SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Catheter, Percutaneous, Cardiac Ablation, For Treatment of Atrial Flutter;
Percutaneous, Cardiac Ablation, For Treatment Of Atrial Fibrillation

Device Trade Name: Blazer® Open-Irrigated Ablation Catheter
IntellaNav™ Open-Irrigated Ablation Catheter

Device Procode: OAD, OAE

Applicant's Name and Address: Boston Scientific
Rhythm Management
4100 Hamline Ave. North
St. Paul, MN 55112-5798
USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150005/S014

Date of FDA Notice of Approval: December 21, 2017

The original version of the device, the Blazer Open-Irrigated Ablation Catheter, was approved under P150005 on February 24, 2016, and is indicated for cardiac electrophysiological mapping, delivering diagnostic pacing stimuli and radiofrequency ablation of sustained or recurrent Type 1 Atrial Flutter in patients age 18 or older. The SSED to support the indication is available on the CDRH website (http://www.accessdata.fda.gov/cdrh_docs/pdf15/P150005b.pdf) and is incorporated by reference here.

A modified version of the device, IntellaNav Open-Irrigated Ablation Catheter, was approved on July 7, 2016, under P150005/S005. The current supplement was submitted to expand the indication for use for the Blazer Open-Irrigated and IntellaNav Open-Irrigated Ablation Catheters to include treatment of drug refractory, recurrent, symptomatic, paroxysmal atrial fibrillation (PAF) in patients age 18 years or older.

II. INDICATIONS FOR USE

The Blazer and IntellaNav Open-Irrigated Ablation Catheters, when used with a compatible Radiofrequency Controller and Irrigation Pump, are indicated for:

- cardiac electrophysiological mapping;
- delivering diagnostic pacing stimuli;
- RF ablation of sustained or recurrent type I atrial flutter in patients age 18 years or older; and/or
- Treatment of drug refractory, recurrent, symptomatic, paroxysmal atrial fibrillation (PAF) in patients age 18 years or older, when used with a compatible mapping system.

III. CONTRAINDICATIONS

The Blazer and IntellaNav Open-Irrigated Ablation Catheters are contraindicated for use in patients:

- With active systemic infection;
- With a mechanical prosthetic heart valve through which the catheter must pass;
- Unable to receive heparin or an acceptable alternative to achieve adequate anticoagulation;
- Who have vena cava embolic protection, filter devices and/or known femoral thrombus and who require catheter insertion from the femoral approach;
- Who are hemodynamically unstable;
- Who have myxoma or an intracardiac thrombus;
- Who have had a ventriculotomy or atriotomy within the preceding eight weeks; and/or
- Patients who have had a Patent Foramen Ovale (PFO) occlusion device.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the device labeling for the Blazer and IntellaNav Open-Irrigated Ablation Catheters.

V. DEVICE DESCRIPTION

The Blazer Open-Irrigated Ablation Catheter is a 7.5F (2.5 mm) quadripolar open-irrigated ablation catheter designed to deliver radiofrequency (RF) energy to the 4 mm catheter tip electrode for cardiac ablation. The device is designed to be used in conjunction with the Open-Irrigated System, which is inclusive of the Maestro 4000™ Cardiac Ablation System, MetriQ™ Irrigation Pump, MetriQ™ Irrigation Tubing Set, and associated cables.

The Blazer Open-Irrigated Ablation Catheter incorporates an open-irrigated cooling mechanism through a tip that is partitioned into two chambers. The proximal chamber circulates 0.9% normal saline within the tip to cool the proximal electrode and mitigate overheating while the distal chamber allows the fluid to flow through six irrigation holes into the patient's vasculature, thereby cooling the tip/tissue interface. A Luer connection at

the proximal end of the handle connects the catheter to the MetriQ Irrigation Tubing Set, allowing the MetriQ Irrigation Pump to generate the flow of saline to the catheter.

The electrode segment is comprised of a tip electrode and three ring electrodes. The tip electrode has an embedded temperature sensor and delivers radiofrequency (RF) energy for cardiac ablation. The ring electrodes record electrogram (EGM) signals for mapping and deliver stimulus for pacing. The handle includes the electrical connector for the cable connection to the Maestro 4000 RF Generator (Controller) and one Luer fitting used to connect the catheter to the MetriQ Irrigation Tubing Set. The catheter interfaces with standard recording equipment and the Maestro 4000 RF Generator via accessory extension cables with the appropriate connectors.

The IntellaNav Open-Irrigated Ablation Catheter is a 7.5F (2.5 mm) quadripolar open-irrigated ablation catheter designed to deliver radiofrequency (RF) energy to the 4 mm catheter tip electrode for cardiac ablation. The IntellaNav OI Catheter incorporates a position sensor for magnetic tracking and navigation of the catheter on the Rhythmia Mapping System. The IntellaNav OI Catheter is to be used with the Boston Scientific (BSC) Rhythmia Mapping System, Maestro 4000 Controller, Maestro 4000 100 W Pod (limited to 50 W for the IntellaNav OI Catheter), MetriQ Pump, MetriQ Irrigation Tubing Set, and the IntellaNav Ablation Catheter Cable.

The IntellaNav OI Catheter incorporates an open-irrigated cooling mechanism through a tip that is partitioned into two chambers. The proximal chamber circulates 0.9% normal saline within the tip to cool the proximal electrode and mitigate overheating while the distal chamber allows the fluid to flow through six irrigation holes into the patient's vasculature, thereby cooling the tip/tissue interface. A Luer connection at the proximal end of the handle connects the catheter to the MetriQ Irrigation Tubing Set, allowing the MetriQ Pump to generate the flow of saline to the catheter.

The electrode segment is comprised of a tip electrode and three ring electrodes. The tip electrode has an embedded temperature sensor and delivers RF energy for cardiac ablation. The ring electrodes record EGM signals for mapping and deliver stimulus for pacing. The IntellaNav OI Catheter interfaces with standard RF generators through the Rhythmia Connection Box. The handle includes the electrical connector for the cable connection to the Connection Box and one Luer fitting used to connect the catheter to the MetriQ Irrigation Tubing Set.

The Maestro 4000 Cardiac Ablation System (Maestro 4000 Controller and Accessories) is comprised of the Maestro 4000 Cardiac Controller, Maestro 4000 Pod, Maestro 4000 Remote (optional), Maestro 4000 Foot Switch (optional), and dispersive pads (sold separately).

The Maestro 4000 Controller is an RF Generator specifically designed for cardiac ablation. It produces user-selectable power-controlled or temperature-controlled RF power output in the range of 0 to 150 watts into a nominal tissue impedance of 100 ohms. It delivers RF power via a monopolar method driving current between a single active

electrode at the tip of the ablation catheter and one or two dispersive pads applied on the skin. When used with the Blazer Open-Irrigated Ablation Catheter, the RF Generator communicates with the MetriQ Irrigation Pump to coordinate delivery of RF energy with irrigation flow to the catheter tip.

The Pod, which is connected to the RF Generator, allows connection to the catheter and provides connections for dispersive pad(s) to complete the RF circuit. The Pod also connects to electrophysiology (EP) recording systems and provides RF filtering to allow continuous electrogram recording during RF delivery. The Pod model determines the maximum power setting allowed by the RF Generator.

The optional Remote allows the user to control the RF Generator with up to 75 feet between the user interface and the sterile field.

The optional Foot Switch provides hands-free control to start/stop RF delivery.

Dispersive pads provide external patient contact to complete the RF circuit. It disperses current over a large area to minimize damage due to heating of skin and underlying tissue.

The MetriQ Irrigation Pump is a peristaltic pump used during RF cardiac ablation interventional procedures. Its purpose is to irrigate the open-irrigated ablation catheter tip electrodes with saline solution by providing a single channel of continuous flow. The MetriQ Irrigation Pump can also be used with an optional MetriQ Foot Switch in Manual Mode to switch between the existing flow rate and the high ablation flow rate.

The MetriQ Irrigation Tubing Set is a sterile, disposable tubing assembly which consists of a drip chamber with intravenous (IV) spike for connection to the irrigation source, a peristaltic section that is loaded around the pump head, and a standard Luer fitting for connection to the catheter.

When used in automatic mode, the Maestro 4000 Cardiac Ablation System and the MetriQ Irrigation Pump communicate to coordinate delivery of RF energy and irrigation flow to the catheter tip.

Figure 1 depicts the Blazer Open-Irrigated Ablation Catheter and Figure 2 provides a connectivity diagram showing how the catheter connects to the Maestro 4000 Cardiac Ablation System and the MetriQ Irrigation Pump (known collectively as the Boston Scientific Open-Irrigated System).

