Freedom from Chronic Effectiveness Failure through 15 Months Post-Procedure (Per-Protocol Population, n = 333)**




**Comparison of Primary Effectiveness Endpoint by Sex**
Table 14 presents the primary effectiveness outcome for the per-protocol population by sex. Males subjects had significantly higher success rates as compared to female subjects (64.3% vs 47.1%, nominal p < 0.15).

**Table 14 – Primary Effectiveness Endpoint by Sex (Per-Protocol Population, N = 333)**

| Variable | Male | Female | p-value[1] |
|---|---|---|---|
| Primary Effectiveness Endpoint | | | 0.009 |
| n/N | 135 / 210 | 41 / 87 | |
| % | 64.3% | 47.1% | |
| One-sided Exact 97.5% Lower Confidence Bound | 57.4% | 36.3% | |

[1] Fisher's exact test used to test whether primary effectiveness success rate differed by sex

C.6 – Study Design
In this study, a 6-month blanking period was employed to allow investigators additional time to adjust treatment following the index procedure. In the therapy consolidation period (months 4-6) interventions such as CV, AAD adjustment, and repeat ablation procedures were allowed without a negative impact on the primary effectiveness outcome. 77 subjects received interventions during the therapy consolidation period. Of these subjects, only 27.3% (21/77) went on to successfully complete the 15-month follow-up without recurrence of disease (AF/AFL/AT). While effectiveness success was lower for these subjects, they did contribute to the overall success of the effectiveness at 15 months.

**Table 15 – Primary Effectiveness Endpoint by Heart Rhythm Management in Therapy Consolidation Period (Day 91-180) (Per-Protocol Population, N = 333)**

| Therapy Consolidation Period | Primary Effectiveness Success with Intervention, n/N (%) | Primary Effectiveness Success without Intervention, n/N (%) |
|---|---|---|
| CV | 3 / 15 (20.0) | 173 / 282 (61.3) |
| AAD Adjustment | 12 / 50 (24.0) | 164 / 247 (66.4) |
| Repeat Procedure | 5 / 15 (33.3) | 171 / 282 (60.6) |
| Recurrence | 8 / 25 (32.0) | 168 / 272 (61.8) |
| Any Intervention | 21 / 77 (27.3) | 155 / 220 (70.5) |

C.7 – Study Conclusion
The results demonstrate that the THERMOCOOL SMARTTOUCH® Catheter met the pre-specified performance goals for safety and effectiveness.

**STUDY 2: Safety Study**

**A. Objective**
The primary objective of this trial was to demonstrate the safety of the THERMOCOOL SMARTTOUCH® SF Catheter with Contact Force Sensing Capability in the treatment of drug refractory symptomatic paroxysmal AF during standard electrophysiology mapping and ablation procedures.

**B. Study Design**
The study was a prospective, single-arm, unblinded, multicenter, pivotal, clinical investigation conducted at 19 investigational sites in the US.

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

***Primary Safety Endpoint*** - incidence of any primary adverse event occurring within 7 days of any AF ablation procedure

Primary adverse events include the following conditions:
- Death
- Atrio-esophageal fistula*
- Cardiac Tamponade**/Atrial Perforation
- Myocardial infarction (MI)
- Stroke / Cerebrovascular accident (CVA)
- Thromboembolism
- Transient Ischemic Attack
- Diaphragmatic paralysis
- Pneumothorax
- Heart block
- PV stenosis*
- Pulmonary edema (Respiratory Insufficiency)
- Pericarditis
- Major vascular access complication / Bleeding

* Pulmonary vein (PV) stenosis and atrio-esophageal fistula that occurred greater than one week (7 days) post-procedure were deemed Primary AEs.
** Hemodynamic compromise or instability was defined as Systolic BP < 80 mm Hg.

***Secondary Endpoints***

***Acute success –*** confirmation of entrance block in all pulmonary veins

***Secondary Safety Endpoints*** included:
- Occurrence of Early Onset (within 7 days of initial ablation) Serious Adverse Event
- Occurrence of Peri-Procedural (>7 to 30 days) Serious Adverse Event

B.2 – Pre-specified Performance Goal
The performance goal was prospectively established.

- Safety: Performance Goal = 14.0% upper bound of the 95% CI around the primary AE rate

B.3 – Subject Accountability

**Table 16 – Subject Accountability and Disposition**

| Disposition | N | % |
|---|---|---|
| **Enrolled Subjects** | **165** | **100.0** |
| Excluded Subjects | 6 | 3.6 |
| **Safety Population** | **159** | **96.4** |
| Not Meeting Eligibility Criteria | 4 | 2.4 |
| **mITT Population** | **155** | **93.9** |
| Undergone RF Ablation | 155 | 93.9 |
| **Per-Protocol Population** | **155** | **93.9** |
| Subjects Treated with Non-Study Catheter | 0 | 0 |
| Subjects Treated for Non-Study Arrhythmia | 0 | 0 |

The following definitions were used to classify subjects:

**Safety Population** (n = 159) was comprised of enrolled subjects undergoing insertion of the THERMOCOOL SMARTTOUCH® SF Catheter.

**Modified Intent-To-Treat (mITT) Population** (n = 155) consisted of enrolled subjects who met the eligibility criteria and had the study catheter inserted.

B.4 – Subject Demographics and Baseline Characteristics

**Table 17 – Subject Demographics**
**(Enrolled Subjects, N = 165; mITT Population, N = 155)**

| Demographics | Enrolled n/164 | mITT n/155 |
|---|---|---|
| **Gender (%)** | | |
| Male | 95 (57.9) | 93 (60.0) |
| Female | 69 (42.1) | 62 (40.0) |
| **Ethnicity – Hispanic or Latino (%)** | 2 (1.2) | 1 (0.6) |
| **Race (%)** | | |
| Asian | 1 (0.6) | 1 (0.6) |
| White | 159 (97.0) | 151 (97.4) |
| Pacific Islander | 1 (0.6) | 1 (0.6) |
| Black | 2 (1.2) | 2 (1.3) |
| Other | 1 (0.6) | 0 |
| **Age (Years)** | 62.7 ± 10.44 | 62.7 ± 10.13 |
| **AF History (months)** | 47.9 ± 67.45 (163) | 46.0 ± 63.82 (155) |
| **LA Dimension (mm)** | 38.8 ± 5.96 (154) | 38.9 ± 5.87 (150) |
| **LVEF (%)** | 60.1 ± 6.98 (155) | 59.9 ± 6.74 (150) |

**Table 18 – Baseline Characteristics**
**(Enrolled, N = 165; mITT Population, n = 155)**

| Medical History | Enrolled n/163 (%) | mITT n/155 (%) |
|---|---|---|
| **Hypertension** | **93 (57.1%)** | **90 (58.1%)** |
| **Diabetes** | **23 (14.1%)** | **22 (14.2%)** |
| **AAD Failed** | | |
| Class I & III | 116/161 (72.0) | 110/155 (71.0) |
| Class II & IV Only | 45/161 (28.0) | 45/155 (29.0) |
| **Heart Disease** | **44 (27.0%)** | **43 (27.7%)** |
| Coronary artery disease | 29 (17.8%) | 28 (18.1%) |
| Congestive heart failure | 6 (3.7%) | 5 (3.2%) |
| Prior Myocardial infarction | 6 (3.7%) | 6 (3.9%) |
| Cardiac surgical procedures | 12 (7.4%) | 12 (7.7%) |
| **Thromboembolic Event** | **10 (6.1%)** | **10 (6.5%)** |
| Transient ischemic attack | 3 (1.8%) | 3 (1.9%) |
| Stroke | 4 (2.5%) | 4 (2.6%) |
| **Other Arrhythmia** | **68 (41.7%)** | **63 (40.6%)** |
| Atrial Flutter | 51 (31.3%) | 47 (30.3%) |
| Atrial Tachycardia | 8 (4.9%) | 8 (5.2%) |

**C. Results**

C.1 – Procedural Data
Table 19, Table 20, and Table 21 present the procedural data. There were 159 procedures in 159 subjects. All subjects underwent one (1) study ablation procedure.

**Table 19 – Summary of Power, Temperature, and Impedance Data per Procedure (Safety Population, n = 159)**

| Description | Mean ± SD (n) |
|---|---|
| Mean Maximum Power (W) | 31.3 ± 3.98 (151) |
| Mean Temperature (°C) | 27.8 ± 3.30 (151) |
| Mean Impedance (ohms) | 127.2 ± 15.13 (151) |

On average, less power was used on the posterior wall during RF applications.

**Table 20 – Mean Max Power by Pulmonary Vein Anatomical Location (Safety Population, n = 159)**

| Location | Mean ± SD | Median | Min / Max |
|---|---|---|---|
| Anterior | 33.3 ± 4.24 | 35.0 | 12.0 / 45.8 |
| Inferior | 31.1 ± 5.30 | 30.9 | 15.3 / 45.4 |
| Posterior | 28.7 ± 5.84 | 30.0 | 10.0 / 45.5 |
| Ridge | 34.5 ± 4.64 | 35.5 | 15.4 / 45.9 |
| Roof Line | 32.2 ± 5.27 | 31.0 | 15.3 / 50.0 |

**Table 21 – Summary of Ablation Procedure Parameters (Safety Population, n = 159)**

| Procedure Parameters | Mean ± SD (n) |
|---|---|
| Total Procedure Time (min) | 181.1 ± 74.75 (159) |
| Ablation Procedure Time (min) | 104.3 ± 51.48 (159) |
| Total Fluoroscopy Time (min) | 18.5 ± 13.93 (159) |
| Fluid Input (ml) | 2148.9 ± 1179.6 (158) |
| Fluid via Catheter (ml) | 898.4 ± 586.33 (156) |
| Fluid via IV (ml) | 1261.8 ± 901.76 (158) |
| Fluid Output (ml) | 937.2 ± 962.98 (95) |
| Balance (input - output) (ml) | 1443.0 ± 882.04 (95) |

All AF ablation procedures began with circumferential lesions targeting all pulmonary veins, with additional atrial ablation lines created as clinically required.

