SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. General Information:

Device Generic Name:	Electrode, percutaneous, conduction tissue ablation
Device Trade Names:	THERMOCOOL SMARTTOUCH® SF Bi-Directional Navigation Catheter THERMOCOOL SMARTTOUCH® SF Uni-Directional Navigation Catheter
Applicant's Name and Address:	Biosense Webster, Inc. 31 Technology Drive, Suite 200 Irvine, CA 92618
Premarket Approval Numbers:	P030031/S072 (for paroxysmal atrial fibrillation) P030031/S100 (for persistent atrial fibrillation)
Date of Panel Recommendation:	None
Date of FDA Notice of Approval to Applicant:	P030031/S072 – August 11, 2016 P030031/S100 - September 30, 2020

The original PMA P030031 was approved on November 5, 2004. The ThermoCool SmartTouch SF Navigation Catheter was approved in PMA P030031/S072 on August 11, 2016 and is indicated for treatment of (1) Type I atrial flutter in patients age 18 or older, and (2) Drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three-dimensional electroanatomic mapping system. The current supplement P030031/S100 was submitted to expand the indication for the ThermoCool SmartTouch SF Navigation Catheter to treat symptomatic, drug refractory persistent atrial fibrillation.

II. Indications for Use

THERMOCOOL SMARTTOUCH® SF Catheter

The Biosense Webster THERMOCOOL SMARTTOUCH® SF 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 THERMOCOOL SMARTTOUCH® SF 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.

III. Contraindications

The THERMOCOOL SMARTTOUCH® SF Navigation Catheters are contraindicated for the following types of patients:

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 French in order to avoid damage to the catheter shaft.

IV. Warnings and Precautions

A list of Warnings and Precautions can be found in the THERMOCOOL SMARTTOUCH® SF Navigation Catheter labeling (Instructions for Use)

V. Device Description

The THERMOCOOL SMARTTOUCH® SF Catheter utilizes a technology that measures the contact force between the catheter tip and endocardial tissue when connected to the CARTO® 3 System. The contact force sensing technology of the THERMOCOOL SMARTTOUCH® SF Catheter is equivalent to that of the standard THERMOCOOL SMARTTOUCH® Catheter. The THERMOCOOL SMARTTOUCH® SF Catheters are offered in both uni-directional and bi-directional deflectable platforms from product families D-1347-XX-S and D-1348-XX-S respectively as described in Table 1 below.

Table 1: THERMOCOOL SMARTTOUCH® SF Catheters

Family	Curve Type	Part Numbers
THERMOCOOL SMARTTOUCH® SF Bi-Directional Catheter	D-D	D-1348-01-S
	F-F	D-1348-02-S
	J-J	D-1348-03-S
	F-J	D-1348-04-S
	D-F	D-1348-05-S
THERMOCOOL SMARTTOUCH® SF Uni-Directional Catheter	D	D-1347-01-S
	F	D-1347-02-S
	J	D-1347-03-S

The uni-directional catheter is built on a similar platform and deflects with a similar deflection mechanism as the NAVISTAR® THERMOCOOL® Catheter, part number D-1197-XX-S. The bi-directional catheter is designed on a similar platform as the EZ STEER® THERMOCOOL® NAV Catheter, part number D-1292-XX-S. Both uni-directional and bi-directional catheters utilize a multi-hole tip electrode similar to the THERMOCOOL® SF NAV Catheter, part numbers D-1313-XX-S and D-1315-XX-S.

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.

Submission History

The submission history for the NAVISTAR® THERMOCOOL®, EZ STEER® THERMOCOOL® NAV, THERMOCOOL® SF NAV and THERMOCOOL SMARTTOUCH® Catheters is described in Table 2 below.

Table 2: Submission History for Precedent Devices

Submission	Description	Date of Approval
P030031	Approval of the NAVISTAR® THERMOCOOL® Catheter for the treatment of type I atrial flutter.	11-11-2004
P030031/S009	Approval of the EZ STEER® THERMOCOOL® NAV Catheter for the treatment of type I atrial flutter	09-30-2008
P030031/S011	Approval of the NAVISTAR® THERMOCOOL® Catheter and EZ STEER® THERMOCOOL® NAV Catheter for the treatment of drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three-dimensional electroanatomic mapping systems.	02-06-2009
P030031/S025	Approval of the THERMOCOOL® SF NAV Bi-Directional Catheter for the treatment of type I atrial flutter, and drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three-dimensional electroanatomic mapping systems.	12-21-2011

Submission	Description	Date of Approval
P030031/S034	Approval of the THERMOCOOL® SF NAV Uni-Directional Catheter for the treatment of type I atrial flutter, and drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three-dimensional electroanatomic mapping systems.	12-21-2011
P030031/S053	Approval of the THERMOCOOL SMARTTOUCH® Catheters (D-1327 and D-1336) for the treatment of type I atrial flutter, and drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three-dimensional electroanatomic mapping systems.	2-11-2014
P030031/S072	Approval for the THERMOCOOL SMARTTOUCH® SF Catheters, part numbers D-1347-XX-S and D-1348-XX-S, indicated for catheter-based cardiac electrophysiological mapping (stimulating and recording) and, when used with a compatible RF generator, for the treatment of: 1) Type I atrial flutter in patients age 18 or older; and 2) Drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three dimensional electroanatomic mapping systems. The THERMOCOOL SMARTTOUCH® SF 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.	8-11-2016
P030031/S100	Approval for the THERMOCOOL SMARTTOUCH® SF Catheters, part numbers D-1347-XX-S and D-1348-XX-S, for 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 us electroanatomic mapping systems	-

SMARTTOUCH™ Technology

Both the THERMOCOOL SMARTTOUCH® and THERMOCOOL SMARTTOUCH® SF Catheters utilize the same contact force sensing technology. The SMARTTOUCH® Catheters feature a sensor assembly embedded in the tip section that transmits both location and contact force information to the CARTO®3Navigation System. The tip is illustrated in Figure 1. The contact force technology consists of a Nitinol spring located just proximal to the tip dome. A transmitting coil is located at the distal end of the spring and three receiving coils are located at the proximal end. The three receiving coils are positioned 120º apart and measure the signal strength from the transmitting coil. The catheter is calibrated so that the force versus displacement of the spring is calculated and written to an EEPROM located in the catheter handle. As a force is applied to the tip dome, the spring is displaced and the signals from each receiving coil are calculated into a force reading that is displayed to the user on the CARTO®3 Navigation System.

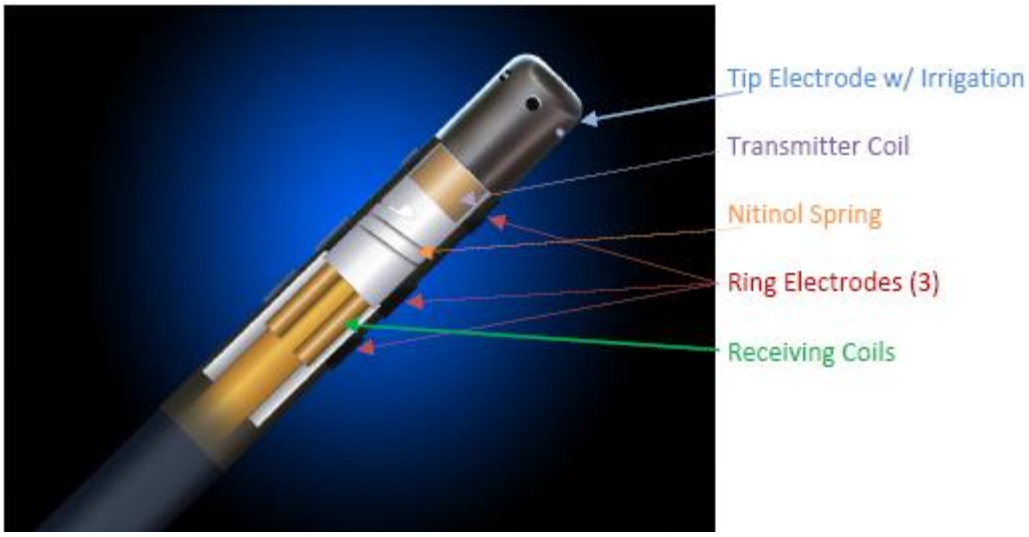

Figure 1. SMARTTOUCH® Tip Section

The amplitude of the force signal emitted from the transmission coil is measured by the three vertical receiving coils proximal to the spring to determine the deflection of the spring. Those signals are used to calculate the force on the spring, and thus on the tip electrode, using the calibration information stored on the EEPROM related to each catheter's unique spring constant. The signal is processed by the CARTO®3 System. The CARTO® 3 System's SMARTTOUCH™ software module enables display of the actual force (in grams) applied to the tissue through the catheter tip, in real-time, using a dedicated graph. Both the force value is displayed (in grams) as well as the force direction as shown in Figure 2 below.

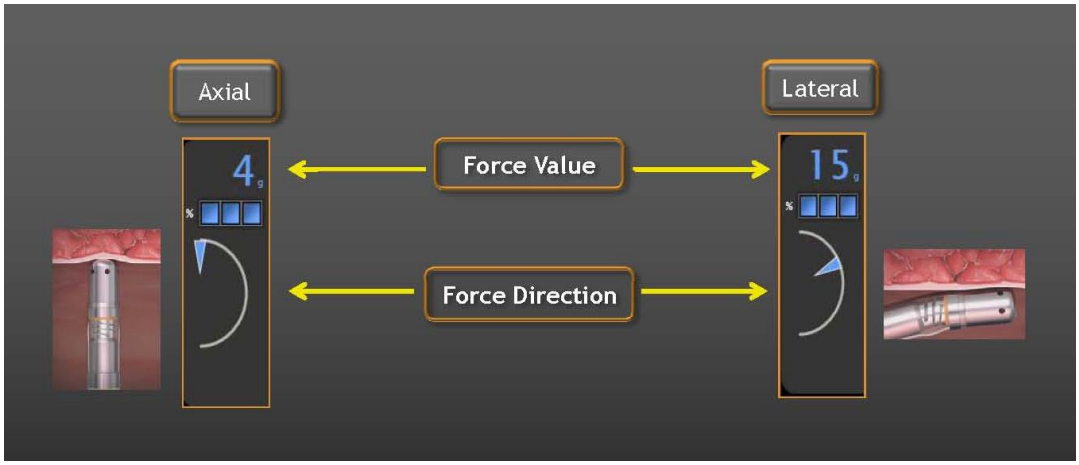

Figure 2: Dashboard Display of force magnitude (grams) and axial-lateral angle for force

The Real-Time Graph Viewer graph on the CARTO® 3 System displays force magnitude over time, as well as power, temperature and impedance graphs (Figure 3).