Figure 1: Blazer Open-Irrigated Ablation Catheter

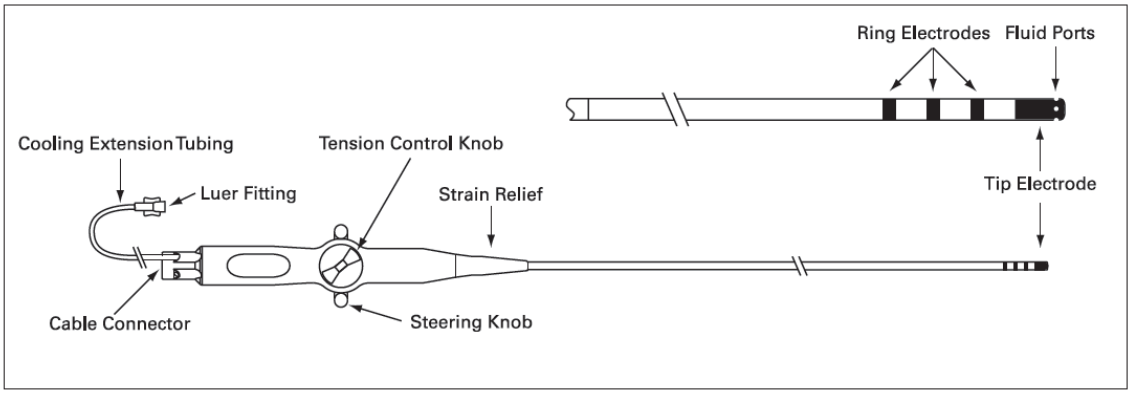


Figure 2: Blazer Open-Irrigated Ablation Catheter Interconnections with the Maestro 4000 Cardiac Ablation System and MetriQ Irrigation Pump

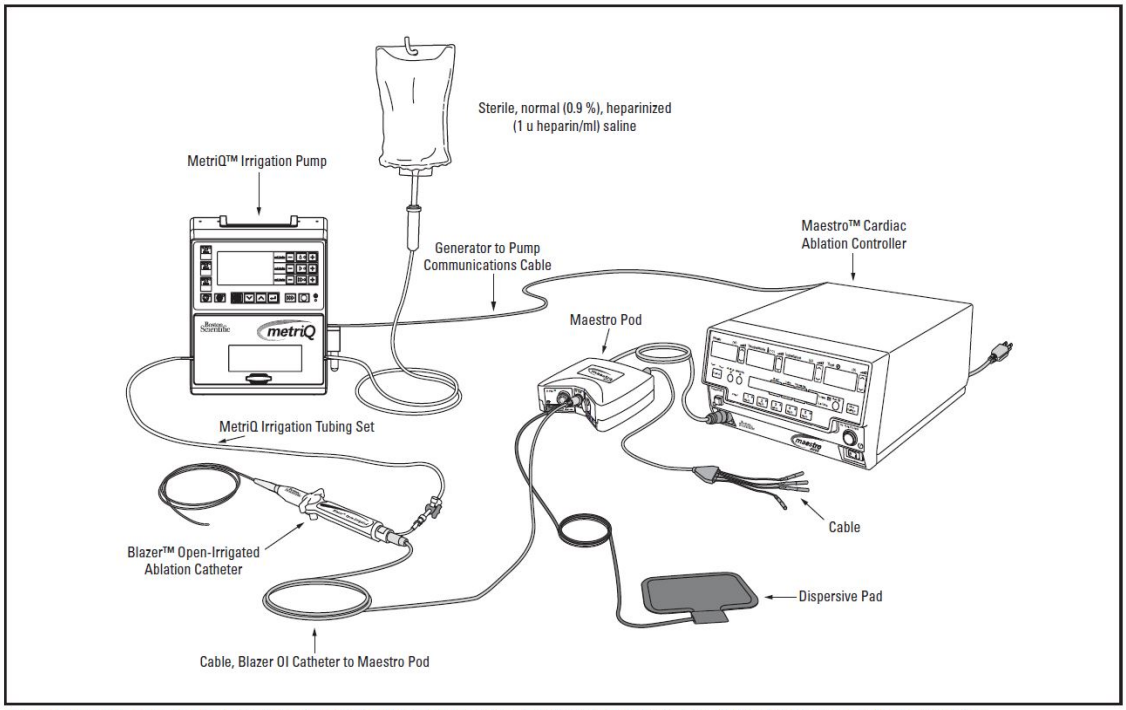


Figure 2. System Set Up for Blazer Open-Irrigated Ablation Catheter with Maestro RF Controller and 100 W Pod, MetriQ Pump and Irrigation Tubing Set, and compatible cables

The IntellaNav OI Catheter is shown in Figure 3. A system connectivity diagram (Figure 4) shows how the catheter connects to the Rhythmia Connection Box and the Maestro 4000 Cardiac Ablation System.

Figure 3: IntellaNav Open-Irrigated Ablation Catheter

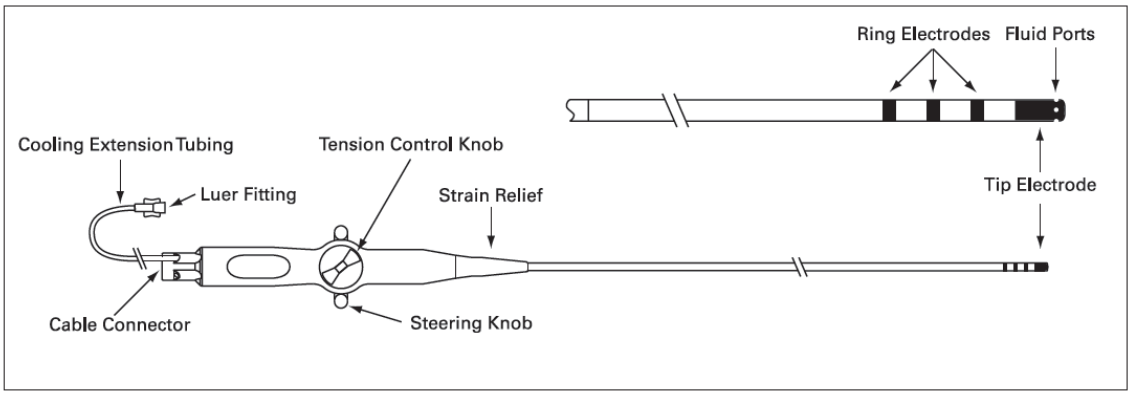
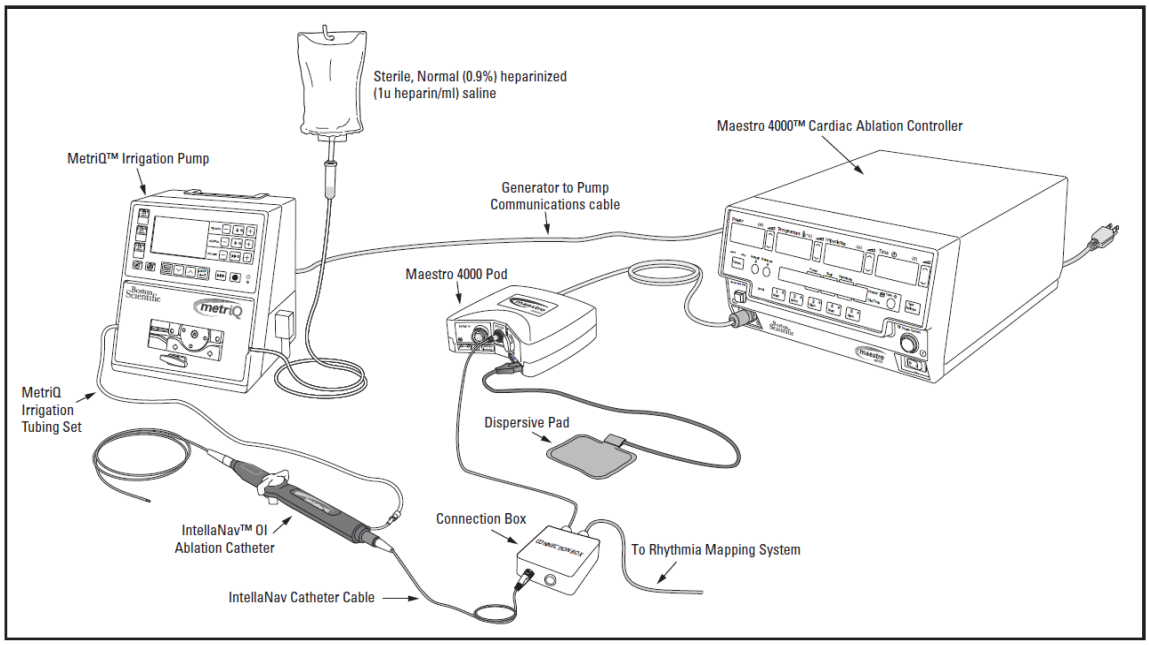


Figure 4: IntellaNav Open-Irrigated Ablation Catheter Interconnections with the Maestro 4000 Cardiac Ablation System and Connection Box



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of drug refractory, recurrent, symptomatic paroxysmal atrial fibrillation, including ablation with another commercially available ablation catheter, pharmacological therapy for rate and/or rhythm control, cardioversion, permanent pacemaker implantation, and surgery. 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

The Blazer Open-Irrigated Ablation Catheter is commercially available in the United States and following countries: Afghanistan, Albania, Algeria, Andorra, Antigua/Barbuda, Armenia, Aruba, Australia, American Samoa, Austria, Azerbaijan, Bahamas, Bahrain, Bangladesh, Barbados, Belgium, Belize, Bermuda, Bonaire Saba, Brazil, Bulgaria, Canada, Chile, Colombia, Croatia, Curacao, Cyprus, Czech Republic, Denmark, Dominican Rep., Dutch Antilles, Egypt, El Salvador, Estonia, Finland, France, Georgia, Germany, Great Britain, Greece, Guam, Haiti, Honduras, Hong Kong, Hungary, Iceland, Iran, Iraq, Ireland, Israel, Italy, Jamaica, Japan, Jordan, Kenya, Kuwait, Kyrgyzstan, Latvia, Lebanon, Libya, Liechtenstein, Lithuania, Luxembourg, Macau, Malaysia, Malta, Martinique, Mexico, Mongolia, Morocco, Myanmar, Nepal, Netherlands, New Zealand, Nicaragua, Norway, North Mariana Island, Oman, Pakistan, Panama, Philippines, Poland, Portugal, Puerto Rico, Qatar, Romania, Russian Fed., Saudi Arabia, Serbia, Singapore, Saint Maarten, Slovakia, Slovenia, South Africa, South Korea, Spain, Suriname, Sweden, Switzerland, Taiwan, Tajikistan, Thailand, Trinidad, Tobago, Tunisia, Turkmenistan, United Arab Emirates, Uzbekistan, Venezuela, Vietnam, American Virgin Island, West Bank and Gaza Strip, Yemen.