Table 22 and Table 23 summarize the lesion sets applied to the subjects undergoing ablation during the index ablation procedures.

**Table 22 – Outcomes by Ablation Targets per Procedure (Safety Population, n = 159)**

| Ablation Targets | n/159 (%) |
|---|---|
| PV Only | 60 (37.7) |
| PV + Atrial Linear Lesions | 78 (49.1) |
| PV + Foci | 5 (3.1) |
| PV + Atrial Linear Lesions + Foci | 16 (10.1) |
| **Total** | **159 (100.0)** |

**Table 23 – Atrial Linear Lesions per Procedure (Safety Population, n = 159)**

| Linear Lesions | n/159 (%) |
|---|---|
| Left Inferior PV to Mitral | 3 (1.9) |
| SVC | 3 (1.9) |
| Cavo-Tricuspid Isthmus | 72 (45.3) |
| Roof line | 29 (18.2) |
| Other | 7 (4.4) |

C.2 – Acute Procedural Success

Acute success was defined as the confirmation of entrance block into all PVs. Any use of non-study catheters and >2 repeat ablations during the blanking period were considered acute procedural failures.

Acute procedural success results are presented in Table 24.

**Table 24 – Acute Effectiveness Summary (Safety Population, n = 159)**

| | Safety |
|---|---|
| Number of Subjects with Success | 153 / 159 |
| Percentage of Subjects with Success | 96.2% |
| 95% Exact Binomial Confidence Interval | (92.0%, 98.6%) |

C.3 – Contact Force Data

The THERMOCOOL SMARTTOUCH® SF Catheter for measuring the contact force (CF) applied to the endocardial wall of the heart is comprised of the THERMOCOOL SMARTTOUCH® SF Catheter and CARTO® 3 EP navigation workstation with the CARTO SMARTTOUCH™ Module installed. The graphical user interface (GUI) of the CARTO® 3 workstation displays the pressure applied to the endocardial surface of the heart as gram forces that the investigator can visualize during the procedure.

Table 25 presents the overall average contact force applied during the procedure for all subjects who underwent a study ablation procedure. As shown, the overall average CF applied during ablation procedures was 16.7 ± 6.14 grams. Figure 6 presents a distribution of average contact force in 5 gram increments. In the majority of procedures (125/152), the average contact force applied was less than 20 grams.

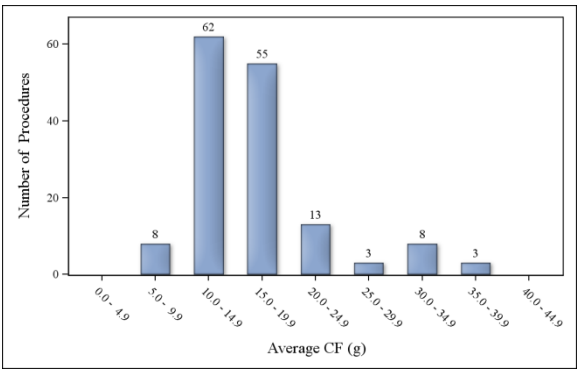
**Table 25 – Average Contact Force Measurements Overall per Ablation Procedure (Safety Population, n = 159)**

| | Average Contact Force (g) |
|---|---|
| n* | 152 |
| Mean | 16.7 |
| Standard Deviation | 6.14 |

| | |
|---|---|
| Median | 15.7 |
| Q1 / Q3 | 12.9 / 18.7 |
| Min / Max | 7.4 / 38.3 |

* Contact force data available for 152 of 159 subjects.

**Figure 6 – Distribution of Average Contact Force Per Ablation Procedure (Safety Population, n = 159)**




An integral part of the CARTO® 3 graph display includes a real-time rolling graph of applied CF which includes a user configurable working range that is displayed on the graph as horizontal lines for a low and high range. The real-time rolling graph display with the working ranges acts as a visual aid providing real-time feedback of the pressure being applied by the operator in relationship to their pre-selected CF values.

Table 26 presents the investigator selected working ranges used during the study ablation procedures with the THERMOCOOL SMARTTOUCH® SF Catheter.

**Table 26 – Working Ranges (g) Configured by Investigators (Safety Population, n = 159)**

| Lower | Upper | n / 159 (%) |
|---|---|---|
| 0 | 38 | 1 (0.6%) |
| 0 | 40 | 1 (0.6%) |
| 2 | 23 | 1 (0.6%) |
| 2 | 48 | 1 (0.6%) |
| 3 | 50 | 5 (3.1%) |
| 4 | 50 | 1 (0.6%) |
| 5 | 20 | 6 (3.8%) |
| 5 | 24 | 2 (1.3%) |
| 5 | 25 | 8 (5.0%) |
| 5 | 30 | 2 (1.3%) |
| 5 | 35 | 16 (10.1%) |
| 5 | 38 | 2 (1.3%) |
| 5 | 40 | 70 (44.0%) |
| 5 | 50 | 1 (0.6%) |
| 5 | 60 | 1 (0.6%) |
| 6 | 30 | 1 (0.6%) |
| 6 | 40 | 1 (0.6%) |
| 6 | 49 | 1 (0.6%) |
| 7 | 46 | 1 (0.6%) |
| 8 | 30 | 1 (0.6%) |
| 9 | 58 | 1 (0.6%) |
| 10 | 30 | 3 (1.9%) |
| 10 | 40 | 28 (17.6%) |
| 10 | 70 | 1 (0.6%) |
| 15 | 20 | 1 (0.6%) |
| 20 | 35 | 1 (0.6%) |
| 20 | 40 | 1 (0.6%) |

* Contact force data available for 152 of 159 subjects.

C.3.1 – Average CF by Sex

Table 27 presents a comparison of average contact force by sex. There was no significant difference in the use of contact force between sexes

**Table 27 – Average Contact Force Measurements (g) by Sex per Ablation Procedure (Safety Population, n = 159)**

| | Male | Female | p-value |
|---|---|---|---|
| n* | 92 | 60 | |
| Mean ± SD | 16.6 ± 6.43 | 17.0 ± 5.73 | 0.3777 |
| Median | 15.5 | 15.8 | |
| Min / Max | 7.4 / 35.1 | 9.9 / 38.3 | |

* Contact force data available for 152 of 159 subjects.

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 Safety Population (n=159) was comprised of all enrolled subjects who had the study catheter inserted.

**Primary Safety Endpoint** – Primary Adverse Events

Table 28 presents the protocol-specified endpoint and safety results. There were 4 primary AEs reported for 4 subjects. One Primary AE was deemed related to the investigational catheter. Three (3) were deemed possibly device-related. The

overall percentage of subjects in the Safety Population who experienced a serious primary AE was 2.5% (4/159) with upper confidence at 6.3%. The safety endpoint specified in the protocol was 7.0% (upper confidence bound of 14.0%). Therefore, the results met the pre-specified performance goal for the safety endpoint.

**Table 28 – Primary Safety Endpoint Outcome – Primary Adverse Events (Safety Population, n = 159)**

| | Protocol Established Endpoint | n |
|---|---|---|
| Number of Subjects in Safety Cohort | | 159 |
| Number of Subjects with Primary AEs | | 4 |
| % Primary AEs | 7.0 | 2.5 |
| Upper Bound of 95% Exact CI | 14.0 | 6.3 |

Table 29 summarizes the Primary AEs. Of the two subjects who experienced cardiac tamponade/perforation, one underwent emergent open chest surgical repair and the other was managed medically. All Primary AEs improved or resolved by the 30 day follow-up visit.

**Table 29 – Primary Safety Endpoint – Early-Onset (within (≤) 7 Days) Primary Adverse Events (Safety Population, n = 159)**

| Description | Number of Safety with Primary AEs n/159 (%) |
|---|---|
| **Total Primary AEs** | **4 (2.5)** |
| Death | 0 |
| Atrio-Esophageal Fistula | 0 |
| Cardiac Tamponade/Perforation* | 2 (1.3) |
| Myocardial Infarction | 0 |
| Stroke | 0 |
| Cerebrovascular Accident | 0 |
| Thromboembolism (Ischemic Colitis) | 1 (0.6) |
| Transient Ischemic Attack | 1 (0.6) |
| Diaphragmatic Paralysis | 0 |
| Pneumothorax | 0 |
| Heart Block | 0 |
| Pulmonary Vein Stenosis | 0 |
| Pulmonary Edema (Respiratory Insufficiency) | 0 |
| Pericarditis | 0 |
| Major Vascular Access Complication / Bleeding | 0 |

* The Cardiac Tamponades/Perforation for subject 106-002 was adjudicated as both definitely device and definitely procedure related; the second for subject 265-003 was adjudicated as possible device related and definitely procedure related.

Table 30 summarizes the SAEs occurring within 30 days of a study ablation procedure that were not classified as Primary AEs by protocol definition.

**Table 30 – SAEs Occurring within 30 of the Ablation Procedure by Causality and Category (Safety Population, n = 159)**

| Description | Total Number of Subjects with SAEs | Total Number of SAEs |
|---|---|---|
| SAEs | 6 | 6 |
| Device-Related | 0 | 0 |
| Possibly Device-Related | 0 | 0 |
| Procedure-Related | 2 | 2 |
| Sepsis due to UTI | 1 | 1 |
| Aspiration pneumonia | 1 | 1 |
| Possibly Procedure-Related | 3 | 3 |
| Hospitalization due to transient neurological symptoms | 1 | 1 |
| Gastrointestinal disorder | 1 | 1 |
| Septic shock due to pneumonia with abscess | 1 | 1 |
| Not Related to device or procedure | 1 | 1 |
| AF Recurrence with Rapid Ventricular Response | 1 | 1 |

There were no deaths during the study.

C.4.1 – Average CF and Primary AEs

Table 31 compares the average CF during procedures in subjects experiencing Primary AEs with those who did not. Procedural average contact force used in subjects who experienced Primary AEs was similar to those that did not.