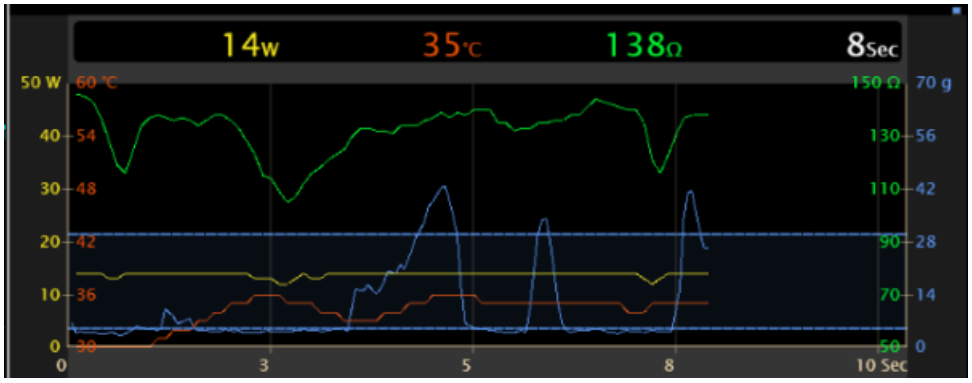

Figure 3: Real-Time Viewer Graph

VI. Alternative Practices and Procedures

Alternatives to ablation therapy with the THERMOCOOL SMARTTOUCH® SF Catheter include ablation therapy with a non-contact force sensing catheter, use of drug therapy for arrhythmia control, ablating the natural pacemaker of the heart and implanting an artificial pacemaker, or implantation of a device that paces or shocks the heart to stop the arrhythmia.

There are several other alternatives for the correction of drug refractory, recurrent, symptomatic persistent atrial fibrillation, including:

- Commercially available PMA-approved devices
- Pharmacological therapy for rate and/or rhythm control
- Electrical or pharmacologic cardioversion
- Surgical intervention to create atrial lesions
- Implantable devices to control heart rate

Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. Marketing History

THERMOCOOL SMARTTOUCH® SF Catheters (D-1347 and D-1348) are marketed worldwide, including in the United States and European Union. Other major regions where the product has been approved include Japan, China, Australia, Latin America, Canada, New Zealand, Israel and Turkey.

VIII. Potential Adverse Events

Potential adverse events that could occur during cardiac ablation therapy to treat arrhythmias include the following:

Table 3: Anticipated Adverse Events

1.	Acute Respiratory Distress Syndrome (ARDS)
2.	Air embolism
3.	Allergic reaction
4.	Anaphylactic shock
5.	Anemia
6.	Allergic reaction to Anesthesia (e.g., hair loss)
7.	Apnea - sedation induced
8.	Arrhythmia: bradycardia
9.	Arrhythmia: tachycardia
10.	Arrhythmia: pro-arrhythmias
11.	Arrhythmia: ventricular tachyarrhythmia / pro-arrhythmia
12.	Aspiration pneumonia
13.	Asthmatic attack
14.	Atelectasis
15.	Atrial fibrillation
16.	Exacerbation of pre-existing arrhythmia
17.	Atrio-Esophageal fistula
18.	Atypical left atrial flutter
19.	Arteriovenous (AV) fistula
20.	Bleeding complications
21.	Bleeding requiring transfusion
22.	Cardiac arrest
23.	Cardiac perforation
24.	Cardiac tamponade
25.	Cardiac thrombo-embolism
26.	Cerebro-vascular accident (CVA) / stroke
27.	Chest pain/discomfort
28.	Complete heart block, temporary or permanent
29.	Conduction block
30.	Congestive Heart Failure
31.	Coronary artery dissection
32.	Coronary artery occlusion
33.	Coronary artery spasm
34.	Coronary artery thrombosis
35.	Death
36.	Deep venous thrombosis
37.	Dislodgement of ICD (Implantable Cardioverter Defibrillator) lead
38.	Dislodgement of permanent pacing leads
39.	Disseminated Intravascular Coagulation
40.	Dyspnea
41.	Endocarditis
42.	Epistaxis

43.	Expressive aphasia
44.	Fainting
45.	Fatigue
46.	Gastro-intestinal NOS
47.	Gastric reflux
48.	Nausea
49.	Gastrointestinal diverticulosis
50.	Heart Failure
51.	Hematoma (local) /ecchymosis
52.	Hemorrhage
53.	Hemothorax
54.	High / increased creatine phosphokinase (CPK)
55.	Hypotension
56.	Hypoxia
57.	Infection, localized
58.	Infection, systemic
59.	Laceration
60.	Leakage of air or blood into the lungs or other organs due to perforation
61.	Liver toxicity
62.	Mobile strands in Inferior Vena Cava
63.	Myocardial Infarction
64.	Neurological disorders (tremor)
65.	Neurological disorders (poor coordination)
66.	Neurological disorders (headache)
67.	Obstruction to the vascular system
68.	Perforation to the vascular system
69.	Damage to the vascular system
70.	Pericardial effusion resulting in tamponade
71.	Pericardial effusion without tamponade
72.	Pericarditis
73.	Peripheral embolus
74.	Peripheral nerve injury
75.	Peripheral thromboembolism
76.	Phlebitis
77.	Phrenic nerve damage
78.	Diaphragmatic paralysis
79.	Pleural effusion
80.	Pneumothorax
81.	Pseudoaneurysm
82.	Pulmonary edema
83.	Heart failure
84.	Pulmonary embolism
85.	Pulmonary hypertension

86.	Pulmonary toxicity, like acute pulmonary syndrome
87.	Pulmonary vein dissection
88.	Pulmonary vein Stenosis
89.	Pulmonary vein thrombus
90.	Pump failure
91.	Renal failure
92.	Respiratory depression
93.	Respiratory failure
94.	Retroperitoneal hematoma
95.	Rhabdomyolysis, including produced by body position or propofol
96.	Sedation induced CO2 retention with lethargy and cholecystitis
97.	Seizure
98.	Sepsis
99.	Skin burns (due to cardioversion, tape, etc.)
100.	Skin discoloration
101.	Skin injury / muscle or connective tissue injury due to body position, electrical cardioversion
102.	Skin rash
103.	Thrombocytopenia
104.	Thromboembolism
105.	Thrombosis
106.	Thyroid disorders
107.	Transient extremity numbness
108.	Transient ischemic attack (TIA)
109.	Unintended complete or incomplete AV, Sinus node, or other heart block or damage
110.	Urinary retention
111.	Urinary tract infection
112.	Urinary tract injury or infection related to the urinary catheter
113.	Valvular damage/insufficiency
114.	Vasovagal reactions
115.	Vision change
116.	Volume overload
117.	Worsening obstructive, restrictive, or other form of pulmonary disease
118.	X-ray radiation injury of skin, muscle and/or organ

For a table of adverse events observed during paroxysmal atrial fibrillation clinical study, G140189, please refer to Section XI-C.4. For a table of adverse events observed during the persistent atrial fibrillation clinical study, G140102, please refer to Section XII-C.4.

IX. Summary of Non-clinical Studies

For non-clinical testing, a risk assessment based testing program was used to validate the THERMOCOOL SMARTTOUCH® SF Catheters. Catheter designs were evaluated per guidance documents and recognized consensus standards to confirm the necessary verification / validation activities. Ablation in the canine model was determined to be the

method of choice to validate the clinical equivalence of the THERMOCOOL SMARTTOUCH® SF Catheters to the commercially available and clinically tested devices. Thigh preparation studies in an animal evaluated lesion equivalence. Bench studies evaluated mechanical and electrical performance, and material safety (biocompatibility).

a. Bench Testing

Design verification tests (DVT) were performed to evaluate the performance and integrity of the THERMOCOOL SMARTTOUCH® SF Catheters following three times ethylene oxide (EtO) sterilization, the equivalent of one (1) year of accelerated aging, thermal cycling and simulated transportation. Testing evaluated visual attributes; deflection characteristics such as curve profile and stability; electrical characteristics including DC resistance and isolation, RF impedance and leakage current; irrigation pressure and flow; thermocouple temperature accuracy; biosensor and force sensor integrity; mechanical integrity including tip stiffness and tip buckle force; integrity following simulated use conditioning; handle temperature; and finally, catheter strength and integrity following destructive tests. Results of DVT tests concluded that the THERMOCOOL SMARTTOUCH® SF Catheters met design requirements and are safe for use.

Proof of Design (POD) studies were performed to evaluate the contact force technology. Separate studies evaluated contact force magnetic sensor location accuracy; contact force accuracy using CARTO® 3; contact force influence on ECG signal quality; distortion in the magnetic field when paramagnetic material is placed in close proximity to the coils thus interfering with force readings and causing Shaft Proximity Interference (SPI); overall catheter testing including location-related (electromagnetic sensor) tests, force-related (contact force sensor) tests and system-level tests to ensure that the catheter met requirements when connected to a CARTO®3 system. Results of POD tests concluded that the THERMOCOOL SMARTTOUCH® SF Catheters met design requirements and are safe for use.

Electromagnetic compatibility testing was conducted on the complete system, including the THERMOCOOL SMARTTOUCH® Catheter which is designed with equivalent circuitry to the SF model, with satisfactory results.

b. Animal Testing – Thigh Preparation Studies

A head to head ablation characteristics study was conducted in a canine thigh muscle preparation to compare lesions created by the THERMOCOOL SMARTTOUCH® SF Catheter to the currently approved NAVISTAR® THERMOCOOL® Catheter. Ablation procedures were conducted with the THERMOCOOL SMARTTOUCH® SF Catheter using the currently recommended flow rates of 8ml/min and 15ml/min, as outlined in the Instruction for Use (IFU). Lesions were compared to the control catheters. Recommended power settings between 30W-50W were used.

Ablation characteristics evaluated included:

i) Quantification of lesion size (depth, width, volume)
ii) Quantification of coagulum, char, and pop incidence (percent incidence of coagulum, char, pop)

A statistical analysis was performed to support equivalency of the ablation characteristics. There was no statistical difference in maximum depth, maximum diameter, and volume of the lesions generated by the commercially available NAVISTAR® THERMOCOOL® Catheter in comparison to the THERMOCOOL SMARTTOUCH® SF Catheter for each orientation-power set. Occurrence of pop, thrombus, and char was equivalent or less for the THERMOCOOL SMARTTOUCH® SF Catheter compared to NAVISTAR® THERMOCOOL® Catheter for each orientation-power set.

c. GLP Animal Studies

In-vivo testing in the canine model was determined to be the method of choice to validate the safety and overall functionality of the THERMOCOOL SMARTTOUCH® SF Catheters in simulated use. Acute and chronic testing was performed in animals using the catheter and complete system. Both acute and chronic studies complied with the guidelines for nonclinical laboratory studies as described in the Code of Federal Regulations, 21 Part 58 (GLP compliant).