The Maestro 4000 is marketed in the United States and the European Union. The MetriQ Irrigation Pump and Tubing Set are both marketed in the United States and the European Union.

There are no countries from which the Blazer Open-Irrigated Ablation Catheter, the IntellaNav Open-Irrigated Ablation Catheter, or the Boston Scientific Open-Irrigated System has been withdrawn from marketing for any reason related to safety and effectiveness.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the probable adverse effects (e.g., complications) associated with the use of the device:

- Allergic reaction (including anaphylaxis)
- Angina
- Arrhythmias (new or exacerbation of existing arrhythmias)
- Cardiac perforation
- Cardiac/respiratory arrest
- Catheter entrapment
- Cerebrovascular accident (CVA)
- Chest discomfort
- Complete heart block (transient/permanent)
- Complications of sedative agents/anesthesia/medications
- Conduction pathway injury
- Congestive heart failure
- Death

- Edema
- Effusion (i.e., pericardial/pleural)
- Embolism (venous/arterial) (i.e., cerebrovascular accident, myocardial infarction, pulmonary embolism, peripheral embolism)
- Esophageal injury
- Exacerbation of existing conditions
- Fistula (arterial-venous, atrial-esophageal)
- Fluid volume overload (i.e., diuresis/electrolyte imbalance)
- Gastrointestinal events
- Gastroparesis
- Hemothorax
- Hematoma
- Hemorrhage
- Hypertension/Hypotension
- Inadvertent injury to adjacent structures
- Infection
- Lead dislodgement
- Myocardial infarction
- Nerve weakness/palsy/injury (i.e., phrenic/vagus)
- Pericarditis
- Pneumothorax
- Pseudoaneurysm
- Pulmonary complications (i.e., edema, pulmonary hypertension, pleuritis, pneumonia)
- Pulmonary vein stenosis
- Radiation exposure
- Renal insufficiency/failure
- Residual atrial septal defect (ASD)
- Skin burns (i.e., radiation/defibrillator/cardioverter)
- Tamponade
- Thrombus/thrombosis
- Transient ischemic attack (TIA)
- Valvular damage
- Vasospasm
- Vasovagal reactions
- Vessel trauma (i.e., injury/ulceration/ perforation/ dissection/rupture)

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

Pre-clinical testing of the Blazer Open-Irrigated Ablation Catheter included verification and validation testing (device, system, and software), biocompatibility of patient-contacting materials, sterilization, packaging and shelf life testing, and animal studies.

Performance testing was conducted to demonstrate design integrity. Tests that were identified in standards or guidance documents were performed based on product specification requirements. Test results confirming that the Blazer Open-Irrigated Ablation Catheter, Maestro 4000, and MetriQ Irrigation Pump and Tubing Set met product specifications were submitted as part of a prior PMA P150005 for this device. The results of the preclinical testing submitted under PMA P150005 can be found in the SSED at: http://www.accessdata.fda.gov/cdrh_docs/pdf15/P150005b.pdf.

There have been no changes to the design or materials for this application. No further laboratory preclinical testing was needed for the current submission.

Maestro 4000 versus Stockert 70 Radiofrequency Generator

The clinical study was performed with the Blazer Open-Irrigated Ablation Catheter with the Stockert 70 RF generator; however, the device is approved for use with the Maestro 4000 RF generator. The PMA P150005 submission included bench comparisons of the waveform frequency, maximum temperature, temperature accuracy, time accuracy, maximum time, maximum impedance range, minimum impedance range, impedance accuracy, and lesion dimensions between the two generators to support equivalency in clinical use with the Blazer Open-Irrigated Ablation Catheter. However, differences of greater than 5% were identified for the power output and power accuracy between the two generators. Approval of the Maestro 4000 RF generator under PMA P150005 was supported by additional preclinical animal study data which demonstrated clinically equivalent lesions with the Blazer Open-Irrigated Ablation Catheter using the Stockert 70 RF and Maestro 4000 RF generators.

MetriQ versus CoolFlow Irrigation Pump

The clinical study was performed with the Blazer Open-Irrigated Ablation Catheter with the CoolFlow Irrigation Pump; however, the device is approved for use with the MetriQ Irrigation Pump. Bench test comparisons of the specifications, flow rates, and safety features between the two pumps were submitted to demonstrate expected equivalent clinical performance with the Blazer Open-Irrigated Ablation Catheter in PMA P150005.

Animal Studies

An additional GLP preclinical study, GLP Study No. 11-043G, was conducted to support the atrial fibrillation indication for the Blazer Open-Irrigated Ablation Catheter in addition to the four GLP preclinical studies that were conducted to support an atrial flutter indication for the Blazer Open-Irrigated Ablation Catheter as part of PMA P150005, the results of which can be found in the P150005 SSED referenced above.

The objective of GLP Study No. 11-043G was to characterize factors related to the safety profile of the Blazer Open-Irrigated Ablation Catheter when used at the upper limit of the anticipated clinical operating range (power of 50W and flow rate of 30 ml/min) at 7 and 30 days post lesion creation along the pulmonary vein and mitral isthmus. A thorough

evaluation of the catheter's adverse event profile was demonstrated by engaging three specialists. All study endpoints in this study were met. Results of this study demonstrated the safe creation of RF ablation lesions in the left atria of 14 canines without any deaths, complications or adverse events, either during the procedure or at 7 (+1) and 30 (+5) days post-procedure.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study (the ZERO-AF study) to establish a reasonable assurance of safety and effectiveness of catheter ablation with the Blazer Open-Irrigated Ablation Catheter for the treatment of drug refractory, recurrent, symptomatic Paroxysmal Atrial Fibrillation (PAF) in the US under IDE #G120082. Due to design similarities, clinical data from the Blazer OI Catheter can be used to support the IntellaNav OI Catheter. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were enrolled between November 1, 2012, and August 26, 2015. The dataset used to support this application reflected data collected through October 13, 2016, and included 398 patients. There were 39 investigational sites (26 sites in United States, 13 sites outside the United States).

The study was a prospective, randomized, controlled, single-blinded, multi-center, pivotal clinical study. Subjects with symptomatic paroxysmal atrial fibrillation refractory to one or more antiarrhythmic drugs (Class I – IV) were randomized 1:1 to catheter ablation using the Investigational Blazer Open-Irrigated Ablation Catheter or the Control Biosense Webster ThermoCool catheters (Biosense Webster ThermoCool SF NAV, NaviStar ThermoCool, or EZ Steer ThermoCool NAV Ablation Catheters). The control devices received FDA approval for the treatment of paroxysmal atrial fibrillation (P030031/S011).

Subjects were followed for 12 months with scheduled and symptom-driven assessment to detect recurrent atrial arrhythmia (atrial fibrillation [AF], atrial flutter [AFL], or atrial tachycardia [AT]) by means of periodic electrocardiograms, twice monthly trans-telephonic monitoring, patient-initiated trans-telephonic monitoring, and 24-hour Holter monitoring at 6 and 12 months. The first 90 days following the index ablation procedure was considered a blanking period for all subjects.

A core lab evaluated and assessed the electrocardiograms, trans-telephonic monitor tracings, and 24-hour Holter recordings. A separate core lab reviewed and assessed all pulmonary vein (PV) imaging studies.

All adverse events and deaths reported in this study were reviewed and adjudicated by a Clinical Events Committee (CEC). The CEC was comprised of independent physicians, and its decisions were based upon independent physician review of data.

A Data Monitoring Committee (DMC), which was comprised of three independent electrophysiologists and one independent biostatistician, was responsible for the oversight review of all adverse events throughout the conduct of the study.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the ZERO-AF study was limited to patients who met the following inclusion criteria:

- History of recurrent symptomatic PAF* with ≥2 episodes reported within the 365 days prior to enrollment;
- At least 1 episode of PAF documented by Holter monitor, rhythm strip, trans-telephonic monitor (TTM), or 12-lead ECG in the 365 days prior to enrollment;
- Refractory or intolerant to at least one Beta Blocker, Calcium Channel Blocker, Class I OR Class III anti-arrhythmic drug (AAD);
- Age 18 or above, or of legal age to give informed consent specific to state and national law; and
- Competent and willing to provide written informed consent to participate in the study and agree to comply with follow-up visits and evaluation.

* Definition of PAF is AF episodes that last ≥30 seconds in duration and terminate within seven days. Clinical symptoms associated with PAF may include, but are not limited to, palpitations, syncope, lightheadedness, chest pain/tightness, shortness of breath, and extreme fatigue.