**Table 31 – Average Contact Force (g) by Primary Adverse Event (Safety Population, n = 159)***

| Subject ID | Primary AE | Mean ± SD | Median | Min / Max |
|---|---|---|---|---|
| 106-001 | Thromboembolism | 19.4 ± 7.37 | 18.3 | 9.2 / 38.6 |
| 106-002 | Cardiac Tamponade | 15.7 ± 6.17 | 14.0 | 6.9 / 27.4 |
| 131-003 | TIA | 14.7 ± 4.79 | 15.0 | 8.2 / 25.4 |
| Subjects who did not experience a Primary AE (n = 155) | | 16.7 ± 6.14 | 15.7 | 7.4 / 38.3 |

* Necessary procedural data for subject 265-003 (adjudicated as cardiac tamponade/perforation due to the size of the pericardial effusion [1.3 cm]) was unavailable for analysis.

C.5 – Study Conclusion
The results demonstrate that the THERMOCOOL SMARTTOUCH® SF Catheter met pre-specified performance goal for safety.

**SUMMARY OF CLINICAL STUDIES CONDUCTED FOR THE THERMOCOOL SMARTTOUCH® CATHETER**

**STUDY 1: Pivotal Study**

**A. Objective**
The primary objective of this trial was to demonstrate the safety and effectiveness of the THERMOCOOL SMARTTOUCH® Catheter with Contact Force Sensing Capability 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, single-arm, unblinded, multicenter, pivotal clinical investigation conducted at 21 investigational sites in the US.

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

**Primary Effectiveness Endpoint** – freedom from documented symptomatic atrial fibrillation (AF), atrial tachycardia (AT), or atrial flutter (AFL) episodes (hereinafter collectively referred to as "atrial tachyarrhythmias") based on electrocardiographic data during the effectiveness evaluation period (Day 91-361) post a three-month blanking period

**Acute success –** confirmation of entrance block in all targeted pulmonary veins

**Primary Safety Endpoint** – incidence of early onset (within 7 days of an AF 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

  * PV stenosis and atrio-esophageal fistula that occur greater than one week (7 days) post-procedure were also classified as Primary AEs

***Secondary safety endpoints*** included:

- Occurrence of peri-procedural serious adverse events > 7 but ≤ 30 days
- Occurrence of late onset (> 30 days) serious adverse events excluding PV stenosis and atrio-esophageal fistula.
- Non-serious adverse events

B.2 – Objective Performance Criteria (OPC)
Objective performance goals were prospectively established.

Effectiveness: Performance Goal = 50% lower bound of the 95% CI around the primary success rate
Safety: Performance Goal = 16.6% upper bound of the 95% CI around the primary AE rate

B.3 – Subject Accountability

**Table 32 – Subject Accountability and Disposition**

| Disposition | N | % |
|---|---|---|
| **Enrolled Subjects** | **172** | **100.0** |
| Subjects Not Meeting I/E Criteria | 15 | 8.7 |
| **ITT Cohort** | **157** | **91.3** |
| **Enrolled Subjects** | **172** | **100.0** |
| Excluded Subjects | 11 | 6.4 |
| **Safety Cohort** | **161** | **93.6** |
| Discontinued Subjects | 1 | 0.6 |
| Subjects Undergone RF Ablation | 160 | 93.0 |
| Roll-In Cases | 38 | 22.1 |
| Effectiveness Cohort | 122 | 70.9 |
| Subjects with non-study Arrhythmia | 0 | 0 |

| | | |
|---|---|---|
| Subjects not meeting I/E Criteria | 8 | 4.7 |
| **Primary Effectiveness Cohort** | **114** | **66.3** |

The following definitions were used to classify subjects:

**Enrolled Subjects** (n = 172) Patients who signed the informed consent.

**Excluded Subjects** (n = 11) Subjects that were enrolled but never underwent insertion of the study catheter. Excluded subjects were not included in either the effectiveness or safety evaluation of the study catheter.

**Discontinued Subjects** (n = 1) Subjects that had the investigational catheter inserted but were not treated with the investigational device (i.e., no RF energy applied). Subjects were categorized as "discontinued" if ablation was not possible due to non-investigational equipment failure or if their arrhythmia was determined at the time of electrophysiologic study to be a non-study arrhythmia (e.g., atrial flutter). These discontinued subjects remained in follow-up for 7 days as part of the safety evaluation**.**

**Intent-To-Treat (ITT) Cohort** (n = 157) Enrolled subjects who met the inclusion/exclusion criteria.

**Primary Effectiveness Cohort** (n = 114) was comprised of subjects that received the treatment with the THERMOCOOL SMARTTOUCH® Catheter and met the Inclusion/Exclusion criteria and did not meet the definitions of being excluded or discontinued. Roll-in cases were excluded from the primary effectiveness cohort.

**Safety Cohort** (n = 161) was comprised of enrolled subjects undergoing insertion of the THERMOCOOL SMARTTOUCH® Catheter. The calibration roll-in subjects were included in this cohort.

B.4 – Subject Demographics

**Table 33 – Subject Demographics (Enrolled Subjects, N = 172)**

| | **Total** n/172 (%) | **Male** n/124 (%) | **Female** n/48 (%) | **p-value** |
|---|---|---|---|---|
| **Gender** | | | | |
| | 172 (100.0) | 124 (72.1) | 48 (27.9) | |
| **Ethnicity** | | | | |
| Hispanic | 4 (2.3) | 4 (3.2) | 0 (0.0) | 0.5772 |
| **Race** | | | | |
| Asian | 0 (0) | 0 (0) | 0 (0.0) | 0.8141 |
| Other | 3 (1.7) | 3 (2.4) | 0 (0.0) | |
| Black | 4 (2.3) | 3 (2.4) | 1 (2.10 | |
| White | 165 (95.9) | 118 (95.2) | 47 (97.9) | |
| **Age (years)** | | | | |
| Mean | 58.8 ± 11.00 | 57.3 ± 10.86 | 62.5 ± 10.60 | 0.0026 |
| Median | 60.0 | 58.0 | 65.0 | |
| Min / Max | 23 / 79 | 23 / 79 | 27 / 78 | |

The age in the above table was when the subject signed the informed consent. The p-value listed compares the ethnicity, race and age by gender.

**C. Results**

C.1 - Procedural Data

Table 34 and Table 35 present the procedural data. There were 175 procedures in 160 subjects. One hundred and forty-five (145) underwent one ablation procedure, 15 subjects (3 roll-in subjects and 12 in the effectiveness cohort) underwent a second ablation procedure. Of the 12 in the effectiveness cohort, 6 repeat ablations were during the blanking period and the remaining 6 were post-blanking due to effectiveness failure.

**Table 34 – Summary of Power, Temperature and Impedance Data (Subjects Undergoing Ablation, n = 160)***

| **Description** | **Roll-In Subjects Mean ± SD (n)** | **Effectiveness Cohort Mean ± SD (n)** | **Total Mean ± SD (n)** |
|---|---|---|---|
| Mean Power (W)/procedure (n = 135 procedures) | 31.2 ± 5.2 (29) | 31.0 ± 3.7 (106) | 31.1 ± 4.1 (135) |
| Mean Temperature (°C)/procedure (n = 136 procedures) | 36.3 ± 1.31 (29) | 35.9 ± 1.9 (107) | 36.0 ± 1.8 (136) |
| Mean Impedance (ohms)/procedure (n = 136 procedures) | 112.7 ± 11.6 (29) | 120.4 ± 14.9 (107) | 118.8 ± 14.5 (136) |

* Complete procedural data were not reported for all subjects.

**Table 35 – Summary of Ablation Procedure Parameters – All Ablation Procedures (Subjects Undergoing Ablation, n = 160)***

| **Procedure Parameters** | **Roll-In Subjects Mean ± SD (n)** | **Effectiveness Cohort Mean ± SD (n)** | **Total Mean ± SD (n)** |
|---|---|---|---|
| Number of RF Applications (n = 175 procedures) | 59.0 ± 38.8 (41) | 59.6 ± 44.2 (134) | 59.5 ± 42.9 (175) |
| Mean Saline Infused (ml) by THERMOCOOL SMARTTOUCH® Catheter (n = 173 procedures) | 1725.7 ± 860.8 (39) | 1803.6 ± 910.5 (134) | 1786.0 ± 897.6 (173) |
| Total Procedure Time (min) | 236.4 ± 89.1 (41) | 211.6 ± 86.0 (134) | 217.4 ± 87.1 (175) |
| Ablation Procedure Time (min) | 116.3 ± 46.3 (39) | 117.6 ± 62.6 (127) | 117.3 ± 59.1 (166) |
| Total Fluoroscopy Duration (min) | 47.2 ± 28.1 (39) | 38.6 ± 24.6 (134) | 40.5 ± 25.6 (173) |
| Total Fluid Input (ml) | 3071.0 ± 1378.6 (40) | 3541.6 ± 1606.6 (134) | 3433.4 ± 1565.9 (174) |

| | | | |
|---|---|---|---|
| Total Fluid Output (ml) | 986.8 ± 738.9 (37) | 1079.3 ± 919.4 (116) | 1056.9 ± 877.8 (153) |
| Balance (input-output) (ml) | 2145.3 ± 1314.1 (36) | 2689.6 ± 1511.6 (116) | 2560.7 ± 1481.4 (152) |

* Data parameters not available for all ablation procedures.

Note: Table 35 reflects available data from index procedures for roll‑in subjects and effectiveness cohort subjects.

All AF ablation procedures began with circumferential lesions targeting all pulmonary veins, with additional atrial ablation lines created as clinically required. Table 36 summarizes the lesion sets applied to the subjects undergoing ablation during the index ablation procedures.

**Table 36 – Outcomes by Ablation Targets per Subject – 1st Ablation Procedure (Subjects Undergoing Ablation, n = 160)**

| Ablation Targets | Roll-In Subjects n*/38 (%) | Effectiveness Cohort n*/122 (%) | All n*/160 (%) |
|---|---|---|---|
| PV Only | 19 (50.0) | 61 (50.0) | 80 (50.0) |
| PV + Atrial Lines | 14 (36.8) | 52 (42.6) | 66 (41.3) |
| PV + Foci | 1 (2.6) | 2 (1.6) | 3 (1.9) |
| PV + Atrial Lines + Foci | 4 (10.5) | 7 (5.7) | 11 (6.9) |
| **Total** | **38 (100.0)** | **122 (100.0)** | **160 (100.0)** |

* n represents number of subjects.