The purpose of GLP animal studies was to demonstrate that the THERMOCOOL SMARTTOUCH® SF Catheters with contact force measurement capability (i.e. Test Catheters) could safely perform their intended function in an animal study without any unforeseen clinically adverse effects during the procedure when using standard practice percutaneous techniques. A comparison of performance was made to a Control Catheter (NAVISTAR® THERMOCOOL® Catheter), which is the commercially approved version of the same catheters but without contact force measurement capability. The studies evaluated the complete system including interface cables, Stockert Generator, COOLFLOW® Irrigation Pump, and CARTO® 3 System with contact force software.

Attributes evaluated included acute safety and any incidence of steam pops, perforation, thrombus, or char; mapping performance and the range of contact forces measured during mapping; ablation performance including the effectiveness of lesion creation; intracardiac signal recording; overall catheter performance.

All animals were electively euthanized at the study's conclusion for evaluation. All studies were successfully completed and verified the safe performance of the THERMOCOOL SMARTTOUCH® SF Catheters in an animal model without any clinically significant adverse events. Table 4 summarizes the results for both thigh preparation and GLP animal studies.

Table 4: Summary Table of Thigh Preparation and GLP Animal Studies

Study Type	Number of Animals	Follow-up Duration	Relevant Findings
Canine Thigh Prep Study	10 (48-80lb)	Acute	*A priori* acceptance criteria were pre-defined for lesion depth, width, volume for side-by-side comparison of the THERMOCOOL SMARTTOUCH® SF Catheter and NAVISTAR® THERMOCOOL® Catheter, respectively, to quantify lesion size (depth, width, volume) and adverse event (steam pop, char, and thrombus). "Char" is referred to as blackened tissue surface without removable material and "thrombus" describes coagulated blood which is elevated red or brawn material on the surface of the lesion or on the ablation electrode, which can be removed by wiping with gauze. • Lesion measurements, parallel tip orientation: ○ At 30W, 7.8mm depth, 11.3mm width, 572mm^3 volume vs. 7.8mm depth, 11.2mm width, 560mm^3 volume ○ At 50W, 9.5mm depth, 13.7mm width, 1,005 mm^3 volume vs. 9.5mm depth, 13.3mm width, 939mm^3 volume • Lesion measurements, perpendicular tip orientation: ○ At 30W, 7.9mm depth, 10.8mm width, 521mm^3 volume vs. 7.7mm depth, 10.3mm width, 474mm^3 volume ○ At 50W, 9.6mm depth, 13.2mm width, 949mm^3 volume vs. 9.4mm depth, 13.0mm width, 886mm^3 volume • Adverse Events, parallel tip orientation: ○ At 30W, 0 pop, 0 thrombus, 0 char vs. 0 pop, 10 thrombus, 1 char ○ At 50W, 2 pop, 5 thrombus, 0 char vs. 5 pop, 19 thrombus, 3 char • Adverse Events, perpendicular tip orientation: ○ At 30W, 0 pop, 0 thrombus, 0 char vs. 0 pop, 0 thrombus, 0 char ○ At 50W, 1 pop, 0 thrombus, 1 char vs. 1 pop, 1 thrombus, 0 char All acceptability criteria were met. There was no statistical difference in the lesions created by the two catheters. Adverse events were equivalent or less for THERMOCOOL SMARTTOUCH® SF compared to NAVISTAR® THERMOCOOL® for each orientation-power set
GLP Canine Study	12 (24-34kg)	Acute and Chronic: 28 $\pm$ 2 days	*A priori* acceptance criteria were pre-defined for study objectives. • Catheters performed as intended: mapping the cardiac chambers, recording intracardiac signals, pacing/capturing electrical activity of the heart, and delivery of RF energy. • Maneuverability and Functionality tests were free of complications. • RF ablation lesions were created at all targeted locations without complications: ○ THERMOCOOL SMARTTOUCH® SF Catheter -- 111 RF ablations, 22 in RA and 89 in LA

			○ NAVISTAR® THERMOCOOL® Catheter -- 49 RF ablations, 11 in RA and 38 in LA • Of total RF ablations delivered using maximum settings of 50W power and 120sec duration, 22.5% THERMOCOOL SMARTTOUCH® SF Catheter and 10.2% NAVISTAR® THERMOCOOL® Catheter were stopped (< 30s duration) for various reasons including steam pop, arrhythmia, catheter movement, achievement of PVI, etc. • All acute test animals passed post-ablation defibrillation withstand test at 360J without adverse events. • Up to three (3) PVI successfully achieved in all animals (a minimum of one pulmonary vein per animal was left untreated to serve as a vein diameter control). • Contact Force measurement during ablation averaged 8-16g with < 4g drift. • Adverse Events were minimal: ○ PV stenosis (acute or at 28d follow-up) was < 50% (20.8%-36.7%). ○ Rates of occurrence of steam pop and char formation on catheter tip were statistically similar (Fisher's Exact p-Test). ○ Microscopic analysis revealed one perforation associated with steam pop (Acute Control Animal) and one organized thrombus (Chronic Test Animal). All study objectives were met. The study did not raise questions of safety.

d. Biocompatibility

The product design for the THERMOCOOL SMARTTOUCH® SF Catheters was evaluated to determine its biocompatibility based on similarity to currently approved/cleared products including the EZ STEER® THERMOCOOL® NAV, THERMOCOOL® SF, NAVISTAR® THERMOCOOL® Catheters, and Lasso 2515 Nav eco Catheters, and to confirm the applicability of the existing biocompatibility documentation. Device design, materials, construction and manufacturing environment were evaluated. All of the patient contacting materials for the THERMOCOOL SMARTTOUCH® SF Catheters (materials are identical for the uni-directional and bi-directional models) had been previously tested and are currently part of the design of one of the precedent devices. No new patient blood or fluid-contacting materials were used in the design of the THERMOCOOL SMARTTOUCH® SF Catheters. Based on the evaluation, it was determined that no additional biocompatibility testing was necessary.

e. Sterilization

All Biosense Webster catheters are ethylene oxide (EtO) sterilized. The sterilization process incorporates all phases of sterilization (preconditioning, sterilization and aeration) within the sterilization chamber. Sterility assurance was verified to exceed a sterility assurance level (SAL) of 1×10^{-6}. Sterilization validations met the

requirements of ISO 11135. Residual results for EO and ECH are within allowable limits per ISO 10993-7.

Assessments were performed to determine if the THERMOCOOL SMARTTOUCH® SF Catheters could be adopted into the previously validated standard BWI sterilization cycle at the three FDA approved contract sterilizers. Assessment of device packaging, construction, manufacturing environment and lumen size for gas penetration were evaluated. Based on the similarities of the THERMOCOOL SMARTTOUCH® SF Catheters with the precedent devices, the THERMOCOOL SMARTTOUCH® SF Catheters do not provide a greater sterilization challenge when sterilized using the currently validated Biosense Webster EtO sterilization cycle when using the standard 10-pallet configuration.

f. Shelf Life

The packaging for the THERMOCOOL SMARTTOUCH® SF Catheters is identical to that used with the NAVISTAR® THERMOCOOL® and EZ STEER® THERMOCOOL® NAV Catheters, and has been validated to maintain a sterile barrier for three years. Product shelf life for the THERMOCOOL SMARTTOUCH® Catheters has been validated for one year. The product will bear a one shelf life on its labeling.

X. Summary of Clinical Studies

Sections XI and XII provide summaries of clinical investigations performed under IDEs G140189 and G140102 for the THERMOCOOL SMARTTOUCH® SF Catheter. All patients underwent informed consent per the study protocols, and in compliance with the Code of Federal Regulations, 21 §50. The protocols and informed consent materials were reviewed and approved by the appropriate IRBs prior to subject enrollment, and in compliance with the Code of Federal Regulations, 21 §56. Per the requirements of 21 CFR §812.20(b)(5), all participating investigators signed the Clinical Study Agreement prior to enrollment at their center, which included financial disclosure forms, current curricula vitae for the investigator and co-investigators, and written IRB approval for the investigational study. The clinical studies were monitored in a manner consistent with 21CFR, Part 812, Subpart C, Responsibilities of Sponsor. Monitoring visits included, but were not limited to, verification of all study logs, verification that informed consent was being obtained in accordance with requirements described in the study protocols for all subjects participating in the studies, verification of completeness of the Regulatory Binder, data source verification with the eCRFs, and identification and action to resolve any issues or problems with the studies. Data from these clinical studies were the basis for the PMA Supplement approval decisions.

XI. SMART SF Study – IDE G140189

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 occurs greater than one week (7 days) post-procedure shall be deemed Primary AEs.[Error! Reference source not found.,Error! Reference source not found.]

** Hemodynamic compromise or instability is 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 5: 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 6: 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 7: 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

Tables 8, 9 and 10 present the procedural data. There were 159 procedures in 159 subjects. All subjects underwent one (1) study ablation procedure.

Table 8: 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 9: 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 10: 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 11 and Table 12 summarizes the lesion sets applied to the subjects undergoing ablation during the index ablation procedures.

Table 11: 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 12: 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.3 - 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 13.

Table 13: 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%)

C3 – 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 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 14 presents the overall average contact force applied during 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 4 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 14: 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

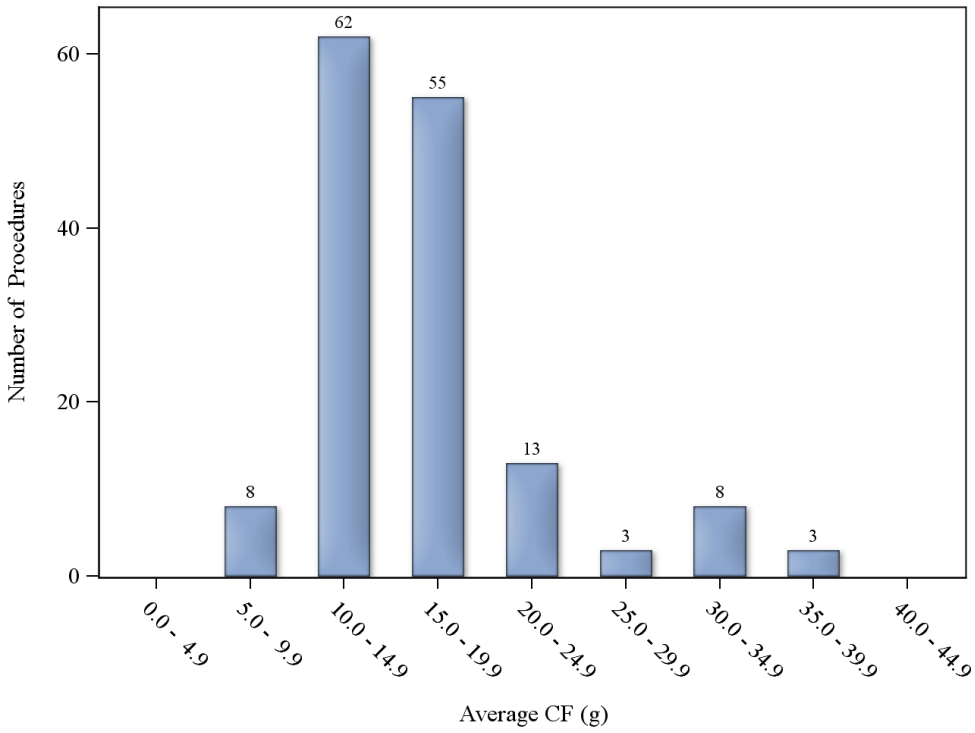

Figure 4: Distribution of Average Contact Force Per Ablation Procedure (Safety Population, n =159)

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

Table 15: 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%)

Lower	Upper	n / 159 (%)
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 16 presents a comparison of average contact force by sex. There was no significant difference in the use of contact force between sexes.