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

- Have any of the following heart conditions within 90 days prior to enrollment:
  - New York Heart Association (NYHA) Class III or IV;
  - Left ventricular ejection fraction (LVEF) <35%;
  - Left atrial (LA) diameter >5.5 cm;
  - Unstable angina or ongoing myocardial ischemia; or
  - Transmural myocardial infarction (MI);
- Congenital structural heart disease that increases the risk of ablation or precludes catheter placement;
- Undergone any left atrial catheter or surgical ablation;
- Have had a coronary intervention, cardiac surgery, or other cardiac ablation within 90 days prior to enrollment;
- Had >1 AF episode lasting greater than 7 days, with no episodes having lasted greater than 30 days, within the past year;
- Subjects regularly prescribed amiodarone therapy during the 120 days prior to enrollment;
- Contraindication to anticoagulation therapy;

- Creatinine >2.5mg/dl or creatinine clearance <30mL/min within 90 days prior to enrollment;
- Prosthetic mitral or tricuspid heart valves;
- Confirmed cardiac thrombus within 30 days prior to enrollment;
- Implanted pacemaker, ICD, or CRT leads within 180 days prior to enrollment;
- History of CVA, TIA or PE within 180 days prior to enrollment;
- Left atrial appendage closure device;
- Any other significant uncontrolled or unstable medical condition (e.g., sepsis, acute metabolic illness, end stage COPD);
- Enrolled in any concurrent clinical trial without documented pre-approval from BSC;
- Women who are pregnant or plan to become pregnant within the course of their participation in the investigation; or
- Life expectancy ≤ 2 years (730 days) per physician opinion.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at pre-discharge, one month, two months, three months, six months and 12 months post-procedure. Approximately one third of subjects received a second randomization to participate in the PV Imaging sub-study; selected subjects underwent a baseline cardiac MRI or spiral CT scan prior to the index procedure and a scan at the 3-month follow-up. Adverse events and complications were recorded at all visits.

The key timepoints are summarized below in Table 1.

Table 1: Data Collection Schedule

Procedure/Assessment	Enrollment	Index Procedure (<60 D PE)	Blanking Period			Repeat Proc.	Effectiveness Evaluation Period			
			Pre-Discharge (5-72 H Post-IP)	1-Mo (±7 D) FU	2-Mo (±7 D) Phone Check	Repeat- (≤90 D Post-IP)	Additional FU	3-Mo (±14 D) FU	6-Mo (±14 D) FU	12-Mo (±21 D) FU
Informed Consent Process	X	--	--	--	--	--	--	--	--	--
Eligibility Criteria	X	--	--	--	--	--	--	--	--	--
Subject Demographics	X	--	--	--	--	--	--	--	--	--
Medical History	X	--	--	--	--	--	--	--	--	--
Physical Assessment	X	--	X	X	--	--	--	--	--	X
Quality of Life (SF36v2.0)	X	--	--	--	--	--	--	--	X	X
NIH Stroke Scale	X	--	X	--	--	X (2)	--	--	--	X
PV Sub-Study Cardiac CT/MRI	X[i]	--	--	--	--	--	--	X[i]		--
Non-Sub-Study PV Visualization		X		X[vi]	X[vi]	X	X[vi]	X[vi]	X[vi]	X[vi]
Neurology Consultation	--	--	X[iv]			X[iv]				X[iv]
Brain MRI Scan[v]	--	--	X[v]	--	--	X[v]	--	--	--	X[v]
TTE	X[ii]	--	--	--	--	--	--	--	--	--
TEE	X[ii]	X[iii]	--	--	--	--	--	--	--	--
Procedural Data	--	X	--	--	--	X	--	--	--	--
12-Lead ECG	--	--	X	X	--	--	X	X	X	X
Holter Monitor (24H)	--	--	--	--	--	--	--	--	X	X
Event Monitor (TTM)	--	--	X	X	X	--	X	X	X	X
Medications	X	X	X	X	X	X	X	X	X	X
Adverse Events	--	X	X	X	X	X	X	X	X	X
Protocol Deviations	X	X	X	X	X	X	X	X	X	X

X = required; -- = not required
Abbreviations: D = day(s), H = hour(s), PE = post-enrollment, IP = index procedure, NIH = National Institutes of Health, ECG = electrocardiogram, TTM = trans-telephonic monitor, Mo = Month, TTE = trans-thoracic echocardiogram, TEE = trans-esophageal echocardiogram, CT = Computed Tomography, MRI = Magnetic Resonance Imaging, SF = Short Form, FU = follow-up
i = only required if part of PV Imaging sub-study
ii = either TTE or TEE only required if data not available within 6 months prior to enrollment
iii = only required if anticoagulation requirements are not met, if subject's $CHADS_2$ score is ≥ 1, or subjects's left atrium is enlarged (≥4.5cm)
iv = Neurology consult is only required if NIH scale worsens from the previous assessment
v = Brain MRI scan preferred, CT accepted if MRI not available. Only required if neurology consultation determines possibility of new stroke
vi = Cardiac CT/MRI scan will be required for all subjects if PV stenosis is suspected at any time throughout the follow-up period

3. Clinical Endpoints

Primary Safety Endpoint:

Primary safety endpoint events were defined as any of the following:

- procedure-related serious adverse events (SAEs) at 7 days post-index procedure or hospital discharge, whichever was later;

- significant pulmonary vein stenosis (≥70% reduction in diameter from baseline) that occurred within 12 months of the index procedure; and/or
- atrio-esophageal fistulas that occurred within 12 months of the index procedure.

All adverse events were adjudicated by an independent committee of physicians as to their severity and relationship to the investigational and control catheters and/or procedure.

Primary Effectiveness Endpoint:

Primary effectiveness failure was defined as a Randomized subject being an acute procedure failure, having more than one repeat procedure during the Blanking Period, having a repeat procedure outside the Blanking Period, or having any of the following between 91 days and 12 months post-procedure:

- a documented symptomatic AF, AT, or AFL (≥30 seconds in duration or from a 10-second 12-Lead ECG);
- prescribed a higher dose of a previously failed AAD*; and/or
- prescribed a new AAD*.

*AADs for this endpoint consisted of all Class I/III medications and Class II/IV medications taken explicitly for control of arrhythmia recurrence.

Study Success Criteria:

The study is considered a success when both of the following criteria are met:

- The Investigational group primary safety endpoint event rate is non-inferior to that of the Control group (non-inferiority margin of 9%)

  $H_o: p_t - p_c \geq \delta$
  $H_1: p_t - p_c < \delta$

  Where
  p_t = the proportion of Investigational subjects with a primary safety endpoint event
  p_c = the proportion of Control subjects with a primary safety endpoint event
  $\delta = 9\%$

and

- The proportion of subjects free from failure in the investigational group is non-inferior to those in the control group at 12 months after the index ablation procedure (non-inferiority margin of 15%)

$H_o: p_c - p_t \geq \delta$
$H_1: p_c - p_t < \delta$

Where
p_t = the proportion of Investigational subjects free from failure at 12 months post-procedure.
p_c = the proportion of Control subjects free from failure at 12 months post-procedure.
$\delta = 15\%$

B. Accountability of PMA Cohort

At the time of database lock, of 398 (339 Randomized and 59 Roll-In) patients enrolled in the PMA study, 327 (82.2% overall, 284/83.4% Randomized and 43/72.9% Roll-In) patients were available for analysis at the 12-month post-operative visit.

The following definitions were used to classify study populations:

Roll-In Cohort (n = 59): To help facilitate Investigators' familiarity with the new investigational system, the first two subjects enrolled by the first two Investigators at each site could be classified as "Roll-In" subjects and would not undergo randomization.

Randomized Cohort (n = 339): After the Roll-In subject criteria or case review was satisfied for the treating physician, their subjects were randomized 1:1 to either the Investigational (n=167) or Control (n=172) arm of the study. Randomization was stratified by Investigational site. Study subjects were not informed of their randomization assignment. Subjects could be informed of their randomization assignment at the end of the 12-Month follow-up visit upon request. Randomized subjects were further classified as:

- Intent (n = 13): Refers to a subject who was enrolled but withdrew from the study and did not undergo the protocol-required ablation procedure;

- Attempt (n=5): Refers to a subject who was enrolled and had anesthesia or sedation administered in preparation for the ablation procedure but did not receive ablation therapy with the Investigational or Control catheter per protocol; or

- Treatment (n=321): Refers to all enrolled subjects who received ablation therapy with the Investigational or Control catheter.

All 321 Treatment patients (Control: 164, Investigational: 157) were included in the safety analysis and eligible for the primary effectiveness endpoint analysis.

Subject disposition is given in Table 2 below for all Roll-In and Randomized subjects. Data from Roll-In subjects are not included in endpoint analyses.

Table 2: Participant Disposition

	Control	Investigational	Total
Enrolled subjects			**398**
Roll-In Cohort	**3**	**56**	**59**
Randomized Cohort	**172**	**167**	**339**
Intents	**5**	**8**	**13**
Adverse Event	0	1	1
Did not meet eligibility criteria	2	2	4
Investigator Discretion	1	1	2
Lost to follow-up	0	1	1
No longer meets protocol criteria	1	2	3
No product available	1	0	1
Withdrew from study participation	0	1	1
Attempts	**3**	**2**	**5**
Treatment subjects (eligible for endpoint analysis)	**164**	**157**	**321**
12-Month Follow-Up Visit Completed	145	139	284
12-Month Follow-Up Visit Not Completed	19	18	37
Death	1	1	2
Withdrawals	16	16	32
Missed 12-month follow-up	2	1	3
Endpoint Accountability for Randomized Treatment Subjects (n=321)			
Primary Safety Endpoint and Secondary Effectiveness Endpoint			
Modified Intention-to-treat	**164**	**157**	**321**
Per Protocol	**160**	**157**	**317**
Excluded due to randomization error *	4	0	4
Primary Effectiveness Endpoint			
Modified Intention-to-treat	**164**	**157**	**321**
Complete data	**152**	**146**	**298**
Imputed data	**12**	**11**	**23**
Per Protocol	**148**	**146**	**294**
Excluded due to randomization error *	4	0	4
Excluded due to incomplete follow-up endpoint event (includes death, withdrawal, and missed visit with no TTM in window)	12	11	23

***** Four subjects randomized to the Control group were treated with the Investigational catheter

Study populations for analysis were defined as follows:

- Safety Populations
  - Modified intent-to-treat (mITT) (n = 321): pre-specified, included all treated in their assignment group.
  - Per Protocol (PP) (n = 317): pre-specified, included all subjects who completed their full course of assigned treatment, have no major protocol violations, and have outcome assessment.