C.2 - Acute Procedural Success

Acute success was defined as the confirmation of entrance block into all targeted PVs. Any use of non-study catheters and > 2 repeat ablations during the blanking period were considered acute procedural failures.

Acute procedural success results are presented in Table 37.

**Table 37 – Acute Effectiveness Summary (Primary Effectiveness Cohort, n = 114)**

| | Number of Subjects n / n | Percentage of Subjects with Acute Success (%) | 95% Exact Binomial Confidence Interval |
|---|---|---|---|
| Subjects Undergoing Ablation | 158/160 | 98.8 | (95.6, 99.8) |
| Roll-In | 36/38 | 94.7 | (82.3, 99.4) |
| Effectiveness Cohort | 122/122 | 100.0 | (97.0, 100.0) |
| **Primary Effectiveness Cohort** | **114/114** | **100.0** | **(96.8, 100.0)** |

C.3 – Primary Effectiveness Endpoint - Freedom from Symptomatic Atrial Tachyarrhythmia

**Primary Effectiveness Analysis**

The primary effectiveness endpoint was defined as freedom from documented symptomatic AF/AT/AFL (“atrial tachyarrhythmias”) based on electrocardiographic data and freedom from failure modes during the effectiveness evaluation period (Day 91-361). Any AF recurrence or repeat ablation procedure occurring greater than Day-361 post index procedure was deemed primary effectiveness successes at 12 months.

In the worst-case scenario analysis, over seventy-percent (70.2%, 80/114) of the primary effectiveness cohort were free from documented symptomatic atrial tachyarrhythmias during their effectiveness evaluation period. This includes 2 subjects who were protocol-adjudicated failures at 12 months follow-up who did not have documented symptomatic AF/AFL/AT recurrence. The lower bound of the 95% confidence interval of the primary effectiveness rate was 60.9%, significantly higher than the pre-determined performance goal of 50% ($p < 0.0001$).

Primary Effectiveness results are described in Table 38.

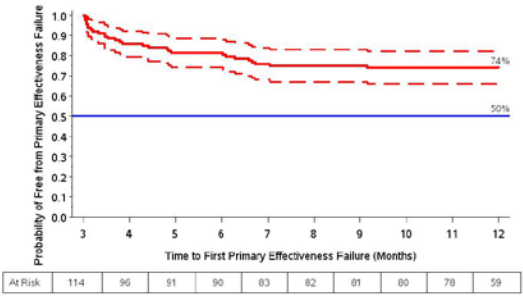
**Table 38 – Primary Effectiveness Endpoint through 12 Month Follow-Up Visit (Primary Effectiveness Cohort, n = 114)**

| | Number of Subjects (n) | Percentage of Subjects (%) | 95% Exact Binomial Confidence Interval | p-value |
|---|---|---|---|---|
| Freedom from Documented Symptomatic AF/AT/AFL | 80 | 70.2 | (60.9%, 78.4%) | <0.0001 |
| Primary Effectiveness Failures | 29* | 25.4 | | |
| Missing Outcomes | 5** | 4.4 | | |

* 2 subjects were protocol adjudicated failures without documented symptomatic AF/AFL/AT recurrence.
** 5 LTFU subjects were included in the denominator of the binomial exact analysis.

Figure 7 shows the Kaplan-Meier survival curves for the primary effectiveness cohort. The probability of freedom from primary effectiveness endpoint failure at 12 months post-blanking was 75.8% with a protocol-adjudicated success for this cohort of 74.0% (95% CI, 65.9%-82.2%). The lower bound of the 95% CI for this KM graph (as indicated by the lower dotted line) is greater than 50% pre-determined performance criterion. The primary effectiveness performance goal was met.

**Figure 7– Kaplan-Meier Analysis – Probability of Freedom from Chronic Effectiveness Failure Through 12 Months Post-Procedure (Primary Effectiveness Cohort = 114)**



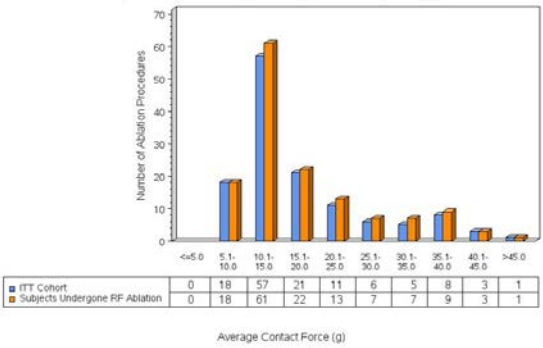

| At Risk | 114 | 96 | 91 | 90 | 83 | 82 | 81 | 80 | 78 | 59 |
|---|---|---|---|---|---|---|---|---|---|---|

C.4 – Contact Force Data

The THERMOCOOL SMARTTOUCH® system for measuring the contact force (CF) applied to the endocardial wall of the heart is comprised of the THERMOCOOL SMARTTOUCH® Catheter and CARTO® 3 EP navigation work station with the CARTO SMARTTOUCH™ Module installed. The graphical user interface (GUI) of the CARTO® 3 work station displays the pressure applied to the endocardial surface of the heart as gram forces that the investigator can visualize during the procedure.

Figure 8 presents the distribution of average contact force (CF) per ablation procedure. Overall the average CF applied during the trial was 17.9 g ± 9.42 g.

**Figure 8 – Distribution of Average Contact Force per Ablation Procedure (ITT Cohort, n = 157; Subjects Undergoing RF Ablation, n = 160)**




| | <=5.0 | 5.1-10.0 | 10.1-15.0 | 15.1-20.0 | 20.1-25.0 | 25.1-30.0 | 30.1-35.0 | 35.1-40.0 | 40.1-45.0 | >45.0 |
|---|---|---|---|---|---|---|---|---|---|---|
| ITT Cohort | 0 | 18 | 57 | 21 | 11 | 6 | 5 | 8 | 3 | 1 |
| Subjects Undergone RF Ablation | 0 | 18 | 61 | 22 | 13 | 7 | 7 | 9 | 3 | 1 |

An integral part of the CARTO® 3 graph display includes a real-time rolling graph of applied CF which includes a user configurable working range that is displayed on the graph as horizontal lines for a low and high range. The real-time rolling graph display with the working ranges acts as a visual aid providing real-time feedback of the pressure being applied by the operator in relationship to their pre-selected CF values.

Table 39 presents the investigator selected working ranges used during the study ablation procedures with the THERMOCOOL SMARTTOUCH® Catheter.

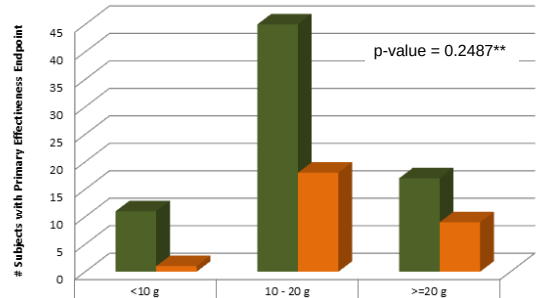
**Table 39 – Working Ranges Configured by Investigators (Subjects Undergoing an Ablation Procedure, n = 160)**

| Investigator Range (g) | | n / 141 (%) |
|---|---|---|
| Lower | Upper | |
| 4 | 40 | 2 (1.4) |
| 5 | 20 | 1 (0.7) |
| 5 | 25 | 16 (11.3) |
| 5 | 30 | 9 (6.4) |
| 5 | 40 | 95 (67.4) |
| 5 | 44 | 1 (0.7) |
| 5 | 45 | 1 (0.7) |
| 5 | 50 | 4 (2.8) |
| 5 | 60 | 1 (0.7) |
| 10 | 40 | 10 (7.1) |
| 15 | 25 | 1 (0.7) |

C.4.1 – Correlation of Average CF and Primary Effectiveness

In this study the average CF during RF application for individual procedures did not correlate with the primary effectiveness endpoint. Figure 9 presents the analysis.

**Figure 9 – Number of Subjects with Primary Effectiveness Endpoint by Average CF (Primary Effectiveness Cohort, n = 114)***




| | <10 g | 10 - 20 g | >=20 g |
|---|---|---|---|
| Success | 11 | 45 | 17 |
| Failure | 1 | 18 | 9 |

* Subjects with censored primary effectiveness endpoint are not included in the analysis.
** Fisher's exact test

C.4.2 – Correlation of Average CF and Safety

Table 40 compares the average CF during procedures in subjects experiencing Primary AEs with those who did not. Using CF as a continuous variable, there was no statistically significant difference in the average CF applied during procedures resulting in Primary AEs and in those procedures that did not.

**Table 40 – Average Contact Force by Primary Adverse Event (Primary Safety Cohort, n = 161)**

| Primary Adverse Event | Average Contact Force (g) | | | p-value |
|---|---|---|---|---|
| | Mean ± SD | Median | Min / Max | |
| Yes (n = 13) | 18.2 ± 6.15 | 17.1 | 10.9 / 33.4 | 0.1995 |
| No (n = 128) | 17.8 ± 9.71 | 14.2 | 5.4 / 45.7 | |

C.4.3 – Correlation of CF and Tamponade

Table 41 presents the correlation of subjects experiencing cardiac tamponade AEs with the percentage of time with CF measurements were ≥ 40 grams and ≥ 50 grams. It was assumed that higher percentage of time with CF ≥ 40 grams and with CF ≥ 50 grams signified more excursions of CF applied during the procedure and that these excursions may possibly have resulted in more primary AEs and tamponades. On average 8.3% of the time was spent over 40 grams of CF with a median of 2.1% and on average only 4.8% of time was spent over 50 grams of CF, with a median of 0.8%. The data was skewed by one site where 23 cases had a mean of 35% of time with CF ≥ 40 grams and 23% of the time with CF ≥ 50 grams. 2.1% of all cases were completed with average CF greater than or equal to 40 grams. In comparing procedures with CF ≥ 40 grams more than 2.1% of the time vs. those that were less than 2.1% of the time, there were no statistically significant differences exhibited in the comparisons presented in the table below. The four tamponade subjects all had percentage of time with CF ≥ 40 grams over 2.1%. Due to the sparse data of tamponade, the correlation was only borderline significant (p-value = 0.0581).