Table 16: 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 17 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 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 17: 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 pf 95% exact CI	14.0	6.3

Table 18 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 18: 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 15 summarizes the SAEs occurring within 30 days of a study ablation procedure that were not classified as Primary AEs by protocol definition.

Table 19: 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
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 20 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 20: Average Contact Force 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 [1.3cm]) was unavailable for analysis

C.5 – Study Conclusion

The results demonstrate that the THERMOCOOL SMARTTOUCH® SF Catheter met pre-specified performance goal for safety.

XII. PRECEPT Study – IDE G140102

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

Patients were enrolled and treated between 7/27/2016 and 2/6/2018. The database for this Panel Track Supplement reflected data collected through October 10, 2019 and included 381 patients. There were 27 investigational sites (25 US sites and 2 Canadian sites).

The study was a prospective, non-randomized, uncontrolled, open-label, multicenter, pivotal clinical trial. The study enrolled subjects with symptomatic persistent atrial fibrillation refractory to at least one Class I or III antiarrhythmic drug (AAD). Enrolled subjects underwent catheter ablation with the investigational THERMOCOOL SMARTTOUCH SF ablation catheters and were followed for 15 months.

After the study ablation procedure, subjects entered a 3-Month Medication Adjustment Period (Day 0 – 90) followed by a 3-Month Therapy Consolidation Period (Day 91-180). Thereafter, subjects were followed for arrhythmia recurrence in the 9-Month Evaluation Period (Days 181-450).

The study success was assessed by freedom from documented atrial fibrillation, atrial flutter, and atrial tachycardia recurrence during the evaluation period (Day 181 – 450 following the index ablation procedure) and any Primary Adverse Event occurring within 7 days of the AF ablation procedure (PV stenosis and AE fistula occurring at any time). The study would be considered successful by meeting the predetermined performance goal for each primary endpoint.

The study utilized an independent Global Safety Monitoring Committee (GSMC) to oversee study progress, adjudicate adverse events and review clinical data and safety. An

independent core laboratory provided interpretation of all electrocardiographic data (24-Hour Holter Monitors, ECGs, and TTMs).

B.1- Clinical Inclusion and Exclusion Criteria

Enrollment in the PRECEPT study was limited to patients who met the following inclusion criteria:

1) Documented symptomatic persistent AF, which is defined as continuous AF sustains beyond 7 days and less than 1 year and is documented by the following:
   i. Physician's note indicating continuous AF ≥ 7 days but no more than 1 year; **AND**
   ii. Two electrocardiograms (from any forms of rhythm monitoring) showing continuous AF, with electrocardiogram taken at least 7 days apart (electrograms cannot be >365 days prior to enrollment) **OR**
   iii. 24-hour Holter within 90 days of the ablation procedure showing continuous AF
2) Failed at least one antiarrhythmic drug (AAD) (class I or III) as evidenced by recurrent symptomatic AF, or intolerable to the AAD.
3) Age 18 years or older.
4) Signed Patient Informed Consent Form (ICF).
5) Able and willing to comply with all pre-, post-, and follow-up testing and requirements.

Patients were not permitted to enroll in the PRECEPT study if they met any of the following exclusion criteria:

1) Continuous AF > 12 months (1-Year) (Longstanding Persistent AF)
2) Previous surgical or catheter ablation for atrial fibrillation
3) Any cardiac surgery within the past 2 months (60 days) (includes PCI)
4) CABG surgery within the past 6 months (180 days)
5) Valvular cardiac surgical/percutaneous procedure (i.e., ventriculotomy, atriotomy, and valve repair or replacement and presence of a prosthetic valve)
6) Any carotid stenting or endarterectomy
7) Documented LA thrombus on imaging
8) LA size > 50 mm (parasternal long axis view)
9) LVEF < 40%
10) Contraindication to anticoagulation (heparin or warfarin)
11) History of blood clotting or bleeding abnormalities
12) MI within the past 2 months (60 days)
13) Documented thromboembolic event (including TIA) within the past 12 months (365 days)

14) Rheumatic Heart Disease
15) Uncontrolled heart failure or NYHA function class III or IV
16) Severe mitral regurgitation (Regurgitant volume ≥ 60 mL/beat, Regurgitant fraction ≥ 50%, and/or Effective regurgitant orifice area ≥ 0.40cm^2)
17) Awaiting cardiac transplantation or other cardiac surgery within the next 12 months (365 days)
18) Unstable angina
19) Acute illness or active systemic infection or sepsis
20) AF secondary to electrolyte imbalance, thyroid disease, or reversible or noncardiac cause.
21) Diagnosed atrial myxoma.
22) Presence of implanted ICD/CRT-D.
23) Significant pulmonary disease, (e.g., restrictive pulmonary disease, constrictive or chronic obstructive pulmonary disease) or any other disease or malfunction of the lungs or respiratory system that produces chronic symptoms.
24) Gastroesophageal Reflux Disease (GERD; active requiring significant intervention not including OTC medication)
25) Significant congenital anomaly or medical problem that in the opinion of the investigator would preclude enrollment in this study.
26) Women who are pregnant (as evidenced by pregnancy test if pre-menopausal)
27) Enrollment in an investigational study evaluating another device, biologic, or drug.
28) Presence of intramural thrombus, tumor or other abnormality that precludes vascular access, or manipulation of the catheter.
29) Presence of any other condition that precludes appropriate vascular access.
30) Life expectancy less than 12 months

B.2. - Follow-up Schedule

All patients were scheduled to return for follow-up examinations at baseline, operative/discharge, 7 days, 1, 3, 6, 9, 12, and 15 months following the index procedure. Preoperatively, all subjects were screened for left atrial thrombus. Post-ablation rhythm monitoring included symptomatic and monthly asymptomatic TTM transmissions during the evaluation period, 12-lead ECG at 6, 9, 12, and 15 months, and 24-hour Holter at 6, 12, and 15 months. Adverse events and complications were assessed and recorded at all visits.

The key timepoints are shown below in the table summarizing schedule of treatments and evaluations.

Table 21: Schedule of Treatments and Evaluations

	Pre-Procedure				Phone Call	Phone/ Office visit	Follow-Up Visits					
	Screening / Baseline		Ablation Procedure[1]	Discharge	7-9 Days	1 Month +/- 1 wks.	3 Month +/- 1 wks.	6 Month +/- 2 wks.	9 Month +/- 4 wks.	12 Month +/- 4 wks.	15 Month +/- 4 wks.	Unscheduled Visit
Visit no.	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Informed consent[1]	X											
Inclusion & exclusion criteria	X											
Demographics	X											
Medical history / Hospitalization history	X				X	X	X	X	X	X	X	X
Arrhythmias	X [history]			X	X	X	X	X	X	X	X	X
NIH Stroke Scale[12]		X		X[12]								
ECG		X		X				X	X	X	X	X
NYHA		X										
CCS-SAF		X						X	X	X	X	
QOL assessment[2]		X						X	X	X	X	
Pregnancy test[3]		X										
LA thrombus Imaging[4]			X									
TTE[5]		X[5]		X[16]								
Ablation assessments			X									
Holter monitor (24 hr)		X optional						X		X	X	
TTM monitoring[13,14]								X[13,14]	X[13,14]	X[13,14]	X[13,14]	
Device deficiency			X									
Concomitant medications[6]		X	X	X	X	X	X	X	X	X	X	X
Health Economic Data Collection[7]				X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]
Adverse events[8,9]	X	X	X	X	X[10]	X[10]	X	X	X	X	X	X
PV stenosis imaging assessment[11]					X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]	X[11]
AF recurrence								X	X	X	X	X
End-of study follow-up											X[15]	

1 Initial ablation procedure should be done within 30 days of consent.
2 Quality of life tools (AFEQT and Symptom and Severity Checklist)
3 Pregnancy test must be done on pre-menopausal women only, within 24 hours of the procedure.
4 Imaging for the presence of LA thrombus (TEE, CT, ICE, MRI) on day prior or the day of the procedure.
5 Imaging TTE to determine the atrial size (if the subject has undergone an imaging procedure within the last 6 months where the atrial size was assessed, the pre-procedure imaging assessment is not required)
6 Concomitant medications: only cardiac related (anti-arrhythmia drugs, anticoagulation regimen, etc.)
7 Health Economic Data for hospitalizations (UB04), ER visits and outpatient visits, if any
8 AEs collected once consent has been signed
9 If AE results in Hospitalization health economic data collection is required
10 Collected via phone follow-up
11 PV imaging (CT/MRI) for subjects who have symptoms suggestive of PV stenosis
12 Performed prior to hospital discharge or 24 hours after the procedure, whichever is later or any time after the subject experiences a CVA/Stroke, perform Neuro consult as needed
13 Asymptomatic TTM: should be recorded monthly (i.e. at months 7, 8, 9, 10, 11, 12, 13, 14, 15) and transmitted to the Core Lab.
14 TTM: all symptomatic cardiac episodes should be recorded and transmitted at the time the event occurs.
15 15-month visit or last completed visit
16 Subjects who develop symptoms suggestive of pericardial effusion and/or pericarditis should undergo a transthoracic echocardiogram (TTE) to assess the pericardium

B.3 – 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 following the index ablation procedure) and freedom from the following primary effectiveness failure modes:

- Acute procedural failure: entrance block not confirmed for all PVs post-procedure and subjects in whom a non-study catheter has been used to treat the study arrhythmia for the initial ablation procedure.
- Non-study catheter failure: use of a non-study catheter to treat the study arrhythmia for repeat ablation procedure during the 3-Month Medication Adjustment or 3-Month Therapy Consolidation Periods.
- Repeat ablation failure: > 2 repeat ablation procedures during Day 0 – 180 or any repeat ablation during the evaluation period.
- AAD failure: taking a new AAD or a previously failed AAD at a greater than the highest ineffective historical dose for AF during the evaluation period.
- Surgical failure: any surgical AF ablation or AF surgery

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.4 – 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

With regards to success/failure criteria, each primary endpoint was compared to a predetermined performance goal. The study would be considered a success when both of the following criteria are met:

- The primary safety endpoint event rate meets the prespecified performance goal of 0.16. The following primary safety hypotheses were evaluated using the exact test for a binomial proportion at a two-sided significance level of 5%:

  H_o: $P_s \geq 0.16$
  H_1: $P_s < 0.16$

  Where
  P_S = proportion of subjects with the early onset (within seven days of the initial and repeat ablation procedure for AF*) primary AE.