- Effectiveness Populations
  - Modified intent-to-treat (n = 321): pre-specified, included all treated subjects in their assigned randomization group.
  - Supplementary modified intent-to-treat (n = 298): pre-specified, included all treated subjects with complete endpoint data in their assigned randomization group.
  - Per Protocol (n = 294): pre-specified, included all subjects who completed their full course of assigned treatment, have no major protocol violations, and have outcome assessment.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a PAF catheter ablation study performed in the US. The average age of the subjects was 59 ± 10 years for the Control group and 60 ± 11 years for the Investigational group. For both treatment groups, the majority of subjects were male; the Control group had 107 male subjects (62%) and the Investigational group had 105 male subjects (63%). Overall, there were no significant imbalances in baseline characteristics between the two treatment groups. Table 3 below presents the demographics and physical assessment data for all Randomized patients (N=339).

Table 3: Baseline Characteristics

Characteristic	Measurement	Control (N=172)	Investigational (N=167)	P-value
Age at Index Procedure (years)	N	172	167	
	Mean ± SD	59 ± 10	60 ± 11	0.32
	Range	31 - 82	22 - 84	
Gender [N (%)]	Female	65 (38)	62 (37)	0.90
	Male	107 (62)	105 (63)	
Height (cm)	N	169	165	
	Mean ± SD	174 ± 9	173 ± 9	0.50
	Range	150 - 200	150 - 193	
Weight (kg)	N	169	165	
	Mean ± SD	90 ± 22	89 ± 19	0.55
	Range	53 - 218	46 - 167	
Resting Heart Rate (bpm)	N	169	164	
	Mean ± SD	67 ± 15	71 ± 19	0.08
	Range	39 - 130	43 - 156	
Resting Systolic BP (mmHg)	N	169	164	
	Mean ± SD	130 ± 20	131 ± 16	0.70
	Range	90 - 191	96 - 171	
Resting Diastolic BP (mmHg)	N	169	164	
	Mean ± SD	76 ± 11	77 ± 11	0.38
	Range	48 - 110	50 - 116	
Creatinine (mg/dL)	N	166	161	
	Mean ± SD	0.9 ± 0.2	0.9 ± 0.2	0.42
	Range	0.4 - 1.5	0.5 - 2.5	
NYHA Class	I	64 (37.2)	67 (40.1)	0.30
	II	13 (7.6)	17 (10.2)	
	Non HF	92 (53.5)	76 (45.5)	
	Not Assessed	3 (1.7)	7 (4.2)	
Left Atrial Diameter (cm)	N	165	162	
	Mean ± SD	3.97 ± 0.65	3.96 ± 0.65	0.86
	Range	2.30 – 5.50	2.30 - 5.50	
LVEF (%)	N	164	161	
	Mean ± SD	60.4 ± 7.4	60.2 ± 7.2	0.76
	Range	38.0 - 86.0	35.0 - 84.0	

Pre-existing conditions of Randomized subjects are summarized in Table 4 below:

Table 4: Pre-existing Conditions Recorded at Baseline

Characteristic	Category	Control (N=172)	Investigational (N=167)	P-value
Cardiac/cardiovascular disease history	Dilated Cardiomyopathy [N (%)]	0 (0)	3 (1.8)	0.08
	Hypertrophic Cardiomyopathy [N (%)]	4 (2.3)	2 (1.2)	0.43
	Ischemic Cardiomyopathy [N (%)]	3 (1.7)	5 (3.0)	0.45
	Nonischemic Cardiomyopathy [N (%)]	1 (0.6)	6 (3.6)	0.05
	Cerebral Vascular Disease [N (%)]	3 (1.7)	2 (1.2)	0.68
	Congestive Heart Failure (CHF) [N (%)]	5 (2.9)	8 (4.8)	0.37
	Coronary Artery Disease [N (%)]	21 (12.2)	18 (10.8)	0.68
	Hypertension [N (%)]	84 (48.8)	98 (58.7)	0.07

	Myocardial Infarction [N (%)]	1 (0.6)	6 (3.6)	0.05
	Peripheral Vascular Disease [N (%)]	2 (1.2)	4 (2.4)	0.39
	Pulmonary Hypertension [N (%)]	1 (0.6)	2 (1.2)	0.54
	Aortic Valvular Disease [N (%)]	1 (0.6)	5 (3.0)	0.09
	Mitral Valvular Disease [N (%)]	7 (4.1)	7 (4.2)	0.96
	Pulmonic Valvular Disease [N (%)]	1 (0.6)	3 (1.8)	0.30
	Tricuspid Valvular Disease [N (%)]	3 (1.7)	5 (3.0)	0.45
	Other Cardiac Disease History* [N (%)]	9 (5.2)	5 (3.0)	0.30
Cardiac intervention/surgery history	Aneurysmectomy [N (%)]	0 (0)	2 (1.2)	0.15
	Angiography/Angioplasty [N (%)]	5 (2.9)	8 (4.8)	0.37
	Stent [N (%)]	8 (4.7)	10 (6.0)	0.58
	CABG [N (%)]	3 (1.7)	5 (3.0)	0.45
	Device Implant (CRT) [N (%)]	0 (0)	2 (1.2)	0.15
	Device Implant (ICD) [N (%)]	1 (0.6)	3 (1.8)	0.30
	Pacemaker Implant [N (%)]	3 (1.7)	8 (4.8)	0.11
	Heart valve repair/replacement [N (%)]	0 (0)	2 (1.2)	0.15
	Other Cardiac Intervention/Surgery** [N (%)]	5 (2.9)	6 (3.6)	0.72
Significant non-cardiovascular disease history	COPD [N (%)]	10 (5.8)	5 (3.0)	0.21
	Type I Diabetes [N (%)]	4 (2.3)	1 (0.6)	0.19
	Type II Diabetes [N (%)]	18 (10.5)	18 (10.8)	0.93
	Hepatic Disease [N (%)]	1 (0.6)	1 (0.6)	0.98
	Neurologic Disease [N (%)]	4 (2.3)	5 (3.0)	0.70
	Renal Disease [N (%)]	6 (3.5)	4 (2.4)	0.55
	GI Bleed or other coagulopathies [N (%)]	2 (1.2)	4 (2.4)	0.39
	Hyperlipidemia [N (%)]	69 (40.1)	64 (38.3)	0.74
	Sleep Apnea [N (%)]	27 (15.7)	23 (13.8)	0.62
	Other Non-cardiovascular Disease*** [N (%)]	44 (25.6)	47 (28.1)	0.59

**Other Cardiac Disease History: Aortic Atheroma, Diastolic Dysfunction, ST Abnormality, Left Ventricular hypertrophy, Scleroderma, Syncope, Atypical chest pain, Diastolic Dysfunction, Idiopathic Pulmonary Embolism, Aortic Stenosis, Pericarditis*

***Other Cardiac Intervention/Surgery History: Cardiac Ablation, Loop recorder implantation, Cardioversion, Left brachial embolectomy*

**** Other Non-Cardiovascular Disease History: Allergy, Anemia, Anxiety, Cancer, Dermatological issues, Dyslipidemia, Gastrointestinal, Gynecological Diseases, Hypercholesterolemia, Hyperglycemia, Hyperuricemia, Hypomagnesemia, Hypotension, Hypothyroidism, Medication intolerances, Musculoskeletal Diseases, Neurological Diseases, Obesity, Ophthalmological Diseases, Pulmonary Diseases, Rheumatological Diseases, Sleeping Disorders*

Previous failed AADs were comparable between study groups. Similar proportion of patients (26.2 % vs. 25.1 %, p = 0.83) in the Control group and Investigational group had prior history of atrial flutter.

D. Procedural Data

The goal of the ablation procedure was electrical isolation of all clinically relevant pulmonary veins. Use of multiple catheter curves of a single catheter type was allowed in both arms; however, use of only one catheter type was allowed. Once the Control catheter type was selected, the Investigator could not switch to another Control catheter type. If multiple catheter curves of a single catheter type were required or if a catheter was changed from a unidirectional curve to a bidirectional curve, these were considered the same types of catheters and would not affect the outcome determination of acute success.

The largest proportion of the Control cases were completed with the ThermoCool SF NAV (42%) with the rest of the cases closely split between the EZ Steer NAV ThermoCool (27.4%) and the Navistar ThermoCool (28%). Four Control subjects were incorrectly treated with the Blazer Open-Irrigated Ablation Catheter. For the Investigational group, all index procedures were initiated with the Blazer Open-Irrigated Ablation Catheter. The summary of Control devices used for study procedures is included in Table 5.

Table 5: Number of Catheters Used in a Procedure

Catheter	Control N (%)	Investigational N (%)
Blazer Open-Irrigated	4 (2.4)*	157 (100)
EZ Steer NAV ThermoCool	46 (28)	0 (0.0)
NaviStar ThermoCool	45 (27.4)	0 (0.0)
ThermoCool SF NAV	69 (42.1)	0 (0.0)

*Four subjects were randomized to Control but treated with a Blazer Open-Irrigated Ablation Catheter

Table 6 includes the procedural data for Randomized Treatment subjects treated with only the Randomized catheter.