**Table 41 – Correlation of Tamponade Cases with % of Time CF Measurements ≥ 40 grams (Safety Cohort, n = 161*)**

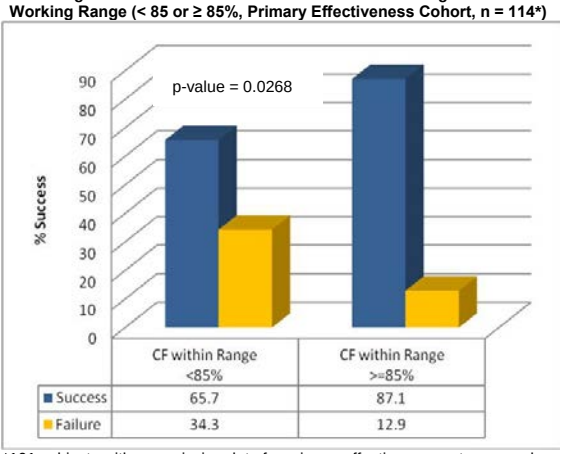
| Tamponade Adverse Event | Percentage of Time with CF Measurements ≥ 40 Grams | | P-value |
|---|---|---|---|
| | < 2.1% n / 71 (%) | ≥ 2.1% n / 70 (%) | |
| Yes | 0 | 4 (5.7%) | 0.0581 |
| No | 71 (100.0%) | 66 (94.3%) | |

* CF data were missing or not analyzable for 19 subjects.

C.4.4 – Percent of Time within Investigator Selected Range and Primary Effectiveness and Safety

Sensitivity analysis showed that the percentage of time the investigator stayed within his selected working range (regardless of the range selected) correlated positively with primary effectiveness success. If the investigator maintained pressure on the heart endocardial surface within their selected working range 85% or more of the time during RF application, the success rate was greater than 87%. Figure 10 presents the results.

**Figure 10 – Number of Subjects with Primary Effectiveness Endpoint by Percentage of Time with CF Measurements within Investigator-Selected Working Range (< 85 or ≥ 85%, Primary Effectiveness Cohort, n = 114*)**




*101 subjects with non-missing data for primary effectiveness outcome and CF data were included in the analysis.

**Figure 11 – Time to Primary Effectiveness Failure through 12 Months Post-Procedure, by Percentage of Time in CF Working Range – Kaplan-Meier Curve (< 85% vs. ≥ 85%, Primary Effectiveness Cohort, n = 114)**

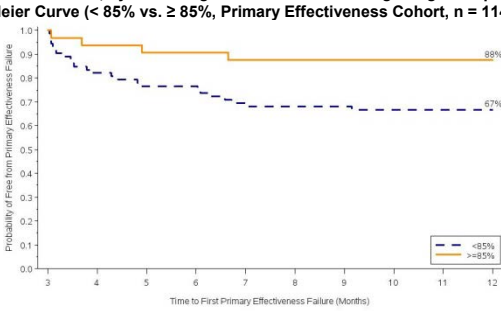



**Table 42 – Primary AEs and Tamponade Adverse Event by Percentage of Time CF Measurements were within the Investigator Selected Working Range (Primary Safety Cohort, n = 161)**

| Primary AE | | | |
|---|---|---|---|
| **Percent Time within Working Range (n)** | **Yes n (%)** | **No n (%)** | **p-value** |
| < 85% (100) | 8 (8.0) | 92 (92.0) | 0.5229 |
| ≥ 85% (41) | 5 (12.2) | 36 (87.8) | |
| **Cardiac Tamponade Events** | | | |
| **Percent Time within Working Range (n)** | **Yes n (%)** | **No n (%)** | **p-value** |
| < 85% (100) | 2 (2.0) | 98 (98.0) | 0.5798 |
| ≥ 85% (41) | 2 (4.9) | 39 (95.1) | |

C.5 - 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 Safety Cohort (n = 161) was comprised of all enrolled subjects who had the study catheter inserted.

**Primary Safety Endpoint** – Primary Adverse Events

Table 43 presents the protocol-established endpoint and safety results. There were 17 primary AEs reported for 16 subjects. One Primary AE was deemed related to the investigational catheter. Two were deemed possibly device-related. The remainder were deemed unrelated to the investigational catheter. The overall percentage of subjects who experienced a serious primary AE was 9.9% (16/161) and the upper confidence bound based on the Primary Safety Cohort was 15.6%. The safety endpoint specified in the protocol was 8.6% (upper confidence bound of 16.6%). Therefore, the results met the protocol-established performance criteria for the safety endpoint.

**Table 43 – Primary Safety Endpoint Outcome – Primary Adverse Events (Primary Safety Cohort, n = 161)**

| | Protocol Established Endpoint | n |
|---|---|---|
| Number of Subjects in Safety Cohort | | 161 |
| Number of Subjects with Primary AEs | | 16 |
| % Primary AEs | 8.6 | 9.9 |
| Upper Bound of the Two-Sided 95% Confidence Interval* | 16.6 | 15.6 |

* Exact binomial using a commercially available software package.

Table 44 summarizes the major Primary AEs.

**Table 44 – Primary Safety Endpoint – Early-Onset (within (≤) 7 Days) Primary Adverse Events (Primary Safety Cohort, n = 161)**

| Description | Number of Subjects with Primary AEs n/161 (%) |
|---|---|
| **Total Serious Primary AEs** | **16* (9.9%)** |
| Death | 0 |
| Atrio-Esophageal Fistula | 0 |
| Atrial Perforation | 0 |
| Cardiac Tamponade | 4 (2.48) |
| Myocardial Infarction | 0 |
| Stroke | 0 |
| Cerebrovascular Accident | 0 |
| Thromboembolism | 0 |
| Transient Ischemic Attack | 0 |
| Diaphragmatic Paralysis | 0 |
| Pneumothorax | 0 |
| Heart Block | 1 (0.62) |
| Pulmonary Vein Stenosis | 0 |
| Pulmonary Edema | 0 |
| Pericarditis | 3 (1.86) |
| Hospitalization (initial and prolonged) | 6 (3.72) |
| Pericardial Effusion | 0 |
| Vascular Access Complication | 3 (1.86) |

* One subject appears in two categories.

Table 45 summarizes the SAEs occurring within 30 days of a study ablation procedure that were not classified as Primary AEs by protocol definition.

**Table 45 – SAEs Occurring within 30 of the Ablation Procedure by Causality and Category (Safety Cohort, n = 161)**

| Description | Total Subjects with SAEs | Total Number of SAEs |
|---|---|---|
| **Non-SAEs** | **8** | **8** |
| **Device-Related** | **0** | **0** |
| **Possibly Device-Related** | **0** | **0** |
| **Procedure-Related** | **1** | **1** |
| *Hospitalization: AF Recurrence* | 1 | 1 |
| **Possibly Procedure-Related** | **1** | **1** |
| *Loss of Consciousness* | 1 | 1 |
| **Not Related** | **6** | **6** |
| *Other: Dysphagia*<br>*Hospitalization: AF Recurrence*<br>*Rectal Bleed* | 1<br>4<br>1 | 1<br>4<br>1 |

There were no deaths during the study.

C.6 – Study Conclusion

The results demonstrate that the THERMOCOOL SMARTTOUCH® Catheter met Objective Criteria Performance for safety and effectiveness.

**STUDY 2: Continued Access Study**

**A. Objective**

The purpose of this study was to allow continued access of the THERMOCOOL SMARTTOUCH® Catheter for the ablation treatment of subjects with drug refractory symptomatic paroxysmal atrial fibrillation while the sponsor completed analysis of the pivotal study under the current IDE protocol and the FDA reviewed the pre-market application. This study provided additional corroborative safety and effectiveness data for the THERMOCOOL SMARTTOUCH® Catheter system.

**B. Study Design and Endpoints**

The study design and endpoints were the same as those outlined above in the pivotal study.

B.1 - Subject Accountability

**Table 46 – Subject Accountability (N = 148)**

| Subject Disposition | No. of Subjects |
|---|---|
| Enrolled Subjects | 148 |
| Excluded | 3 |
| ITT Cohort | 145 |
| Withdrawn | 1 |
| Data Not Available | 1 |
| Safety Analysis Cohort | 143 |
| Discontinued | 2 |
| Subjects Undergoing Ablation | 141 |
| Number of Subjects Currently in Follow-Up | 141 |

**Enrolled Subjects** (n = 148) patients who sign the informed consent.

**Excluded Subjects** (n = 3) subjects that are enrolled but never undergo insertion of the Study Catheter. Excluded subjects will not be included in either the effectiveness or safety evaluation of the Study Catheter.

**Discontinued Subjects** (n = 2) subjects that have the investigational catheter inserted but are not treated with the investigational device (i.e., no RF energy applied). Subjects will be categorized as "discontinued" if ablation was not possible due to non-investigational equipment failure or if their arrhythmia was determined at the time of electrophysiologic study to be a non-study arrhythmia (e.g., atrial flutter). These discontinued subjects will remain in follow-up for 7 days as part of the safety evaluation**.**

**Intent-To-Treat (ITT) Cohort** (n = 145) Enrolled subjects who meet the inclusion/exclusion criteria.

**Subjects Undergoing Ablation/Effectiveness Cohort** (n = 141) was comprised of subjects that received the treatment with the THERMOCOOL SMARTTOUCH® Catheter and met the Inclusion/Exclusion criteria and did not meet the definitions of being excluded or discontinued. Roll-in cases were excluded from the primary effectiveness cohort.