  The analysis cohort for the primary safety endpoint included all subjects in the Safety Population. Subjects with missing primary safety data were excluded from the primary analysis.

- The primary effectiveness endpoint rate meets the prespecified performance goal of 0.40. The following primary effectiveness hypothese were evaluated using the exact test for a binomial proportion at a two-sided significance level of 5%.

  H_o: $P_E \leq 0.40$
  H_1: $P_E > 0.40$

  Where
  P_E = proportion of subjects who met the effectiveness success criteria at 15-months follow-up.

The analysis cohort for the primary effectiveness endpoint included all Per Protocol subjects. Subjects with missing primary effectiveness outcomes were not included in the primary effectiveness endpoint calculation.

B.5. – Subject Accountability

At the time of database lock, of 381 patients enrolled in the PMA study, 76.9% (N = 293) patients were available for analysis at the completion of the study, the 15-month post-operative visit. Table 22 shows an accounting of follow-up visit attendance during the study. Subjects who died or were withdrawn were not counted as having expected visits.

Table 22. Summary of Compliance of Follow-up Visits (Safety Population, N=348)

Follow-up Visit (Visit Window)	Total Subjects n/N (%)
Phone Call (7-9 days)	344 / 348 (98.9%)
1-Month (23-37 days)	346 / 348 (99.4%)
3-Month (83-97 days)	341 / 345 (98.8%)
6-Month (166-194 days)	322 / 338 (95.3%)
9-Month (242-298 days)	306 / 330 (92.7%)
12-Month (332-388 days)	295 / 323 (91.3%)
15-Month (422-478 days)	293 / 313 (93.6%)

Of the 381 enrolled subjects, 33 subjects never underwent insertion of the study catheter and were excluded from the study. Of the remaining 348 subjects who had the study catheter inserted and underwent the study ablation procedure, 33 subjects withdrew or had early termination, 20 subjects were lost to follow up and 2 subjects died. As of the date of database lock (10/10/2019), 293 subjects completed the 15-month follow-up during the visit window.

The protocol specified analysis populations include:

- *Safety Population (SP)*: The safety population consisted of 348 enrolled subjects who had undergone insertion of the study catheter.

- *Modified Intent-To-Treat (mITT) Population*: The mITT population consisted of 334 enrolled subjects who met all eligibility criteria and in whom the study catheter was inserted.

- *Per Protocol (PP) Population*: The PP population consisted of 333 subjects who met all eligibility criteria and had undergone RF ablation with the study catheter for study-related

arrhythmia (1 subject in the mITT was treated with a non-investigational STSF catheter with commercial labeling).

B.6 – Subject Demographics and Baseline Characteristics

The demographics of the study population were typical for a persistent atrial fibrillation catheter ablation study performed in the US. Table 23 summarizes demographics for all enrolled subjects, safety population, mITT population, and per-protocol population.

Table 23 – Subject Demographics
(Enrolled Subjects, N = 381; Safety, N = 348; Per-Protocol, N = 333)

Demographics	Enrolled n/381 (%)	Safety n/348 (%)	mITT n/334 (%)	Per-Protocol n/333 (%)
Gender (%)				
Male	271 (71.1)	246 (70.7)	237 (71.0)	237 (71.2)
Female	110 (28.9)	102 (29.3)	97 (29.0)	96 (28.8)
Ethnicity – Hispanic or Latino (%)	7 (1.8)	7 (2.0)	7 (2.1)	6 (1.8)
Race (%)				
Asian	3 (0.8)	3 (0.9)	3 (0.9)	3 (0.9)
Black or African American	6 (1.6)	6 (1.7)	6 (1.8)	6 (1.8)
White	349 (91.6)	319 (91.7)	307 (91.9)	307 (92.2)
Not reported	23 (6.0)	20 (5.7)	18 (5.4)	17 (5.1)
Age (years)	65.6 ± 8.72	65.4 ± 8.71	65.4 ±8.78	65.4 ± 8.79

Table 24 summarizes the baseline medical history of the enrolled, Safety, mITT and Per-Protocol populations. Most patients (68.2%, 260/381) had hypertension and 22.6% (86/381) had a history of atrial flutter. In the 6 months before enrollment, 70.1% (267/381) of enrolled subjects had at least one cardioversion. All enrolled subjects failed or were intolerant to at least a class I or III antiarrhythmic drug (AAD). On average, subjects (n=364) failed 1.3 ± 0.57 AADs prior to enrollment.

Table 24 – Baseline Characteristics

Medical History	All Enrolled Subjects (N=381) n/N (%)	Safety Population (N=348) n/N (%)	mITT Population (N=334) n/N (%)	Per-Protocol Population (N=333) n/N (%)
Known Cardiovascular Medical History	296 (77.7%)	270 (77.6%)	259 (77.5%)	258 (77.5%)
Congestive heart failure	61 (16.0%)	55 (15.8%)	52 (15.6%)	52 (15.6%)
NYHA Class I	18 (4.7%)	17 (4.9%)	16 (4.8%)	16 (4.8%)
NYHA Class II	31 (8.1%)	28 (8.0%)	27 (8.1%)	27 (8.1%)
NYHA Class III	1 (0.3%)	1 (0.3%)	0 (0.0%)	0 (0.0%)
Coronary artery disease	86 (22.6%)	77 (22.1%)	74 (22.2%)	74 (22.2%)
Vascular disease	20 (5.2%)	17 (4.9%)	14 (4.2%)	14 (4.2%)
Myocardial infarction	23 (6.0%)	19 (5.5%)	19 (5.7%)	19 (5.7%)
Hypertension (systemic)	260 (68.2%)	238 (68.4%)	228 (68.3%)	227 (68.2%)
Pulmonary hypertension	8 (2.1%)	7 (2.0%)	7 (2.1%)	7 (2.1%)
Cardiomyopathy	43 (11.3%)	42 (12.1%)	39 (11.7%)	39 (11.7%)
Hypertrophic	5 (1.3%)	5 (1.4%)	4 (1.2%)	4 (1.2%)
Ischemic	7 (1.8%)	7 (2.0%)	6 (1.8%)	6 (1.8%)
Non-Ischemic	29 (7.6%)	28 (8.0%)	27 (8.1%)	27 (8.1%)
Pacemaker	21 (5.5%)	18 (5.2%)	18 (5.4%)	18 (5.4%)
Other cardiovascular procedure (e.g. CABG, PCI, etc.)	41 (10.8%)	36 (10.3%)	34 (10.2%)	34 (10.2%)
Left ventricular hypertrophy	11 (2.9%)	11 (3.2%)	11 (3.3%)	11 (3.3%)
Documented Thromboembolic Event	27 (7.1%)	25 (7.2%)	24 (7.2%)	24 (7.2%)
Transient ischemic attacks (TIA)	10 (2.6%)	10 (2.9%)	9 (2.7%)	9 (2.7%)
Stroke	8 (2.1%)	6 (1.7%)	6 (1.8%)	6 (1.8%)
Pulmonary embolus	5 (1.3%)	5 (1.4%)	5 (1.5%)	5 (1.5%)
Any Arrhythmia Other Than Persistent AF	113 (29.7%)	107 (30.7%)	102 (30.5%)	101 (30.3%)
Left/right atrial tachycardia (AT)	7 (1.8%)	7 (2.0%)	7 (2.1%)	7 (2.1%)
AV node re-entry tachycardia (AVNRT)	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)
Accessory pathway (WPW)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Ventricular tachycardia (VT)	7 (1.8%)	6 (1.7%)	6 (1.8%)	6 (1.8%)
Atrial flutter (AFL)	71 (18.6%)	68 (19.5%)	65 (19.5%)	65 (19.5%)
Ventricular fibrillation (VF)	2 (0.5%)	2 (0.6%)	2 (0.6%)	2 (0.6%)
Other: arrhythmia	36 (9.4%)	34 (9.8%)	32 (9.6%)	31 (9.3%)
Diabetes	69 (18.1%)	62 (17.8%)	61 (18.3%)	61 (18.3%)
Obstructive sleep apnea (OSA)	145 (38.1%)	134 (38.5%)	132 (39.5%)	132 (39.6%)
CPAP use	98/145 (67.6%)	92/134 (68.7%)	90/132 (68.2%)	90/132 (68.2%)
$CHADS_2$ score	1.3 ± 1.03	1.3 ± 1.03	1.3 ± 1.03	1.3 ± 1.03

CHA_2DS_2-VASc score	2.3 ± 1.48	2.3 ± 1.48	2.3 ± 1.48	2.3 ± 1.49
AF History				
Length of time of Symptomatic PsAF (Month)	15.2 ± 29.2 (n=378)	15.5 ± 30.2	15.9 ± 30.8	15.9 ± 30.8
AAD Failed (Class I, III)	1.3 ± 0.54	1.3 ± 0.55	1.3 ± 0.56	1.3 ± 0.56
Left Ventricular Ejection Fraction (%)	56.0 ± 7.4 (n=361)	56.2 ± 7.2 (n=346)	56.2 ± 7.2	56.2 ± 7.2
Left Atrial Diameter (cm)	42.6 ± 5.2 (n=357)	42.4 ± 5.1 (n=345)	42.6 ± 5.1	42.6 ± 5.1

C. Results

C.1 – Index Ablation Procedure

Procedure Data

Table 25 and Table 26 present the index procedural data. There were 348 procedures in 348 subjects. All subjects underwent one (1) study ablation procedure.

Table 25 – 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 26 – 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)

Ablation Lesion Sets

All study AF ablation procedures were required to target and achieve electrical isolation of all pulmonary veins. Optional ablation targets were allowed based on clinical findings after PV isolation was completed.

Table 27 summarizes the lesion sets applied to the subjects undergoing ablation during the index ablation procedures. Table 28 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 27 – 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 28 – 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)

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 21 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. **Error! Reference source not found.** 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 21 – 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

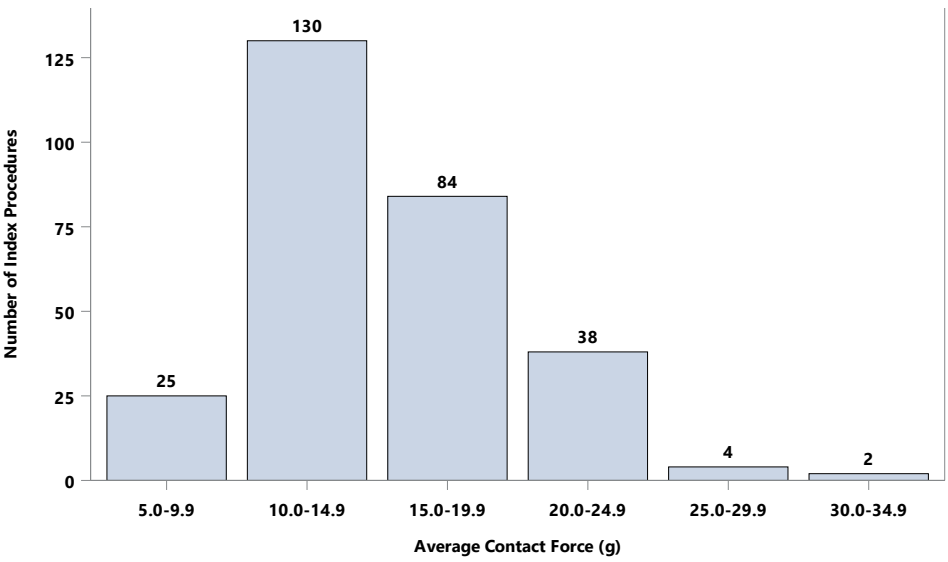

Figure 5 – Distribution of Average Contact Force per Ablation Procedure (Safety Population, n = 348)

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® 3 System produces an auto tag (VISITAG) 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.