Table 6: Ablation Parameters

Procedure Parameter	Measurement	Control	Investigational
Procedure Duration (minutes)	N	164	156
	Mean ± SD	162 ± 66	168 ± 63
	Range	62 - 469	73 - 401
Fluoroscopy Duration (minutes)	N	163	156
	Mean ± SD	25 ± 17	28 ± 18
	Range	0 - 90	3 - 85
Total RF Time for Procedure (minutes)	N	152	129
	Mean ± SD	45 ± 25	41 ± 26
	Range	11 - 139	3 - 172
Fluid infused from catheter sources (L)	N	162	155
	Mean ± SD	1.18 ± 0.64	1.34 ± 0.71
	Range	0.20 – 4.00	0.10 – 3.30
Average Power (W)	N	148	125
	Mean ± SD	30 ± 5	30 ± 5
	Range	17 - 39	20 - 47
Average Temperature (C°)	N	148	125
	Mean ± SD	32 ± 3	31 ± 3
	Range	21 - 40	24 - 42
Average Impedance (Ω)	N	148	125
	Mean ± SD	125 ± 21	152 ± 30
	Range	84 - 191	91 - 242

The majority of the Randomized subjects in the study underwent only ablation of the PVs (N=197) with 98 such cases in the Control group and 99 cases in the Investigational group. For the next two largest categories of procedure, 57 subjects (30 Control, 27 Investigational) underwent pulmonary vein isolation and ablation of the cavo-tricuspid isthmus and 46 subjects (25 Control, 21 Investigational) underwent PV ablation and additional non-PV Foci in the right or left atria. Table 7 shows the full breakdown for all Randomized subjects by assigned group.

Table 7: Ablation Locations for All Randomized Subjects

Ablation Locations	Control N (%)	Investigational N (%)
PV Only	98 (59.8)	99 (63.1)
PV + CTI	30 (18.3)	27 (17.2)
PV + RA/LA	24 (14.6)	20 (12.7)
PV + additional induced	0 (0.0)	4 (2.5)
PV + CTI + RA/LA	11 (6.7)	6 (3.8)
PV + RA/LA + additional induced	1 (0.6)	1 (0.6)

E. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the Modified Intention-to-Treat cohort of 321 patients available for the evaluation. The results of the Primary Safety Endpoint are shown in Table 8. The primary safety event free rate was 90.24% in the Control group and 89.17% in the Investigational group. The difference in the rates between the Control and the Investigational groups was 1.07%. The upper 95% confidence bound of 6.93% was less than the non-inferiority margin of 9%, demonstrating non-inferiority between the two groups.

Table 8: Primary Safety Endpoint Results

Endpoint	Analysis	Study Group	Successful Procedures	Total Procedures	% Success	Difference (One-Sided Upper 95% Bound)	Endpoint Result
Primary Safety Endpoint	MITT	Control	148	164	90.24%	1.07% (6.93%)	Pass
		Investigational	140	157	89.17%		
Non-inferiority margin: 9%	PP	Control	145	160	90.63%	1.45% (7.35%)	Pass
		Investigational	140	157	89.17%		

Of the 321 Randomized Treatment subjects, 33 subjects (16 Control and 17 Investigational) had safety endpoint events as detailed in Table 9. The two groups were comparable in all primary safety events. When combined, cardiac perforation, tamponade or clinically significant pericardial effusion occurred in 1.83% (3/164) of the Control group and 2.55% (4/157) of the Investigational group. Treatment included a pericardiocentesis; however, none of these pericardial complications required surgery.

Table 9: Primary Safety Endpoint Events by Group

Adverse Event	Control Events (Subjects)	Investigational Events (Subjects)
AV Fistula	1 (1)	0 (0)
Arrhythmia (Severe Bradycardia)	0 (0)	1 (1)
Arterial/Venous Thromboembolic Events	0 (0)	1 (1)
Atypical atrial flutter	1 (1)	0 (0)
Cardiac arrest	0 (0)	1 (1)
Cardiac tamponade/perforation	3 (3)	4 (4)
Dizziness	0 (0)	1 (1)
Dyspnea	1 (1)	0 (0)
Fluid volume overload(i.e. diuresis, electrolyte imbalance) (Ablation Procedure)	0 (0)	1 (1)
Gastrointestinal	1 (1)	2 (2)
Genitourinary	0 (0)	1 (1)
Head, eyes, ears, nose, throat (HEENT)	2 (2)	0 (0)
Heart failure/ Pulmonary edema	0 (0)	2 (2)
Hematoma (Ablation Procedure)	0 (0)	1 (1)
Hypotension	0 (0)	1 (1)
Multiple symptoms	0 (0)	1 (1)
Myocardial infarction	0 (0)	1 (1)
Pulmonary	4 (4)	3 (3)
Pulmonary Vein Stenosis - Significant (>70%)	2 (2)	1 (1)
Rectus sheath hematoma	0 (0)	1 (1)
Sanguineous drainage	1 (1)	0 (0)
Total	**16 (16)**	**23 (17)**

Two Randomized Treatment subjects (one Control subject and one Investigational subject) died during the course of the clinical study. Both deaths were adjudicated by the Clinical Events Committee as not procedure-related.

Adverse effects that occurred in the PMA clinical study

Adverse effects are defined in Table 10 and reported in Table 11.

Table 10: Definitions of Adverse Effects

Term	Definition
Complication	A clinical complication is a clinical event that required an invasive intervention, injury, or death (e.g., surgical evacuation of a hematoma, lead dislodgment requiring lead repositioning, generator replacement, loss or abandonment of therapy).
Observation	A clinical observation is a clinical event that did not result in invasive intervention, injury, or death, and is not an unanticipated adverse event. Corrective actions were simple adjustments such as reprogramming of the pulse generator or antibiotic treatment of a pocket infection

Table 11: Ablation Related Adverse Effects

	Control N=167				Investigational N=159			
	Complications		Observations		Complications		Observations	
Adverse Event	N Events	N Patients (%)	N Events	N Patients (%)	N Events	N Patients (%)	N Events	N Patients (%)
Ablation Related Events	**13**	**13 (7.8)**	**30**	**21 (12.6)**	**20**	**14 (8.8)**	**48**	**36 (22.6)**
AV Fistula	1	1 (0.6)	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)
Allergic reaction (Ablation Procedure)	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	1	1 (0.6)
Anesthesia/Sedation related complication (Ablation Procedure)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	3	1 (0.6)
Arrhythmia (Ablation Procedure)	1	1 (0.6)	1	1 (0.6)	3	3 (1.9)	1	1 (0.6)
Atrial tachycardia	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)
Atypical atrial flutter	1	1 (0.6)	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)
Back discomfort	1	1 (0.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Breathing difficulties	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	0	0 (0.0)
Cardiac arrest	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)
Cardiac tamponade/perforation	3	3 (1.8)	0	0 (0.0)	4	4 (2.5)	0	0 (0.0)
Chest pain	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	3	3 (1.9)
Dyspnea on exertion	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)
Edema (Ablation Procedure)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (1.3)
Fever	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	1	1 (0.6)
Fluid volume overload(i.e. diuresis, electrolyte imbalance) (Ablation Procedure)	0	0 (0.0)	0	0 (0.0)	2	2 (1.3)	0	0 (0.0)
Gastroparesis (Ablation Procedure)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)
Genitourinary	0	0 (0.0)	3	3 (1.8)	2	2 (1.3)	4	3 (1.9)
Groin pain	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)
Heart failure	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)
Hematoma (Ablation Procedure)	0	0 (0.0)	5	5 (3.0)	1	1 (0.6)	8	7 (4.4)
Hemorrhage (Ablation Procedure)	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	2	2 (1.3)

	Control N=167				Investigational N=159			
	Complications		Observations		Complications		Observations	
Adverse Event	N Events	N Patients (%)	N Events	N Patients (%)	N Events	N Patients (%)	N Events	N Patients (%)
Hypotension (Ablation Procedure)	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	0	0 (0.0)
Long QT	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	0	0 (0.0)
Multiple symptoms	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)
Non-toxic LLE cellulitis	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	0	0 (0.0)
Pain neuromuscular/non cardiovascular (Ablation Procedure)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (1.3)
Pericardial Effusion (Ablation Procedure)*	1	1 (0.6)	3	3 (1.8)	0	0 (0.0)	5[@]	5 (3.1)
Pericarditis (Ablation Procedure)	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)
Peripheral neuropathy	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	0	0 (0.0)
Pleuritis (Ablation Procedure)	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	0	0 (0.0)
Pulmonary	2	2 (1.2)	3	3 (1.8)	2	2 (1.3)	1	1 (0.6)
Pulmonary Vein Stenosis - Mild or Moderate (<70%)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	4	4 (2.5)
Pulmonary Vein Stenosis - Significant (>70%)	2	2 (1.2)	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)
Rectus sheath hematoma	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)
Sanguineous drainage	1	1 (0.6)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)
Sore throat	0	0 (0.0)	3	3 (1.8)	0	0 (0.0)	0	0 (0.0)
Swollen groin	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	2	2 (1.3)
Tachycardia (Ablation Procedure)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)
Typical atrial flutter	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	1	1 (0.6)
Vagal denervation symptoms	0	0 (0.0)	1	1 (0.6)	0	0 (0.0)	0	0 (0.0)
Visual Blurring/Disturbances (Ablation Procedure)	0	0 (0.0)	0	0 (0.0)	0	0 (0.0)	1	1 (0.6)

*Non-significant pericardial effusion, no hemodynamic compromise, no action taken

[@]One subject experienced a perforation/tamponade both reported as an initial primary adverse event and also reported as a pericardial effusion without any intervention 19 days post procedure.