**Safety Cohort** (n = 143) was comprised of enrolled subjects undergoing insertion of the THERMOCOOL SMARTTOUCH® Catheter. The calibration roll-in subjects were included in this cohort.

B.2 – Subject Demographics

**Table 47 – Subject Demographics (N = 148)***

| Characteristic | | |
|---|---|---|
| Gender | | n/147 (%)* |
| | Male | 104 (70.7) |
| | Female | 43 (29.3) |
| Race | | n/147 (%)* |
| | Caucasian | 146 (99.3) |
| | Black | 1 (0.7) |
| | Asian | 0 (0.0) |
| | Other | 0 (0.0) |
| Ethnic Origin | | n/147 (%)* |
| | Hispanic/Latino | 2 (1.4) |
| Age (years) | | |
| | N | 147* |
| | Mean | 61 |
| | S.D. | 10.44 |
| | Median | 62 |
| | Min / Max | 32 / 88 |

* At the time of publication, data was only available for 147 subjects.

**C. Results**

C.1 - Acute Procedural Success

Acute success was defined as the confirmation of entrance block into all targeted PVs. Any use of non-study catheters and > 2 repeat ablations were considered acute procedural failures.

At the time of publication, data analysis results for acute procedural success are not available for the Continued Access Study.

C.2 – Primary Effectiveness Endpoint - Freedom from Symptomatic Atrial Tachyarrhythmia

**Primary Effectiveness Analysis**

The primary effectiveness endpoint was defined as freedom from documented symptomatic AF/AT/AFL ("atrial tachyarrhythmias") based on electrocardiographic data and freedom from failure modes during the effectiveness evaluation period (Day 91-361). Any AF recurrence or repeat ablation procedure occurring greater than Day-361 post index procedure was deemed primary effectiveness successes at 12 months.

At the time of publication, the Continued Access Study data analysis is ongoing and 12 month follow-up data is not available.

C.3 – Primary Safety Endpoint

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 Safety Cohort (n = 143) was comprised of all enrolled subjects who had the study catheter inserted.

There were 27 Primary AE in 25 subjects who have had the investigational catheter inserted or undergone an ablation procedure. The percentage of subjects who experienced a Primary AE in the safety cohort was 17.5% (25/143) and upper bound of the two-sided 95% interval was 24.7%.

**Table 48 – Primary Safety Endpoint – Early-Onset (within (≤) 7 Days) Primary Adverse Events (Primary Safety Cohort, n = 143)**

| Description | # of Subjects with Primary AEs n/143 (%) |
|---|---|
| **Total Serious Primary AEs** | **25* (17.5)** |
| Death | 0 |
| Atrio-Esophageal Fistula | 0 |
| Atrial Perforation | 0 |
| Cardiac Tamponade | 2 (1.40) |
| Myocardial Infarction | 0 |
| Stroke | 0 |
| Cerebrovascular Accident | 1 (0.70) |
| Thromboembolism | 0 |
| Transient Ischemic Attack | 0 |
| Diaphragmatic Paralysis | 0 |
| Pneumothorax | 0 |
| Heart Block | 2 (1.40) |
| Pulmonary Vein Stenosis | 0 |
| Pulmonary Edema | 2 (1.40) |
| Pericarditis | 1 (0.70) |
| Hospitalization (initial and prolonged) | 10 (6.99) |
| Pericardial Effusion** | 1 (0.70) |
| Vascular Access Complication | 8 (5.59) |

* Two subjects had events in two categories.
** Treated with pericardiocentesis.

**No deaths have occurred during the reporting period, and there have been no unanticipated adverse effects.**

**SUMMARY OF CLINICAL STUDIES CONDUCTED FOR ATRIAL FLUTTER INDICATION**

**STUDY 1: Pivotal Study**

**A. Objective**
The objective of the study was to determine if the NAVISTAR® THERMOCOOL® Catheter, when used in conjunction with the 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 49 – 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 50 – 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
Table 51 and Table 52 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 51 – 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 52 – 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 53 describes the acute ablation outcomes.

**Table 53 – 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 54 summarizes the composite results.

**Table 54 – 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 55 – 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 56 summarizes the major adverse events.

**Table 56 – Major Adverse Events Observed within 7 days Post-Ablation**

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

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

**Table 57 – Comparison of Endpoints between NAVISTAR® THERMOCOOL® Catheter Study and OPC**

| Endpoint | OPC | NAVISTAR® THERMOCOOL® Catheter 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.

**STUDY 2: Post-Approval Study**

**A. Objective**
The primary objective was to provide additional, corroborative safety and efficacy data for the NAVISTAR® THERMOCOOL® Catheter for the treatment of subjects with typical atrial flutter (AFL).

**B. Study Design**
This study was a prospective, non-randomized, single-arm, multi-center post-approval evaluation.

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

**Primary safety endpoint** – the percentage of subjects experiencing cardiovascular-specific adverse events (CSAE) within seven (7) days of the ablation procedure; and

**Primary efficacy endpoint** – defined as complete bi-directional conduction block (BDB) across the sub eustachian (cavo-tricuspid) isthmus at a minimum of 30 minutes following the last RF application.

B.2 – Objective Performance Criteria (OPC)
Objective performance criteria (OPC) were prospectively established. The OPCs are defined below:

**Safety:** A CSAE rate below 2.7%, corresponding to a one-sided 95% upper confidence bound of 7%, was required to successfully achieve the safety endpoint.

**Efficacy:** An efficacy success rate of 88% with a one-sided lower confidence bound of 80% was required for effectiveness success.

B.3 - Subject Accountability
Table 58 documents the accountability and disposition of enrolled subjects.

**Table 58 – Subject Disposition (N = 291)**

| Category | N | Percentage |
|---|---|---|
| Total Subjects Enrolled | 291 | 100% |
| Excluded Group | 24 | 8.2% |
| Safety Cohort | 267 | 91.8% |
| Discontinued Group (no RF energy delivered via study catheter) | 5 | 1.7% |
| Subject with typical AFL – Non-Evaluable[1] | 1 | 0.3% |
| Subjects found to not have typical AFL | 8 | 2.7% |
| Efficacy Cohort (Evaluable subjects) | 253 | 86.9% |
| Subjects with only typical AFL | 236 | 81.1% |
| Subjects with typical AFL and other concomitant arrhythmia requiring ablation | 17 | 5.8% |

[1] Bidirectional block was not assessable in one subject due to an altered CS anatomy.

**Safety Analysis cohort** (n = 267) The primary safety endpoint is the rate of occurrence of Cardiovascular Specific Adverse Events (CSAE), which is defined as "an event which occurs within the first week (7 days) following use of the device and is one of the following Cardiovascular Specific adverse events: cardiac perforation, pericardial effusion, pulmonary embolus, complete heart block, stroke, acute myocardial infarction, and death." The protocol predetermined rate of CSAE was 2.7% with corresponding one-sided 95% upper confidence bound of 7%. The CSAE rate observed in the Safety Cohort (N = 267) was 1.5% (4/267). The one-sided 95% upper confidence bound for the Safety Cohort was 3.4%, which was below the cutoff rate of 7% required to achieve the safety endpoint.

**Efficacy Analysis cohort** (n = 253) The primary efficacy endpoint of this study was defined as confirmation of complete bidirectional conduction block across the sub-eustachian (cavo-tricuspid) isthmus at a minimum of 30 minutes following the last RF application. An acute success rate of 88% was anticipated and the one-sided 95% lower confidence bound was compared to 80%. There was a total of 253 subjects in the Efficacy Cohort. The overall acute efficacy success in the Efficacy Cohort was 93.3% (236/253), corresponding with a one-sided lower confidence bound of 90.1%. Acute efficacy success exceeded one-sided lower confidence bound of 80% as established in the protocol, thus the primary efficacy endpoint was met.

B.4 - Subject Demographics
The table below summarizes the demographic information of all study subjects enrolled in the study.

**Table 59 – Subject Demographics (All Enrolled Subjects, n = 291)**

| **Gender** | N | % |
|---|---|---|
| Female | 48 | 16.5 |
| Male | 243 | 83.5 |
| | | |
| **Age (years)** | | |
| Mean ± standard deviation | 65.2 ± 12.1 | |

| | |
|---|---|
| Range | 19-92 |

**C. Results**

C.1 - Intraprocedural Data
Table 60 and Table 61 describe the procedural data.

Seventeen (17) subjects received ablation therapy for an arrhythmia other than Type I atrial flutter during the same index ablation procedure. The additional arrhythmias ablated were: 10 right atrial tachycardia/non isthmus dependent flutter/scar flutter/ectopic, 4 left atrial tachycardia/flutter/scar flutter, 3 AVNRT, and 2 atrial fibrillation. One subject had multiple concomitant arrhythmias treated.

C.2 - Efficacy Success
Efficacy success, defined as complete bi-directional conduction block across the isthmus at a minimum of 30 minutes following application of the last RF application, was analyzed. If conduction across the isthmus was present at the end of the procedure or if another device (non-study catheter), in addition to the study catheter, was utilized for ablation, the procedure was considered to be an acute failure.

Table 60 describes the efficacy success.

**Table 60 – Efficacy Success (n = 253)**

| | **# Efficacy Success / # Subjects Ablated** | **Percentage (one-sided 95% confidence bound)** |
|---|---|---|
| Efficacy Success | 236/253 | 93.3% (90.1) |
| OPC | | 88% (80%) |

C.3 - Adverse Events
A cardiac-specific adverse event (CSAE) was defined as an event that occurred within the first week (7 days) following use of the device and was one of the following Cardiovascular Specific adverse events: cardiac perforation, pericardial effusion, pulmonary embolus, complete heart block, stroke, acute myocardial infarction, and death.

Of the 267 subjects who received ablation therapy with the study catheter, four (4) CSAEs were reported in four (4) subjects (1.5% of safety cohort). The one-sided 95% confidence bound rate was 3.4%. Table 61 summarizes the CSAEs observed.