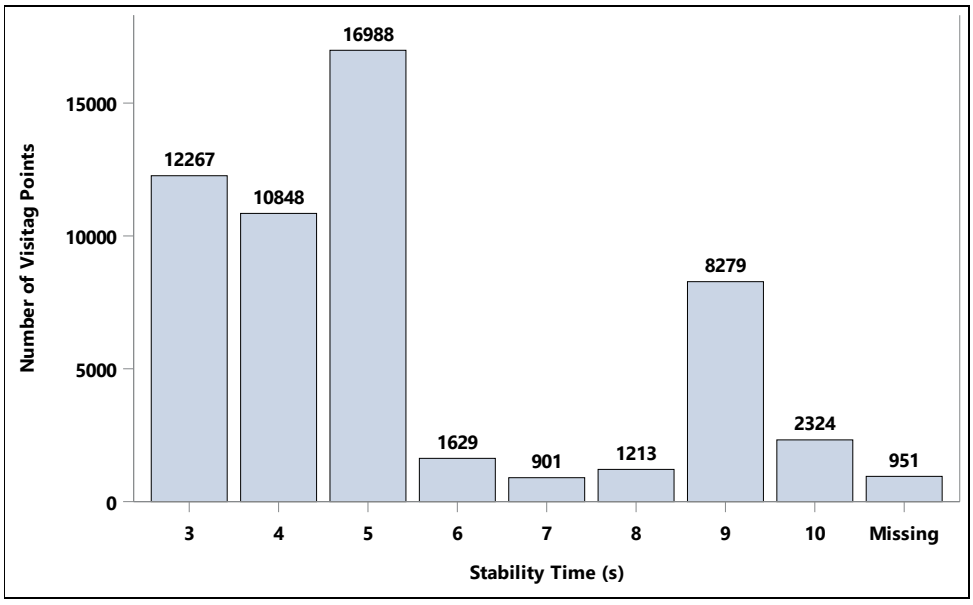

Figure 6 – Operator-Configured VISITAG™ Stability Time per VISITAG™ Point (Safety Population, N = 348)

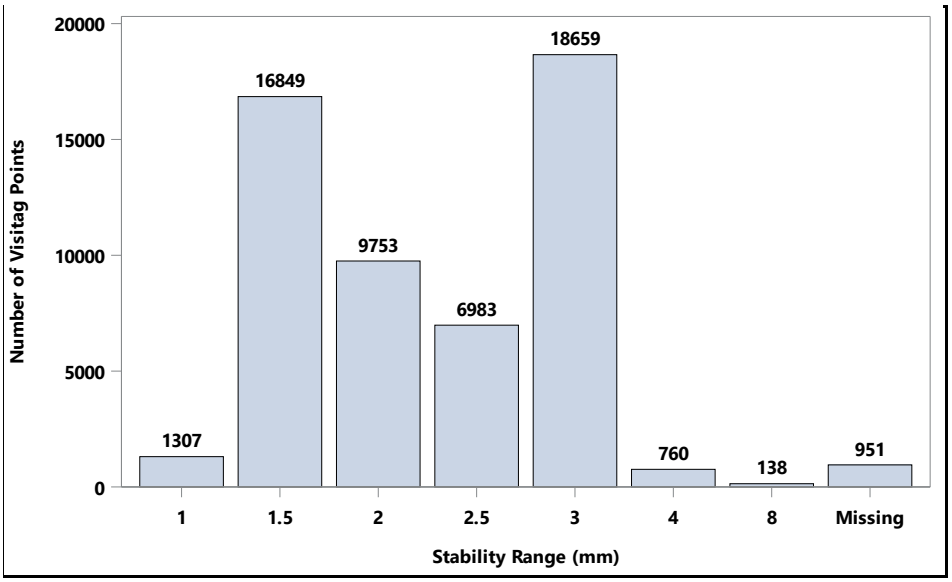

Figure 7 – Operator-Configured VISITAG™ Stability Range per VISITAG™ Point (Safety Population, N = 348)

C.2 - Rhythm Monitoring Compliance

In the 9-month evaluation period, rhythm monitoring included symptomatic and monthly asymptomatic TTM transmissions during the evaluation period, 12-lead ECG at 6, 9, 12, and 15 months, and 24-hour Holter at 6, 12, and 15 months. Figure 4 shows the TTM, 12-lead ECG, and Holter compliance rates at each evaluation time point in the Per-Protocol Population (n=333). The overall TTM, ECG, and Holter compliance rates were 65.9%, 93.9%, and 83.5%, respectively.

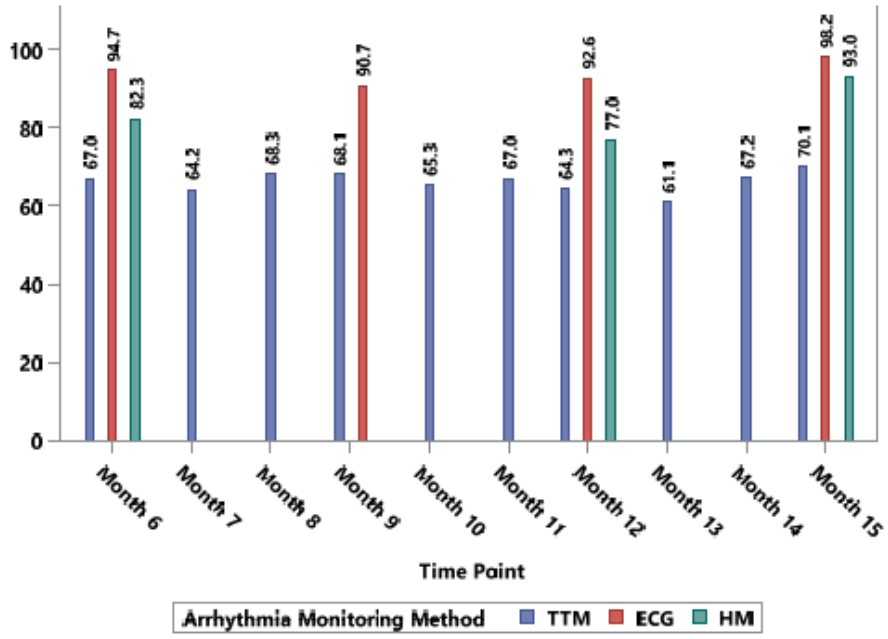

Figure 8. TTM/ECG/HM Compliance by Time Point (Per-Protocol Population, N=333)

C.3 – Safety Results

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

The primary safety analysis was based on the Safety Population cohort of 348 patients who were available for the 3-month evaluation. Table 30 presents the protocol-specified

endpoint and safety results. Of 348 Safety Population subjects, 4 had missing outcomes (2 lost to follow up, 2 withdrawn). 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 30 – 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)	
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 31 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. GSMC adjudicated all serious adverse events of cardiac origin with 30 days of ablation procedure.

Table 2 – 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
Fluid overload	2	2
Esophageal ulcer	1	1
Sepsis	1	1
Hypotension	2	2
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 adjudicated to be device or procedure-related by the GSMC. 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.

C.4 – Average CF and Primary AEs

Figure 9 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 black 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.

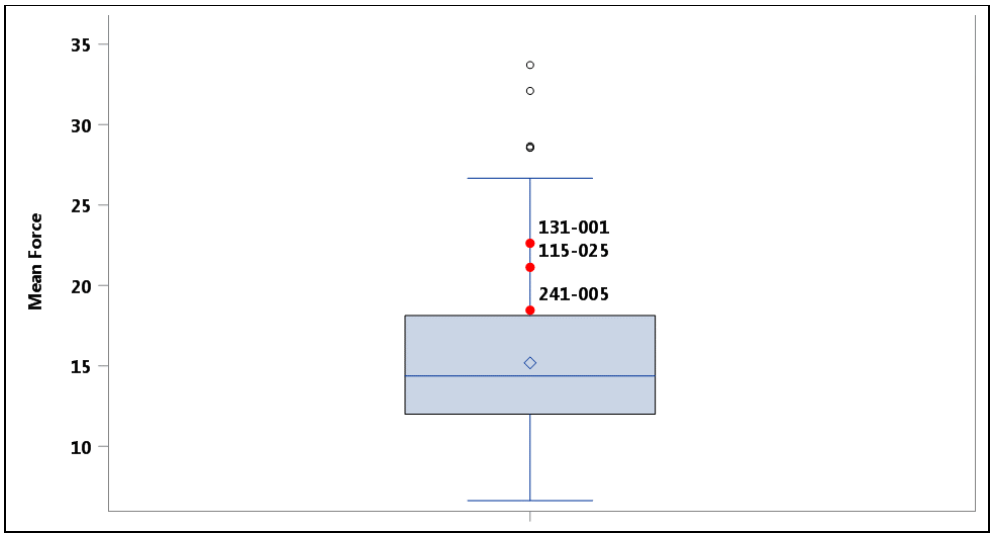

Figure 9 – Comparison of Average Contact Force in Subjects with Tamponade vs Safety Population (Safety Population, n = 348)

C.5 – Effectiveness Results

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).

The analysis of effectiveness was based on the 333 subjects in the Per-Protocol cohort. Of these, 36 subjects had missing outcomes (15 lost to follow-up, 1 death, and 20 withdrawals) and were not included in the primary effectiveness endpoint calculation. 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 32.

Table 3 – 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 9 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 95% 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.