PV Stenosis

A PV Imaging Sub-study was conducted to evaluate the risk of pulmonary vein stenosis after PVI using RF ablation with open-irrigated catheters. A total of 107 Randomized subjects received a second randomization to participate in the sub-study. All 107 PV Imaging Sub-Study subjects underwent a baseline cardiac MRI or spiral CT scan prior to the index procedure and 86 subjects (44 Control and 42 Investigational) completed a follow-up scan using the same test as was performed for the pre-ablation scan. In addition, 3 Investigational subjects underwent PV imaging studies for suspected symptoms. All scans were reviewed and evaluated for degree of PV narrowing by an independent core lab. Significant pulmonary stenosis (≥ 70%) was detected in 2 (1.2%) Control subjects and one (0.6%)

Investigational subject. Pulmonary vein stenosis on a per-vein basis is shown in Table 12 below.

Table 12: PV Imaging – Results for all Randomized Subjects

Pulmonary Vein	PV Stenosis Severity	Control N = 44	Investigational N = 45
LC	None	2 (25)	4 (23.5)
	<50 (Mild)	5 (62.5)	13 (76.5)
	50-70 (Moderate)	1 (12.5)	0 (0.0)
LIPV	None	7 (20)	5 (17.9)
	<50 (Mild)	26 (74.3)	21 (75)
	50-70 (Moderate)	0 (0.0)	2 (7.1)
	>=70 (Significant)	2 (5.7)	0 (0.0)
LSPV	None	15 (42.9)	11 (39.3)
	<50 (Mild)	20 (57.1)	17 (60.7)
RIPV	None	18 (40.9)	19 (42.2)
	<50 (Mild)	26 (59.1)	24 (53.3)
	50-70 (Moderate)	0 (0.0)	2 (4.4)
RMVP	None	8 (66.7)	6 (54.5)
	<50 (Mild)	4 (33.3)	5 (45.5)
RSPV	None	19 (43.2)	14 (31.1)
	<50 (Mild)	25 (56.8)	30 (66.7)
	>=70 (Significant)	0 (0.0)	1 (2.2)

Death Summary

No study subject died within 30 days of the index catheter ablation procedure. There was one reported death in each treatment group during 12-month follow-up. A 60-year-old male Investigational subject was found deceased at home 6 months after catheter ablation. The event was determined to be unrelated to the study devices or ablation procedure. The death in the Control group was a 68-year old female with a past medical history significant for diabetes mellitus, coronary artery disease, and symptomatic PAF. She underwent an uncomplicated and successful PV isolation procedure using the control device. She was noted to be in atrial fibrillation at the 2-month follow-up visit and underwent elective cardioversion. She presented with nausea, vomiting, and diarrhea 2 weeks later and was hospitalized for diabetic ketoacidosis. The patient died the following day (81 days after the index procedure) with septic shock. An autopsy was not performed. The event was determined by the CEC as not related to the device or ablation procedure.

Cardiac Tamponade/Perforation

Procedure-related cardiac tamponade/perforation was the most common primary safety event in both groups occurring in 1.83% (3/164) of the Control subjects and 2.55% (4/157) of the Investigational subjects. These pericardial complication rates are slightly higher than the expected rate but within the published rates (0.2-5%) of cardiac tamponade in radiofrequency catheter ablation of AF. In a worldwide survey, Cappato et al. reported 1.3% tamponade rate in 20,825 AF ablation procedures on 16309 patients.[1] In the SMART-AF study, catheter ablation using the Smart Touch catheter was associated with a 2.5% incidence of cardiac tamponade.[2] AF ablation procedure-related tamponade is not universally caused by mechanical perforation or overheating with ablation catheters. Atrial puncture during transseptal LA access is also known to be a common cause of cardiac tamponade. Finally, none of the Roll-In subjects had acute cardiac tamponade/perforation. Combining the results from both Randomized and Roll-In cohorts, tamponade/perforation occurred in 1.80% and 1.88% of the Control and Investigational subjects, respectively.

Heart Failure/Pulmonary Edema/Fluid Overload

Procedure-related serious adverse events of heart failure/pulmonary edema/fluid overload occurred in none of the Control subjects and 1.91% (3/157) of the Investigational subjects. The higher rate of pulmonary edema observed in the Investigational subjects may be explained by a difference in peri-procedrual fluid management. Since the ThermoCool SF catheter, which has lower prescribed irrigation rates, was used in 42.1% of the Control subjects, the mean total fluid infusion was lower in the Control group vs. the Investigational group (1.18 ± 0.64 vs. 1.34 ± 0.71 liters). Pulmonary edema following AF ablation is an uncommon but well-recognized complication. For comparison, AF ablation using the TactiCath catheter was associated with a 1.3% incidence of acute pulmonary edema in the TOCCASTAR study.[3]

2. Effectiveness Results

The analysis of effectiveness was based on the Modified Intention-to-Treat (MITT) cohort of 321 evaluable patients at the 12-month time point. Subjects that withdrew or died with no primary effectiveness event or met pre-defined criteria for incomplete follow-up data were classified as having incomplete data. Multiple imputation methods were used to determine primary effectiveness endpoint outcomes for these subjects in the MITT analysis. The results of the Primary Effective Endpoint are shown in Table 13. The chronic success rate was 65.85% in the Control group and 64.97% in the Investigational group. The difference in the chronic success rates between the Control Group and the Investigational Group was 0.89%. The upper 95% confidence bound of 9.54% was less than the non-inferiority margin of 15%, demonstrating non-inferiority between the two groups. The results of the Per-Protocol and Supplementary Modified Intention-

to-Treat analyses were consistent with the MITT analysis and support the effectiveness of the Blazer OI Catheter for the treatment of PAF.

Table 13: Primary Effectiveness Endpoint Results

Endpoint	Analysis	Study Group	Successful Procedures	Total Procedures	% Success	Difference (One-Sided Upper 95% Bound)	Endpoint Result
Chronic Success Non-inferiority margin: 15%	MITT	Control	108	164	65.85%	0.89% (9.54%)	Pass
		Investigational	102	157	64.97%		
	sMITT	Control	98	152	64.47%	0.09% (9.13%)	Pass
		Investigational	94	146	64.38%		
	PP	Control	95	148	64.19%	-0.19% (8.92%)	Pass
		Investigational	94	146	64.38%		

Secondary Effectiveness Endpoint

An acute success was defined as a subject that successfully had all clinically relevant PVs electrically isolated, by demonstration of entrance block at a minimum and no evidence of exit conduction with the Investigational or Control catheter only. The objective of the Secondary Effectiveness Endpoint was to demonstrate that the proportion of subjects with acute success in the Investigational group was non-inferior to that in the Control group.

The Modified Intention-to-Treat analysis of the Secondary Effectiveness Endpoint included all 321 Randomized Treatment subjects (164 Control and 157 Investigational). Based on the Modified Intention-to-Treat analysis, the acute success rate was 99.39% in the Control group and 98.73% in the Investigational group. The difference in the acute success rates between the Control Group and the Investigational Group was 0.66%. The upper 95% confidence bound of 4.75% was less than the non-inferiority margin of 10%, demonstrating non-inferiority between the two groups.

Table 14: Secondary Effectiveness Endpoint Results

Endpoint	Analysis	Study Group	Successful Procedures	Total Procedures	% Success	Difference (One-Sided Upper 95% Bound)	Endpoint Result
Acute Procedural Success Non-inferiority margin: 10%	MITT	Control	163	164	99.39%	0.66% (4.75%)	Pass
		Investigational	155	157	98.73%		
	PP	Control	159	160	99.38%	0.65% (4.78%)	Pass
		Investigational	155	157	98.73%		

Single Procedure Success

Single procedure success was not a pre-specified effectiveness endpoint in the ZERO-AF study. However, a higher proportion of Investigational patients (16/157, 10.2%) than Control patients (5/164, 3.1%) underwent repeat catheter ablation in the 3-month blanking period. These repeat ablation procedures were done according to the clinical investigational plan. Further statistical analysis did not identify any significant impact on the study outcome. When all repeat procedures were counted, the single procedure success is 58.6% for the Investigational patients and 64.02% for the Control patients.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes:

- Sex (Female vs. Male);
- Geography (International vs. United States);
- Age at time of consent (< 60 years vs. ≥ 60 years); and
- Periprocedural anticoagulation status (bridged to Low Molecular Weight heparin pre-ablation vs. ablated fully anticoagulated).

Gender Subgroup Analysis

A gender analysis was performed to assess the differences in primary safety and effectiveness endpoints between female and male subjects. As shown in Table 15 below, there was no gender discrepancy in either primary safety success or primary effectiveness success. In the female subgroup, the 95% UCB of the differences in primary safety and effectiveness endpoints between the Control and Investigational groups exceeds the non-inferiority margins. However, the study was not powered to determine gender-specific safety and effectiveness profiles of the study device.