**Table 61 – Cardiovascular Specific Adverse Events Observed within 7 Days Post-Ablation**

| Total Number Subjects experiencing a CSAE: n = 4 |
|---|
| Pulmonary Embolus = 1 subject, possibly procedure related<br><br>Complete Heart Block = 2 subjects, both unrelated to device or procedure<br><br>Myocardial Infarction = 1 subject, unrelated to device or procedure |

Three of the four CSAEs were determined by the investigators to be unrelated to the procedure or device and the remaining CSAE was deemed to be possibly procedure related.

There were three reported deaths during the course of the study, though no deaths occurred during the ablation procedure or during the study follow-up period. One subject died prior to the scheduled study procedure due to either pulmonary embolus or myocardial infarction. The other two subjects died after the completion of the study follow up period due to cancers (metastatic adenocarcinoma and lung cancer). All deaths were determined to be unrelated to the device or procedure.

An overall risk benefit evaluation of these adverse events was performed and a detailed review of each adverse event was completed.

C.4 - Statistical Analysis
Table 62 summarizes the safety and effectiveness of the device compared to the OPC established for safety and efficacy.

**Table 62 – Endpoints Comparison between NAVISTAR® THERMOCOOL® Catheter Post-Approval Study and OPC**

| **Primary Endpoints** | **OPC** | | **NAVISTAR® THERMOCOOL® Catheter Study** | |
|---|---|---|---|---|
| | % | One-sided 95% Confidence Bound | % (N) | One-sided 95% Confidence Bound |
| **Safety (CSAEs)** | 2.7% | 7% | 1.5% (4/267) | 3.4% (Upper bound) |
| **Efficacy** | 88% | 80% | 93.3% (236/253) | 90.1% (Lower bound) |

The results demonstrate that the NAVISTAR® THERMOCOOL® Catheter met the OPC for safety and efficacy.

**SUMMARY OF CLINICAL STUDIES CONDUCTED FOR ATRIAL FIBRILLATION INDICATION**

**Summary of Clinical Studies Conducted for Atrial Fibrillation Indication**
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 Anti-Arrhythmic Drug (AAD) regimen during comparable evaluation periods for the THERMOCOOL® Catheter 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:

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

***Secondary safety endpoints*** included comparisons between the THERMOCOOL® Catheter 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 63 – Subject Accountability and Disposition**

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

The following definitions were used to classify subjects:

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

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

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

B.3. – Subject Demographics:

The table below summarizes the demographic information. Subjects were randomized 2:1 upon signing informed consent.

**Table 64 – Subject Demographics**

| | **THERMOCOOL® Catheter** 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 | |
| **Left Atrial Dimension (mm)**** | | | | 0.7118 |
| Mean | 40.0 ± 5.5 | 40.3 ± 5.3 | 40.1 ± 5.4 | |
| Median | 40 | 41 | 40 | |
| Min / Max | 27.0 / 50.0 | 26.5 / 49.0 | 26.5 / 50.0 | |
| **Left Ventricular Ejection Fraction (%)***** | | | | 0.4670 |
| Mean | 62.3 ± 9.8 | 63.1 ± 7.4 | 62.6 ± 9.0 | |
| Median | 62 | 63 | 63 | |
| Min / Max | 30.0 / 86.0 | 44.0 / 80.0 | 30.0 / 86.0 | |

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

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

Subjects enrolled in the study reported a mean of 63.2 ± 92.4 Atrial Fibrillation episodes in the six months prior to baseline. Patients classified as New York Heart Association (NYHA) Class III and IV were excluded from the study. Approximately half of the enrolled subjects had a history of hypertension at baseline; 48.6% (51/105) in the THERMOCOOL® Catheter group and 50.0% (30/60) in the AAD (Control) group. Less than a third of the enrolled subjects (27.7%; 44/159) had a history of atrial flutter at baseline. The overall mean number of AADs failed at baseline was 2.2 ± 1.2, with 27 of the 167 enrolled subjects having previously failed only a Class II/IV AAD.

**C. Results**

C.1. - Procedural Data

Table 65 and Table 66 present the procedural data.

**Table 65 – Summary of RF Applications, Saline Infused, Power, Temperature and Impedance Data (THERMOCOOL® Catheter Effectiveness 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 66 – Summary of Ablation Procedure Parameters – All Ablation Procedures (THERMOCOOL® Catheter Effectiveness Cohort, n = 103*)**

| Procedure Parameters | THERMOCOOL® Catheter 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: Table 65 and Table 66 include all ablation procedures for subjects randomized to the THERMOCOOL® Catheter 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® Catheter) procedure time and all other procedures performed during the subject's stay in the electrophysiology (EP) lab. Therefore, the data do not solely reflect the actual use of the NAVISTAR® THERMOCOOL® Catheter.

All AF ablation procedures began with circumferential lesions targeting all pulmonary veins, with additional atrial ablation lines created as clinically required. Table 67 summarizes the lesion sets applied to THERMOCOOL® Catheter group subjects during the index ablation procedures.

**Table 67 – Outcomes by Ablation Targets per Subject – 1st Ablation Procedure (THERMOCOOL® Catheter Group Subjects, n = 103)***

| Ablation Targets | THERMOCOOL® Catheter Group (n = 103) | | |
|---|---|---|---|
| | Success n (%) | Fail n (%) | Total n (100%) |
| Pulmonary Veins (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.

C.2. - Acute Procedural Success

Acute procedural success results are presented in Table 68.

**Table 68 – Acute Effectiveness Outcome for THERMOCOOL® Catheter Group (n = 103)***

| | THERMOCOOL® Catheter 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® Catheter 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® Catheter group. The posterior probability that the THERMOCOOL® Catheter 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® Catheter group is 0.627 with a standard deviation of0.048. 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 54.

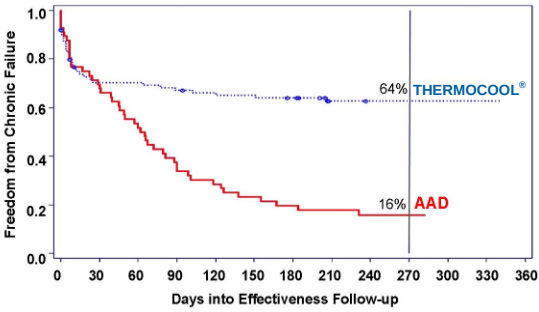
**Table 69 – Summary of Data Available*- June 2008 Dataset**

| Group | *0 < t ≤ 0.5* | | | *0.5 < t ≤ 2* | | | *2 < t ≤ 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 12 shows the Kaplan-Meier curves for each of the treatment groups for freedom from chronic effectiveness failure (n = 159) and shows superiority of the THERMOCOOL® Catheter group (64%) compared to AAD group (16%) for the primary effectiveness endpoint.

**Figure 12 – Kaplan-Meier Analysis – Probability of Freedom from Chronic Effectiveness Failure For Each Treatment Group**




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

The June 2008 dataset status of each of the 159 subjects is reported in Table 70. 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 70 – Summary of the Status for Each of the Enrolled Subjects**

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

Figure 13 shows that the 9-month failure-free rate in the THERMOCOOL® Catheter 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 13 – The Posterior Distributions of the Probabilities of 9 Month Failure- Free Treatment Success for Each Treatment Group**

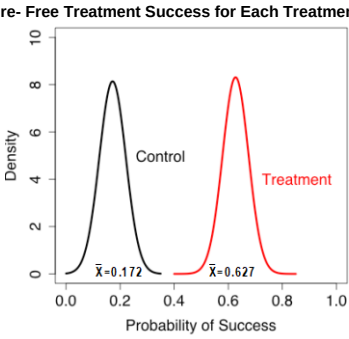
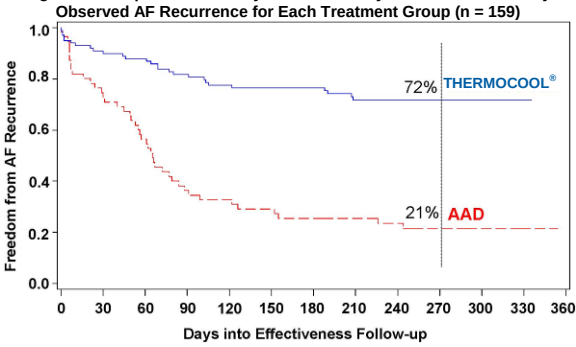



Figure 14 demonstrates that the THERMOCOOL® Catheter group had a higher probability of freedom from any documented symptomatic or asymptomatic AF recurrence, subject to the monitoring provisions of the protocol, than the AAD (Control) subjects. The difference in likelihood of AF recurrence after 9 months of effectiveness evaluation was 51% (72% vs. 21%) in favor of the THERMOCOOL® Catheter treatment group.

**Figure 14 – Kaplan-Meier Analysis – Probability of Freedom from Any Observed AF Recurrence for Each Treatment Group (n = 159)**




C.4. - Adverse Events (AE)

The primary safety endpoint for this study was defined as the incidence of early-onset (within 7 days of ablation procedure) primary AEs for subjects undergoing a study ablation procedure. The Primary Safety Cohort (n = 139) was comprised of THERMOCOOL® Catheter group subjects (n = 103) and AAD (Control) group subjects undergoing an ablation procedure (n = 36).

**Primary Safety Endpoint – Primary Adverse Events**

Table 71 presents the protocol-established endpoint and safety results based on the June 2008 dataset. There were 16 primary AEs reported for 15 subjects. The overall percentage of subjects who experienced a serious primary AE was 10.8 % (15/139) and the upper confidence bounds based on the Primary Safety Cohort was 16.1 %. The safety endpoint specified in the protocol was 7.0% (upper confidence bound of 16.0%). While the primary safety results exceeded the protocol-established primary safety endpoint for this study, the nature and types of adverse events experienced in this trial nonetheless represent an acceptable risk profile.

**Table 71 – 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 72 summarizes the major primary AEs

**Table 72 – 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** | **14 (10.1 %)** |
| 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 73 compares the incidence of early onset serious adverse events (SAE) between the two treatment groups occurring within the first 90 days of initial therapy.