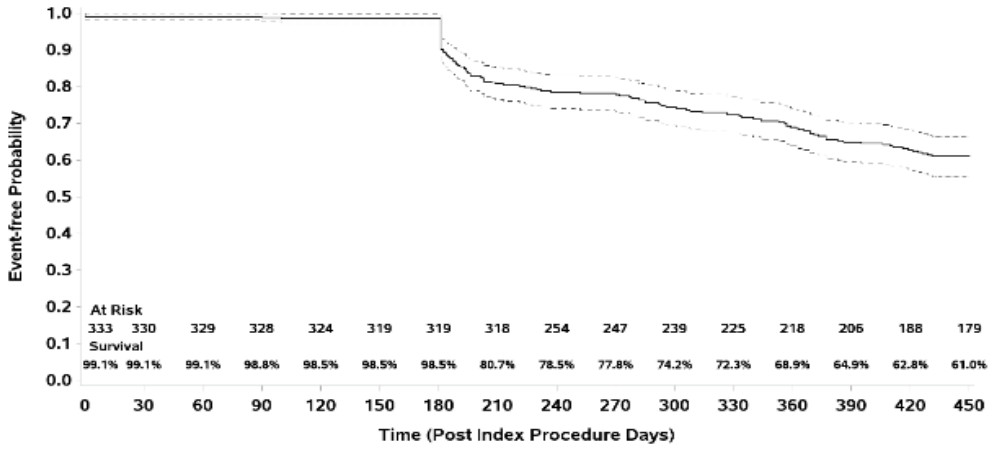

Figure 9 – Kaplan-Meier Analysis – Probability of Freedom from Chronic Effectiveness Failure through 15 Months Post-Procedure (Per-Protocol Population, n = 333)

Primary Effectiveness Failure Modes

Table 33 presents the first failure reason for the per protocol population. If a subject had more than one failure event, only the earliest failure event was summarized. The PRECEPT study protocol did not pre-specify cardioversion in the evaluation period as a primary effectiveness failure mode. One subject underwent elective DCCV for atrial arrhythmia detected on device interrogation during the evaluation period but without electrocardiographic documentation by a protocol specified method. Including cardioversion as a failure mode resulted in the primary effectiveness success rate of 58.9% (175/297).

Table 33: Primary Effectiveness Endpoint - First Reason for Failure (Per protocol population n=333)

Variable	Number of Subjects	Event Rate n/N (%)
First Failures	121	121/297 (40.7%)
Recurrence	77	77/297 (25.9%)
Acute Procedural Failure	3	3/297 (1.0%)
Acute Procedural Failure - Non-study Catheter	0	0/297 (0.0%)
Acute Procedural Failure - Entrance Block	3	3/297 (1.0%)
Non-study Catheter Failure	2	2/297 (0.7%)
Repeat Ablation	7	7/297 (2.4%)
AAD Failure	32	32/297 (10.8%)
AAD Failure - New Drug	28	28/297 (9.4%)
AAD Failure - Higher Dose	4	4/297 (1.3%)
Surgical Failure	0	0/297 (0.0%)
Missing	36	

Sensitivity Analysis

Of the 333 per protocol subjects, 36 had missing primary effectiveness endpoint. The endpoint was considered missing if a subject did not experience any primary effectiveness failure mode, did not complete the 15-month follow-up, and had no post procedural arrhythmia data beyond 422 days after index procedure. Tipping point analysis was performed to evaluate the impact of missing outcomes on the primary effectiveness analyses. There was no tipping point where the study conclusion of primary effectiveness would change. Treating all missing outcomes (N = 36) as effectiveness failures, the primary effectiveness endpoint rate was 52.9% (176/333, 97.5% LCB: 47.3%) and still met the pre-determined performance goal of 40% ($p < 0.001$).

Impact of Therapy Consolidation Period on Primary Effectiveness Success

In the PRECEPT study, a 6-month blanking period was employed to allow investigators additional time to adjust treatment following the index procedure. Among the 297 subjects with primary effectiveness endpoints, 77 subjects received additional interventions (AAD adjustment: 50, cardioversion: 15, repeat procedure: 15) during the therapy consolidation period (months 4-6). Of these subjects, 27.3% (21/77) completed the 15-month follow-up without arrhythmia recurrence in the evaluation period. In comparison, the primary effectiveness success rate in subjects without further intervention during the therapy consolidation period was 70.5% (Table 34).

Table 34 – 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)

Effects of Ablation Strategy (Lesion Set) on Primary Effectiveness

Table 35 presents the primary effectiveness endpoint outcomes by ablation strategy in the per protocol population. The primary effectiveness success rate was 59.3% in subjects undergoing procedure with PVI only ablation, and the primary effectiveness success rates among 3 types of ablation strategy were similar.

Table 35: Primary Effectiveness Endpoint by Ablation Strategy (Per Protocol Population, N=333)

Variable	PVI only group*	PVI + CFAE group	PVI + Non-CFAE group
Primary Effectiveness Endpoint			
n/N (%)	96 / 162 (59.3%)	33 / 55 (60.0%)	47 / 80 (58.8%)

*Subject who did not have non-PV triggers and/or have ablation of the CTI

Primary Effectiveness Endpoint by TTM Compliance

Figure 10 contains a histogram showing TTM compliance per subject and the corresponding primary effectiveness endpoint rate. There wasn't a definite relationship between primary effectiveness success rates and deciles of TTM compliance. Additional post-hoc Kaplan-Meier analyses on the time to first primary effectiveness failure performed in the subgroups dichotomized at TTM compliance of 84% and 89% did not show a significant impact on the primary effectiveness outcomes.

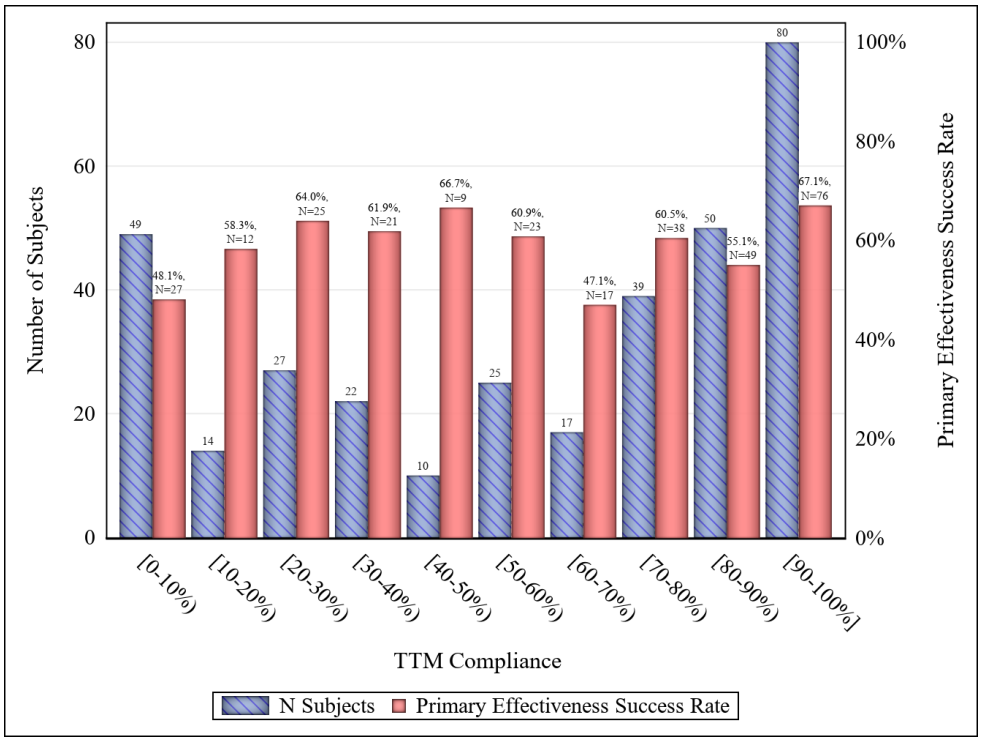

Figure 10: TTM Compliance and Primary Effectiveness Success Rate

Acute Procedural Success

Acute procedural success was defined as confirmation of entrance block in all PVs. In the per protocol population, 3 subjects did not achieve complete PV electrical isolation. The acute procedural success rate was 99.1% (330/333, 97.5% LCB: 97.4%).

Single Procedure Success

The 15-month single procedure success was defined as freedom from documented AF/AFL/AT recurrence (episodes > 30 secs) during the evaluation period after a single ablation procedure. Any repeat ablation procedures post index procedure were deemed effectiveness failures for this analysis. Of the 333 subjects in the per protocol population, 43 had one or more repeat ablation procedures. The single procedure success as defined in the study was 61.9% (182/294, 97.5% LCB: 56.1%).

When the single procedure success was calculated including other failure modes (i.e., non-study catheter failure, AAD failure, surgical failure, and cardioversion failure), the chronic success rate was 56.4% (167/296).

Quality of Life

The quality of life was measured using the Atrial Fibrillation Effect on Quality-of-life (AFEQT) and the Canadian Cardiovascular Scale-Severity of Atrial Fibrillation (CSS-SAF). The AFEQT questionnaire is an AF specific health-related quality of life questionnaire to assess the impact of AF on a patient's life. The summary score ranges from 0 – 100, with 0 corresponding to complete disability and 100 corresponding to no disability. Figure 11 presents the total AFEQT scores at each evaluation time point. The majority of treated subjects reported clinically meaningful improvement in AFEQT scores at 6 months, and the change was sustained at 15 months (mean change of 49.9 ± 32.3 at 15 months).

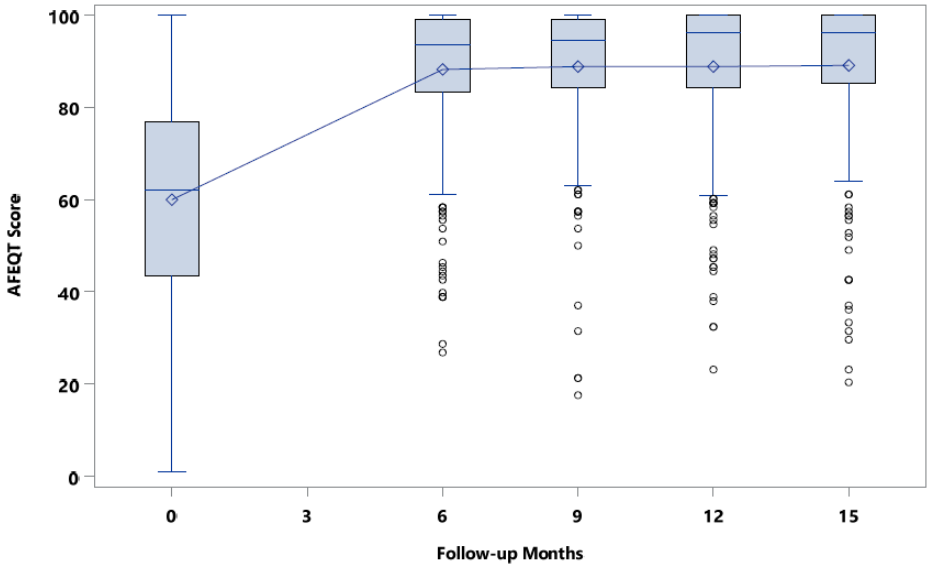

Figure 11 AFEQT Total Score Trend (Per Protocol Population, N=333)

The CCS-SAF score is used to identify AF-related symptoms, assess symptom-rhythm correlation, and evaluate the effect on quality of life (Dorian, et al., 2006). QoL). Table 36 shows the distribution of CCS-SAF class (ranges from 0 (asymptomatic) to 4 (severe impact of symptoms on QoL and activities of daily living)) at baseline and 15-month follow-up visit in the per protocol population. The majority of subjects (81%) were in CCS-SAF class 0 (asymptomatic) at 15 months following index ablation.