Table 15: Gender Subgroup Analysis

Endpoint	Statistic	Female (N=122)	Male (N=199)	p-value
Primary Safety Endpoint	Investigational Group Success Rate Control Group Success Rate Difference (Upper 95% CI)	Investigational: 52 (88.1%) Control: 58 (92.1%) Difference: 3.9 (13.2)	Investigational: 88 (89.8%) Control: 91 (89.1%) Difference: -0.7 (6.9)	0.50
Primary Effectiveness Endpoint	Investigational Group Success Rate Control Group Success Rate Difference (Upper 95% CI)	Investigational: 31(52.5%) Control: 38 (60.3%) Difference: 7.8(22.4)	Investigational: 71(72.4%) Control: 70 (69.3%) Difference: -3.1(7.5)	0.33

Age Subgroup Analysis

An age analysis was performed to assess the differences in both primary endpoints between subjects less than 60 years of age and subjects who were 60 years or older at the time of consent. A significant difference existed between the age subgroups for the Primary Safety Endpoint (p=0.055). The Investigational group had a

higher success rate than the Control group in the ≥ 60 subgroup while the Control group had a higher success rate than the Investigational group in the < 60 subgroup, resulting in a large difference in the Primary Safety success rates between subgroups. In the < 60 subgroup, the 95% UCB of the difference in each primary endpoint exceeded each respective non-inferiority margin. However, the study was not powered to determine age subgroup-specific safety and effectiveness profiles of the study device.

Table 16: Age Subgroup Analysis

Endpoint	Statistic	Age at consent < 60 years (N=135)	Age at consent >= 60 years (N=186)	p-value
Primary Safety Endpoint	Investigational Group Success Rate Control Group Success Rate Difference (Upper 95% CI)	Investigational: 54 (85.7%) Control: 68 (94.4%) Difference: 8.7 (17.3)	Investigational: 86 (91.5%) Control: 80 (87.0%) Difference: -4.5 (3.4)	0.055
Primary Effectiveness Endpoint	Investigational Group Success Rate Control Group Success Rate Difference (Upper 95% CI)	Investigational: 46 (73.0%) Control: 56 (77.8%) Difference: 4.8 (17.1)	Investigational: 56 (59.6%) Control: 52 (56.5%) Difference: -3.1 (8.7)	0.44

An additional analysis was performed to assess differences between the two age groups in catheter related events (Table 17). The analysis did not uncover an interaction between treatment and age group.

Table 17: Age Subgroup Sensitivity Analysis – Primary Safety Endpoint for Catheter Related Events

Endpoint	Statistic	Age < 60 (N=135)	Age > 60 (N=186)	p- value
Primary Safety Endpoint – Catheter Related Events	Investigational Group Success Rate Control Group Success Rate Difference (Upper 95% CI)	Investigational: 62 (98.4%) Control: 70 (97.2%) Difference: -1.2 (5.6)	Investigational: 91 (96.8%) Control: 89 (96.7%) Difference: -0.1 (5.7)	0.71

Geography Subgroup Analysis

Geography subgroup analyses showed no significant differences in the primary endpoints between subjects in the United States and International subjects. For US subjects, the 95% UCBs of the differences in primary endpoints between the Control subjects and the Investigational subjects were less than the non-inferiority margins.

Table 18: Geography Subgroup Analysis

Endpoint	Statistic	International (N=94)	United States (N=227)	p-value
Primary Safety Endpoint	Investigational Group Success Rate Control Group Success Rate Difference (Upper 95% CI)	Investigational: 42 (89.4%) Control: 44 (93.6%) Difference: 4.3 (14.1)	Investigational: 98 (89.1%) Control: 104 (88.9%) Difference: -0.2 (7.0)	0.51
Primary Effectiveness Endpoint	Investigational Group Success Rate Control Group Success Rate Difference (Upper 95% CI)	Investigational: 30 (63.8%) Control: 33 (70.2%) Difference: 6.4 (22.2)	Investigational: 72 (65.5%) Control: 75 (64.1%) Difference: -1.4 (9.0)	0.50

Peri-procedural Anticoagulation Status Subgroup Analysis

An analysis was performed to compare the results from subjects bridged with Low Molecular Weight (LMW) heparin to the results from subjects ablated fully anticoagulated for both primary endpoints. No significant differences exist between

these subgroups for the Primary Safety Endpoint (p=0.33) or the Primary Effectiveness Endpoint (p=0.97). For subjects who received peri-procedure LMW bridging therapy, the 95% UCBs of the differences in primary endpoints between the Control subjects and the Investigational subjects were higher than the non-inferiority margins. However, the subgroup is small (N=48) and cannot provide sufficient power to detect the true differences.

Table 19: Periprocedural Anticoagulation Status Subgroup Analysis

Endpoint	Statistic	Bridged to LMW Heparin Pre-Ablation (N=48)	Ablated Fully Anticoagulated (N=235)	p-value
Primary Safety Endpoint	Investigational Group Success Rate Control Group Success Rate Difference (Upper 95% CI)	Investigational: 20 (90.9%) Control: 21 (80.8%) Difference: -10.1 (7.8)	Investigational: 101 (90.2%) Control: 112 (91.1%) Difference: 0.9 (7.6)	0.33
Primary Effectiveness Endpoint	Investigational Group Success Rate Control Group Success Rate Difference (Upper 95% CI)	Investigational: 14 (63.6%) Control: 17 (65.4%) Difference: 1.7 (24.5)	Investigational: 74 (66.1%) Control: 84 (68.3%) Difference: 2.2 (12.3)	0.97

4. Pediatric Extrapolation

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

D. 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 137 investigators of which none were full-time or part-time employees of the sponsor and 3 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: 3;
- Proprietary interest in the product tested held by the investigator: 0; and
- 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 of the data.

XI. 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 Circulatory System 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.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The effectiveness outcomes of the ZERO-AF study demonstrate that the Blazer OI catheter is as effective as the FDA approved ThermoCool ablation catheters for the treatment of symptomatic paroxysmal atrial fibrillation at 12 months post ablation. The observed primary effectiveness success rate in the Blazer OI group was in line with other paroxysmal AF ablation studies for catheter-based technologies. Moreover, a high rate of acute electrical PV isolation was achieved with the Blazer OI catheter. These data provide a reasonable assurance that the Blazer OI catheter is effective for the treatment of symptomatic paroxysmal atrial fibrillation.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The ZERO-AF study met its primary safety endpoint by demonstrating that the Blazer OI catheter is as safe as the FDA approved ThermoCool ablation catheters with respect to the primary safety event rate as defined in the protocol. Moreover, the nature, rates, and types of adverse events observed in the ZERO-AF study are consistent with those expected clinically with AF ablation procedures. These data provide a reasonable assurance that the Blazer OI catheter is safe for the treatment of symptomatic paroxysmal atrial fibrillation.

C. Benefit-Risk Determination

The pre-clinical and clinical information presented supports that the probable benefits outweigh the probable risks when the Blazer Open-Irrigated Ablation Catheter is used for the treatment of symptomatic drug refractory paroxysmal atrial fibrillation according to the product labeling.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

D. Overall Conclusions

Pre-clinical testing of the Blazer Open-Irrigated Ablation Catheter included verification and validation testing (device, system, and software), biocompatibility of patient-contacting materials, sterilization, packaging and shelf life testing, and animal studies. The testing results confirmed that the Blazer OI Ablation Catheter met the product specifications and its design is suitable for the intended use of the device.

The results of the randomized controlled pivotal ZERO-AF study provided valid scientific evidence in support of safety and effectiveness of the devices for treating paroxysmal atrial fibrillation. A total of 339 symptomatic drug-refractory paroxysmal atrial fibrillation patients were randomized to atrial fibrillation ablation using the investigational Blazer Open-Irrigated Ablation Catheter or the control Biosense Webster ThermoCool catheters. Acute pulmonary vein isolation was achieved in 98.73% of Investigational subjects and 99.39% of the Control group. Chronic treatment success at 1 year was 64.97% in the Investigational group and 65.85% in the Control group. The 95% upper confidence bound of the difference was less than the pre-specified non-inferiority margin, and the study met the primary effectiveness endpoint. Freedom from primary safety failures was 89.17% in the Investigational group and 90.24% in the Control group. The 95% upper confidence bound of the difference was less than the pre-specified non-inferiority margin, and the study met the primary safety endpoint. Taken together, the study outcomes demonstrate that the Blazer Open-Irrigated Ablation Catheter is as safe and effective as the FDA approved ablation catheters for the treatment of paroxysmal atrial fibrillation.

The IntellaNav OI catheter is an incremental change to Blazer OI with an internal magnetic sensor added which allows it to be tracked magnetically via the Rhythmia Mapping System. The distal shaft, steering assembly, tip and ring electrodes are identical between the Blazer OI catheter and the IntellaNav OI catheter, the way in which the RF energy is delivered to the tissue is identical. The IntellaNav OI catheter is clinically equivalent to the Blazer OI catheter; therefore the results of the ZERO AF clinical study are directly applicable to the IntellaNav OI catheter.

In conclusion, the data in this application support the reasonable assurance of safety and effectiveness of the Blazer Open-Irrigated and IntellaNav Open-Irrigated Ablation Catheters when used in accordance with the indications for use.

XIII. CDRH DECISION

CDRH issued an approval order on December 21, 2017. The final conditions of approval are cited in the approval order.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. 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.

XV. REFERENCES

1. Cappato R, Calkins H, Chen SA, et al. *Updated Worldwide Survey on the Methods, Efficacy, and Safety of Catheter Ablation for Human Atrial Fibrillation*. Circulation:Arrhythmia and Electrophysiology. 2010; 3:32-38.

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3. Reddy VY, Dukkipati SR, Neuzil P, et al. A Randomized Controlled Trial of the Safety and Effectiveness of a Contact Force *Sensing Irrigated Catheter for Ablation for Paroxysmal Atrial Fibrillation: Results of the TOCCASTAR Study*. Circulation. 2015; 132(1): 907-15