**Table 73 – 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 to an ablation procedure were considered in this analysis.

One subject in the THERMOCOOL® Catheter group expired during the effectiveness evaluation period. This event occurred 284 days after the ablation procedure and was considered to be unrelated to the investigational device and procedure.

C.5. – Study Conclusion

In conclusion, the results demonstrate that there is a reasonable assurance of safety and effectiveness to support the use of the NAVISTAR® THERMOCOOL® ablation catheter for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with advanced three-dimensional electroanatomic mapping systems.

## How Supplied

- The Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter is supplied STERILE (EtO).
- The catheter is supplied with a choice of three curve types: D, F, and J.
- Additional catheter accessory devices are provided separately.

## Packaging

The Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter is supplied STERILE. 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.

## Storage
Store in a cool, dry, dark place. Storage temperature should be between 5 and 25°C (41 and 77°F).

## Sterilization/"Use By" Date
This catheter has been sterilized with ethylene oxide gas. Product and package testing have been conducted to support the "Use By" date printed on the product labels. **DO NOT USE** after the "Use By" date.

## Disposal
Recycle components, or dispose of the product and its residual elements or waste items in accordance with local laws and regulations.

## Compatible EP Navigation System
The Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter provides location and contact force information only when used with CARTO® 3 Navigation System. Compatibility with the CARTO® 3 System has been demonstrated via bench and animal testing to confirm that the device is capable of providing accurate location and contact force information when used in accordance with the Instructions for Use.

## Directions for Use
Please refer to the User Manuals for the CARTO® 3 Navigation System, the irrigation pump, RF generator, and the irrigation tubing for instructions on connecting and operating these systems in conjunction with the Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter. Use appropriate Biosense Webster accessory cables to connect the Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter to the appropriate accessory equipment.

1. Using aseptic technique, remove the catheter from the package and place in a sterile work area. Inspect the catheter carefully for electrode integrity and overall condition.
2. Create a vascular access in a large central vessel using aseptic techniques.
3. In order to prevent damage to the catheter tip, use the insertion tube supplied with the catheter to advance or retract the catheter through the hemostasis valve of the sheath. After insertion, slide the insertion tube back toward the handle.
4. To verify compatibility between the sheath and catheter, advance the catheter through sheath prior to insertion. Any sheath < 8.5 F is contraindicated.
5. Connect the catheter to the Patient Interface Unit (PIU) via the appropriate Biosense Webster cable. Connect the PIU to the compatible RF generator via the appropriate Biosense Webster cable. Connect the PIU to the appropriate recording and mapping systems, including the CARTO® 3 Navigation System, with appropriate interface cables. Use only Biosense Webster interface cables. To complete the electrical circuit, connect an indifferent electrode to the indifferent electrode input on the generator.
6. Connect the irrigation tubing to a room temperature, heparinized (1 IU 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.
7. Load the irrigation tubing into the pump. Open the stopcock and flush the tubing per irrigation pump instructions until the air is expelled through the open end of the tubing.
8. Connect the stopcock on the end of the irrigation tubing to the Luer fitting of the Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter.
9. Flush the catheter and tubing per standard technique to ensure purging of trapped air bubbles and to verify that the irrigation holes are patent.
10. Start continuous irrigation at a flow rate of 2 ml/min.
11. Insert the Biosense Webster THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter via the entrance site, using the insertion tube and an appropriately sized introducer sheath. Advance the catheter to the area under investigation. Use both fluoroscopy and electrograms (EGM) to aid in proper positioning.
12. In order to achieve optimal force reading accuracy and stability, allow the catheter to warm up for 2 minutes after connection to the CARTO® 3 System prior to use of the force feedback feature.
13. Zero the contact force reading following insertion into the patient. All four electrodes on the catheter tip must be outside of the sheath so that the force sensor is inside the body. Ensure the catheter tip is not in contact with tissue by evaluating the location on fluoroscopy and the CARTO® 3 System, the EGM amplitude, and catheter movement. Variations in the force reading at the same rate as the cardiac or respiration cycle may indicate contact with cardiac structures. Once these markers indicate the tip is not in contact, the reading can be zeroed. Refer to the User Manual for your CARTO® 3 System for instructions on how to zero the contact force reading.
14. Zero the contact force reading when moving the catheter from one chamber of the heart to another or upon re-insertion.
15. The catheter tip can be deflected to facilitate positioning by using the thumb knob to vary tip curvature. Pushing the thumb knob forward causes the catheter tip to deflect; when the thumb knob is pulled back, the tip straightens.
16. Verify that the "TCOOL SF" option is selected on the RF generator. When this option is chosen, the RF generator defaults to the safety parameters established for the THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter. Do not use tip temperature to guide ablation.
17. 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 W, a high flow rate of 8 ml/min should be used. For power levels between 31 - 45 W a high flow rate of 15 ml/min should be used. Do not use this catheter without irrigation flow.
18. 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.
19. Monitor the catheter tip temperature throughout the procedure to ensure adequate irrigation. If the temperature increases to 40°C during RF application, power delivery should be interrupted. The irrigation system must be rechecked prior to restarting RF application. Note: the displayed temperature represents the temperature of the electrode, not the temperature of the tissue.
20. **Recommendation for RF power delivered:**

    For treatment of atrial flutter:

    Start a procedure at 15 - 20 W. 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.

    For treatment of atrial fibrillation:

    - An RF power range of 15 - 45 W is recommended for atrial ablation.

- Do not rely on the catheter tip temperature response to guide ablation. If temperature increases rapidly stop RF application immediately.
- At anatomical locations not on the LA posterior wall or CS:
  - Maximum allowed power should not exceed 45 W.
  - Duration of ablation should not exceed 60 seconds of continuous ablation.
  - Duration of ablation as well as decision to interrupt RF power delivery at any time during ablation should be guided by clinical Investigator judgment and monitoring of ablation effectiveness parameters commonly used such as EGM reduction and/or impedance changes.
- For LA posterior wall ablations close to the esophagus:
  - Start ablation at ≤ 25 W.
  - Move/drag catheter to a new location if clinically effective ablation is achieved within 20 seconds (EGM reduction and/or impedance drop).
  - Power can be increased if clinically effective ablation isn't achieved within 20 seconds (no electrogram reduction and/or no impedance drop). Maximum power used should not exceed 35 W.
- Duration of ablation, as well as decision to interrupt RF power delivery at any time during ablation, should be guided by physician judgment and monitoring of ablation effectiveness parameters commonly used such as EGM reduction and/or impedance changes and esophageal temperature changes monitored by an endoluminal esophageal probe.
- Power should be limited to no more than 35 W if ablation is required in the CS and the duration of ablation should be limited to 20 seconds per ablation location.

21. **Contact Force (CF) ranges during ablation:**

A starting point minimum targeted CF of 5 to 10 grams is reasonable (Calkins H, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation, Heart Rhythm (2017), doi:10.1016/j.hrthm.2017.05.012).

In the PRECEPT study and the SMART-SF study using the THERMOCOOL SMARTTOUCH® SF Catheter, and the SMART-AF IDE study using the THERMOCOOL SMARTTOUCH® Catheter, operators were instructed to monitor CF during initial cases using standard methods for evaluating effective RF applications.

In the PRECEPT study, operators most frequently chose a working range with a low of 5 grams and a high of 40 grams (37.5%, 130/347) as described in Section C.3: Contact Force Data. The overall average contact force recorded during a study ablation procedure for all subjects undergoing ablation was 15.23 ± 4.41 grams as described in Table 9: Average Contact Force Measurements Overall per Ablation Procedure. In the majority of procedures (239/283), the average contact force applied was less than 20 grams as described in Figure 1: Distribution of Average Contact Force per Ablation Procedure.

In the SMART-SF study, operators most frequently chose a working range with a low of 5 grams and a high of 40 grams (44.0%, 70/159) as described in Table 26: Working Ranges Configured by Investigators. The overall average contact force recorded during a study ablation procedure for all subjects undergoing ablation was 16.7 ± 6.14 grams as described in Table 25: Average Contact Force Measurements Overall per Ablation Procedure. In the majority of procedures (125/152), the average contact force applied during ablation was less than 20 grams.

In the SMART-AF study, operators chose working ranges for RF applications that varied for both the low range (4 - 15 grams) and high range (20 - 60 grams) as described in Table 39: Working Ranges Configured by Investigators. During the study, investigators selected a working range of 5 to 40 grams for 67.4% of all study procedures. A low range of 5 grams was selected in more than 90% of the study subjects.

The average contact force applied to the endocardial heart surface during ablation procedures for all subjects undergoing ablation was 17.9 ± 9.42 grams. Results showed that when investigators stayed within their chosen working ranges ≥ 85% of the time during RF applications, there was a significant improvement in the 12-month effectiveness outcome (87.1% vs. 65.7%).

22. **Esophageal monitoring:**

An appropriate strategy to minimize risk of esophageal injury should be used to ensure the physician has accurate information about the location of the esophagus relative to intended sites of ablation.

- At least one of the following methods should be used for esophageal localization:
  - Use of a multipolar esophageal temperature probe
  - Esophageal visualization with CARTOSOUND® and/or ICE
  - Esophageal visualization using barium swallow

23. In using this catheter, operators should select individualized CF target ranges based on their case experience and the SMART-SF and SMART-AF IDE trial results

24. In the event of a generator cutoff (impedance or temperature), the catheter must be withdrawn and the tip electrode inspected for coagulum before RF current is reapplied. To remove any coagulum, if present, 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, or damage may also occur to the contact force sensor and affect measurement accuracy. Prior to reinsertion, ensure that the irrigation holes are not plugged as follows:

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. Uniform streams of fluid should be visible from the tip of the catheter.
c. Repeat steps a and b, if necessary.
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.
f. Zero catheter following reinsertion into patient.

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

***NOTE:** A small syringe provides sufficient pressure to produce a visible stream of fluid.

## DISCLAIMER OF WARRANTY AND LIMITATION OF LIABILITY

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Rev: 2019-12

  Printed in USA