Table 36: Canadian Cardiovascular Society - Severity of Atrial Fibrillation (Per- Protocol Population, N=333)

Variable	Baseline n/N (%)	15M n/N (%)
Canadian Cardiovascular Society - Severity of Atrial Fibrillation (CCS-SAF)		
Class 0	2 / 300 (0.7%)	243 / 300 (81.0%)
Class 1	40 / 300 (13.3%)	17 / 300 (5.7%)
Class 2	83 / 300 (27.7%)	13 / 300 (4.3%)
Class 3	158 / 300 (52.7%)	7 / 300 (2.3%)
Class 4	16 / 300 (5.3%)	1 / 300 (0.3%)
Unknown	1 / 300 (0.3%)	

C.6 - Subgroup Analyses

Subgroup analyses were performed to assess the consistency of primary outcomes across the following preoperative characteristics: age, sex, race, and CHA_2DS_2-VASc score. The primary effectiveness endpoint rates were similar by age (< 65 vs. ≥ 65 years) and race (white vs. non-white).

i. Gender analysis:

The primary endpoints were assessed according to gender. Tables 37 and 38 summarize the primary safety endpoint and primary effectiveness endpoint by sex in the respective analysis cohorts. Safety outcomes were similar between male and female subjects (PAE rate: 4.9% vs. 4.0%, p = 1.0). The primary effectiveness endpoint rate was 64.3% for males and 47.1% for females (nominal p < 0.15). A significant interaction between gender and primary effectiveness endpoint was detected, raising the possibility that catheter ablation for the treatment of persistent atrial fibrillation using the study device has a differential effect on chronic success for men and women.

Table 37 Primary Safety Endpoint by Sex (Safety Population, N=348)

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

Table 38 – 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%	36.8%	

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

ii. Subgroup analysis of the primary effectiveness endpoint by CHA_2DS_2-VASc score at baseline

Per study protocol, time to event analyses were conducted to evaluate the differences in primary effectiveness rate by CHA_2DS_2-VASc Score, a clinical prediction score for estimating the risk of stroke in patients with atrial fibrillation. The probabilities of freedom from primary effectiveness failures at 15 months for subjects with CHA_2DS_2-VASc score of <2 and ≥ 2 were 66.1% and 58.7%, respectively.

D. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 155 investigators, of which none were full-time or part-time employees of the sponsor, and 5 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 5
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study:0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability the data.

XIII. Panel Meeting Recommendation and FDA's Post-Panel Action

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Cardiovascular Devices Advisory panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIV. Conclusions Drawn from Preclinical and Clinical Studies

A. Effectiveness Conclusions

The effectiveness outcomes of the PRECEPT study demonstrate that the Biosense Webster ThermoCool SmartTouch SF catheters are effective for the treatment of symptomatic drug refractory recurrent persistent atrial fibrillation.

The pivotal study met its primary effectiveness endpoint. The observed primary effectiveness endpoint rate was 59.3%, and the one-sided exact 97.5% lower confidence limit of 53.4% exceeded the pre-determined performance goal of 40% derived from the minimum chronic acceptable success rate recommended in the Heart Rhythm Society Expert Consensus Statement on Catheter and Surgical Ablation of AF (Calkins et al., 2017). However, several limitations of the pivotal study introduced uncertainties in the assessment of benefits:

1. About 12% of the Per Protocol subjects did not complete the study. The missing data add uncertainties to the confidence about the primary effectiveness endpoint estimate. However, the results of sensitivity analyses support that the primary effectiveness conclusion is sufficiently robust.

2. Given the nonrandomized, uncontrolled, single-arm study design, the subject device's safety and effectiveness for the intended use could not be directly compared to the current standard care or other alternative therapeutic options.

3. The primary effectiveness endpoint ascertainment was mainly based on a rhythm monitoring schedule that included ECG, Holter monitoring, symptomatic and routine TTM transmission. The overall mean TTM compliance was low (66.2%), with ~1/3 of subjects missed > 50% of scheduled regular transmissions. Poor adherence to the rhythm monitoring schedule could inflate the primary effectiveness endpoint estimate.

The pivotal trial also showed that the study treatment was associated with improved quality of life scores. Although a placebo effect cannot be ruled out in this unblinded single-arm study, the substantial and favorable changes in the quality of life scores and the sustained QoL improvement at 15 months post-procedure support a quality of life treatment benefit in the intended population.

Gender analysis showed that females derived reduced treatment effects in the pivotal study. Future data is needed to determine whether the diminished treatment effect in women is due to the limited number of female subjects or a gender disparity in device effectiveness.

B. Safety Conclusions

The risks of the device are based on data collected in the clinical study conducted to support PMA approval as described above. The observed Primary Safety Endpoint Event rate was 4.8%, and the one-sided exact 97.5% upper confidence bound of 7.7% met the pre-specified performance goal of 16.0%. There were no atrioesophageal fistulas or procedure-related deaths. Each primary adverse event of cardiac tamponade and pulmonary edema occurred in 1.5% of treated patients. The pericardial complication rate is within the published rates (0.2 – 5%) of cardiac tamponade in radiofrequency catheter ablation of AF (Calkin et al., 2017). Pulmonary edema following AF ablation is a well-recognized complication that's usually responsive to diuretic therapy. The observed pulmonary edema rate is similar to that reported in other premarket AF ablation IDE studies (TOCCASTAR, ZERO-AF).

There were no unanticipated adverse device effects. The nature, frequency, and severity of the procedural complications observed in the study were in line with the published literature of catheter ablation for the treatment of persistent atrial fibrillation. Furthermore, the safety data is consistent with the known safety of the study device for the treatment of paroxysmal atrial fibrillation.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in the clinical study conducted to support PMA Supplement approval as described above. For patients with symptomatic atrial fibrillation refractory to the standard of care rhythm

control pharmacological therapy, ablation treatment with the Biosense Webster ThermoCool ST SF catheter followed by 6 months of aggressive rhythm management resulted in freedom from recurrence of atrial arrhythmia for the majority of patients in the following 9 months. In addition, the majority of treated patients derived clinically meaningful improvement in AF-related symptoms, activities of daily living, and quality of life.

The probable risks of the device are also based on data collected in the clinical study conducted to support PMA Supplement approval as described above. The risks associated with paroxysmal atrial fibrillation ablation using the study device or another market approved endocardial irrigated tip contact force sensing radiofrequency ablation catheter are well characterized and understood. The safety data from the pivotal PRECEPT study demonstrates that the subject device's safety profile remains unchanged and clinically acceptable when used as intended to treat patients with persistent atrial fibrillation. The observed severity, types, and rates of harmful events associated with using the study catheters to treat symptomatic drug refractory persistent atrial fibrillation were well in line with the published literature.

The outcomes of a gender analysis of the pivotal data suggest that the treatment effects may be less favorable in women. Multiple prior studies have investigated female sex as a predictor of arrhythmia recurrence after AF ablation and failed to show a consistent finding. The writing group of the 2017 HRS Expert Consensus Statement has concluded that "studies have not shown a significant sex-related difference in outcomes with AF ablation in women compared with men." Given the lack of a definitive biological explanation, conflicting results in the published literature, and the small number of women enrolled in the pivotal study, it is reasonable for the device to be used in women as intended while the results of a Post-Approval Study corroborate the observed gender disparity in device effectiveness.

This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the treatment of drug refractory, symptomatic, recurrent persistent atrial fibrillation, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The THERMOCOOL SMARTTOUCH® SF Catheter with Contact Force and SF technology represents a major advancement in the field of ablation catheters. The benefits of this catheter include feedback to the user of the degree of tissue contact, reduction in infused fluid, and shorter procedure time, as evidenced by the study results. This technology has been thoroughly characterized through clinical testing, which met the primary safety and effectiveness endpoints.

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

It also remains unclear whether the limited treatment effect observed in females is due to the small number of women enrolled in the PRECEPT study or can be attributed to differences in device effectiveness among men and women.

FDA intends to clarify this issue in a Post Approval Study.

XV. CDRH Decision

CDRH issued an approval order on April 11, 2016 to approve the THERMOCOOL SMARTTOUCH® SF Catheter for 1) Type I atrial flutter in patients age 18 or older, and 2) Drug refractory recurrent symptomatic paroxysmal atrial fibrillation, when used with compatible three-dimensional electroanatomic mapping systems. Continued approval of was contingent upon the submission of periodic reports, required under 21 CFR 814.84, at intervals of one year (unless otherwise specified) from the date of approval of the original PMA.

CDRH issued an approval order on September 30, 2020 to approve the THERMOCOOL SMARTTOUCH® SF Catheter for 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 us electroanatomic mapping systems. The final Post Approval Study (PAS) condition of approval cited in the approval order is listed below.

The Real-World Experience of Catheter Ablation of Persistent Atrial Fibrillation PAS is a retrospective analysis of the electronic health records (EHR) to evaluate the long-term effectiveness and safety of persistent atrial fibrillation (PsAF) ablation with the THERMOCOOL SMARTTOUCH SF catheter in real-world setting and evaluate the predictors of effectiveness through 36 months of follow-up. The principle PAS design and analyses are per an agreement dated September 29, 2020. A total of 350 consecutive eligible PsAF patients aged 18 years or older and who underwent first time catheter ablation with the THERMOCOOL SMARTTOUCH SF Catheter in the EHR system will be identified and followed for 36 months. Follow up clinical data will be collected at 3-6 months, 12 months, 24 months, and 36 months. At least 50% of enrollment will be women. The primary effectiveness composite endpoint (i.e. Effectiveness failure) will be direct current cardioversion, repeat ablation, or hospitalization for atrial fibrillation/atrial arrhythmia at 12-month follow-up (with 3-months blanking period). The primary safety measurements will be primary adverse events that occurred within 7 days following ablation procedure. The secondary endpoints include procedural data (procedure time, fluoroscopy time), atrial arrhythmia recurrence, component of the primary effectiveness composite, all-cause & cardiovascular (including HF related) hospitalization, and complications through 1-year, 2-year, and 3-year.

The applicant's manufacturing facilities have been inspected and found to be in

compliance with the device Quality System (QS) regulation (21 CFR 820).

XVI. Approval Specifications

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVII. References

Calkins, H., Hindricks, G., Cappato, R., Kim, Y., Saad, E. B., Aguinaga, L., et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm.* 2017; 14(10), e275-e444.

Dorian, P, Cvitkovic SS, Kerr CR, Crystal E, Gillis AM, Guerra PG, Mitchell LB, Roy D, Skanes AC, Wyse DG. A novel, simple scale for assessing the symptom severity fo atrial fibrillation at the bedside: the CCS SAF scale. *Can J Cardiol*. 2006; 22: 383-386