SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:
Cardiac Radiofrequency (RF) Ablation System

Device Trade Name:
Therapy Cool Path Duo™ Ablation Catheter
Safire BLU Duo™ Ablation Catheter
1500T9-CP V1.6 Cardiac Ablation Generator

Applicant's Name and Address:
Irvine Biomedical, Inc.
a St. Jude Medical Company
2375 Morse Avenue
Irvine, California 92614 USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P110016

Date of FDA Notice of Approval: January 25, 2012

Expedited: Not Applicable

II. INDICATIONS FOR USE

The catheter is intended for use with the compatible Irrigation pump and 1500T9-CP Radiofrequency (RF) Generator at a maximum of 50 watts. The catheter is intended for creating endocardial lesions during cardiac ablation procedures (mapping, stimulation and ablation) for the treatment of typical atrial flutter.

III. CONTRAINDICATIONS

The Therapy Cool Path Duo™ Ablation Catheter and Safire BLU Duo™ Ablation Catheter are contraindicated for:

- Patients with active systemic infection
- Patients with intracardiac mural thrombus or those who have had a ventriculotomy or atriotomy within the preceding four weeks

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Therapy Cool Path Duo Ablation Catheter, Safire BLU Duo Ablation Catheter, and 1500T9-CP V1.6 Cardiac Ablation Generator labeling.

V. DEVICE DESCRIPTION

The Therapy Cool Path Duo Ablation Catheter, Safire BLU Duo Ablation Catheter, and 1500T9-CP V1.6 Cardiac Ablation Generator consist of:

Therapy Cool Path Duo Ablation Catheter is a sterile, single use 7F catheter that is constructed of thermoplastic elastomer material and four noble metal electrodes. This catheter has a through-lumen connected to open conduits at the 4mm tip electrode for heparinized saline irrigation during the ablation procedure. The tip curvature may be manipulated by the thumb control mechanism located on the handle at the proximal end of the catheter. The catheter manipulation is uni-directional. The catheter distal curve is indicated on the catheter label.

The Safire BLU Duo Ablation Catheter is a sterile, single use 7F catheter that is constructed of thermoplastic elastomer material and four noble metal electrodes. This catheter has a through-lumen connected to open conduits at the 4mm tip electrode for heparinized saline irrigation during the ablation procedure. The tip curvature may be manipulated by the thumb and forefinger control mechanism located on the handle at the proximal end of the catheter. The catheter manipulation is bi-directional. The catheter distal curve is indicated on the catheter label.

- Both Catheters connect to the 1500T9-CP (V1.6) RF Generator using an IBI 1641 connecting cable and also connect to the Cool Point Irrigation Pump.

- The Cool Point™ Irrigation Pump is a peristaltic pump that is intended for use in administration of irrigation solution into the patient through an open irrigated ablation catheter. The Cool Point™ Irrigation Pump is intended for use only with the Cool Point™ Tubing Set.

- The Cool Point™ Tubing Set is a sterile and single use device which provides access for the administration of fluids from a container. This tubing set is intended for use with the Cool Point™ Irrigation Pump only. The Cool Point™ Tubing set consists of a vented drip chamber with a spike, a pump head tubing section, and a pressure sensor with a jack connecting to the Cool Point™ Irrigation Pump and terminating in a rotating 3-way stopcock.

- The Cool Point™ Irrigation Pump and Cool Point™ Tubing Set were approved as accessory to 1500T9-CP generator under PMA P060019/S005.

- The 1500T9-CP V1.6 Cardiac Ablation Generator is a microprocessor-controlled RF generator that produces a continuous unmodulated radio frequency (RF) power output at 485 kHz. The front panel displays power output (W), measured tip electrode temperature (°C), impedance (Ω), and ablation duration. The generator display incorporates a visual indication to show whether an irrigated catheter and a compatible irrigation pump are connected and initialized. The physician may establish settings for the following parameters: target tip temperature, maximum impedance, maximum power output, and ablation time. The maximum power output can be set up to 50 Watts when a Duo catheter is connected. The power output is regulated by the measured tip temperature, and is limited to the user selected maximum power output. The generator has built-in safety features, which include automatic power shut-offs for RF power when RF power, impedance or temperature exceeds a target set value. When used with a Duo catheter, the generator will also shut off if the connected compatible irrigation pump alarms.

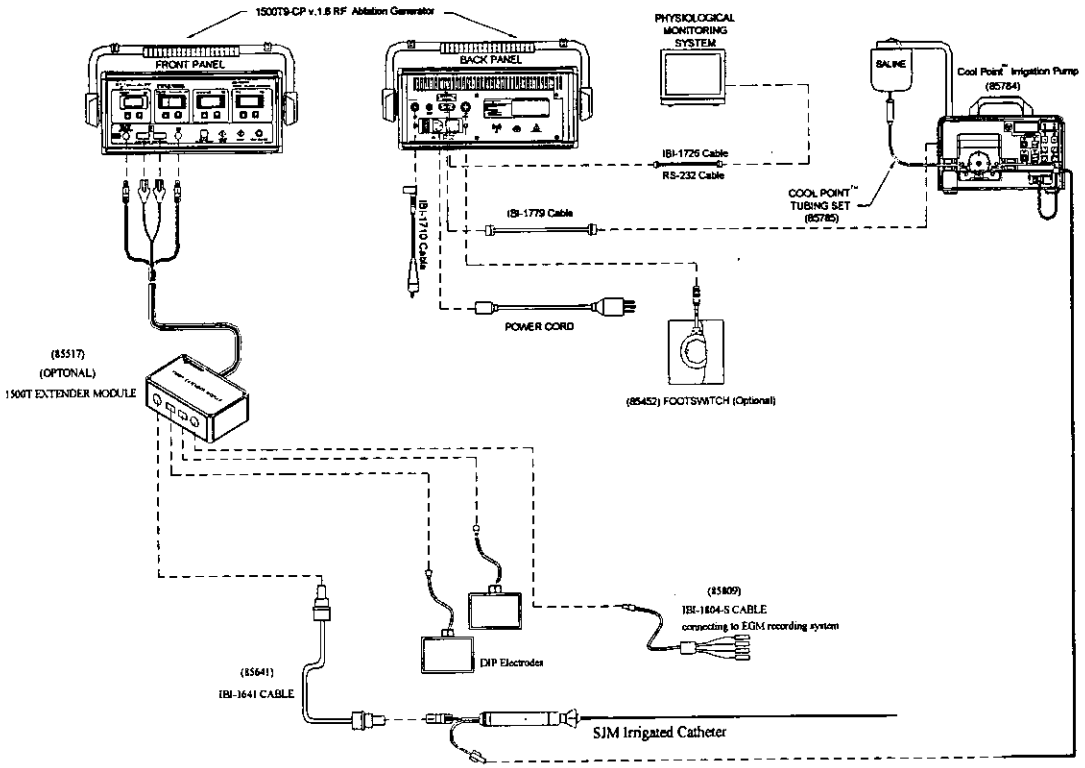
Other required and optional accessories include:

- IBI 1779 series cables for connecting the Generator to the compatible irrigation pump,
- IBI 1804-S cable for electrogram output,
- IBI 1641 cable for connecting the Generator to the Catheters,
- IBI 1710 cable for grounding the Generator chassis,
- Commercially available indifferent grounding pad and cable,
- IBI 1452 Optional foot switch,
- IBI 1726 connecting cable for connecting the Generator to the EP recording system,
- Optional 1500T extender module (20 foot extension connector)

A diagram of the catheters, RF generator, accessories, including how the system is interconnected is depicted in Figure 1 below:

Figure 1.

Set up diagram:
1500T9-CP v.1.6 RF Ablation Generator with 1500T Extender Module & Cool Point™ Irrigation Pump



VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of atrial flutter, including the following:

- 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

The Therapy Cool Path Duo Ablation Catheter and Safire BLU Duo Ablation Catheter have been marketed in the following regions or countries: European Union, Canada, Asia, and Australia.

The 1500T9-CP V1.6 Cardiac Ablation Generator has not been marketed in the United States or any foreign country.

There are no countries from which the Therapy Cool Path Duo Ablation Catheter or Safire BLU Duo Ablation Catheter have been withdrawn from marketing for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Abnormal vision
- Adult respiratory distress syndrome (ARDS)
- Air embolism
- Allergic reaction (anesthesia)
- Anaphylaxis
- Anemia
- Angina
- Arrhythmia
- Arterial/venous thrombus
- Atypical flutter
- Atrioventricular (AV) fistula
- Cardiac perforation/tamponade
- Cardiac thromboembolism
- Cerebrovascular accident (CVA)
- Chest pain/discomfort
- Complete heart block
- Congestive heart failure (CHF) exacerbation
- Component damage to Implantable Cardiac Defibrillator (ICD) or implantable pacemaker.
- Coronary artery dissection
- Coronary artery spasm
- Death
- Dislodgement of implantable cardioverter defibrillator or permanent pacing lead
- Dizziness
- Endocarditis

- Esophageal injury (fistula)
- Exacerbation of pre-existing atrial fibrillation (AF)as evidenced by hospitalization, cardioversion, or worsening of AF symptoms.
- Exacerbation of chronic obstructive pulmonary disease (COPD)
- Expressive aphasia
- Heart failure
- Hematoma (catheter insertion site)
- Hypotension
- Hemothorax
- Hypoxia
- Inadvertent AV block
- Increased phosphokinase level
- Infection/sepsis
- Laceration
- Local hematomas/ecchymosis
- Myocardial infarction
- Neck pain/back pain/groin pain related to the procedure.
- Obstruction or perforation or damage to the vascular system
- Palpitations
- Perforation (cardiac)
- Pericardial effusion
- Pericarditis
- Peripheral venous thrombosis
- Phrenic nerve damage
- Pleural effusion
- Pneumonia
- Pneumothorax
- Pseudoaneurysm
- Pulmonary edema
- Pulmonary embolism
- Radiation injury resulting in dermatitis (inflammation of the skin), erythema (redness), etc.
- Respiratory Depression
- Respiratory Failure
- Seizure
- Skin burns
- Syncope/near syncope
- Temporary complete heart block
- Thrombi
- Thromboembolism
- Transient ischemic attack (TIA)
- Unintended (in)complete AV, sinus node or other heart block or damage
- Vascular bleeding
- Vasovagal reactions

- Ventricular arrhythmia requiring defibrillation
- Vessel wall/valvular damage or insufficiency (i.e. new tricuspid regurgitation)

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

IX. SUMMARY OF PRECLINICAL STUDIES

Pre-clinical testing of the Therapy Cool Path Duo Ablation Catheter, Safire BLU Duo Ablation Catheter, and 1500T9-CP V1.6 Cardiac Ablation Generator included verification and validation testing (device level, system level, and software), biocompatibility of patient-contacting materials, sterilization, packaging and shelf life testing, and animal studies. Performance testing was conducted to demonstrate design integrity. All tests performed which were identified in standards or guidance documents were based on the product specification requirements. In the tests described below, the Therapy Cool Path Duo Ablation Catheter, Safire BLU Duo Ablation Catheter, and 1500T9-CP V1.6 Cardiac Ablation Generator were manufactured by trained manufacturing operators. "Pass" as used below denotes that the devices and system met established product specifications and/or performance criteria, or were in conformance with the requirements of the standards tested to. Testing results confirmed that the Therapy Cool Path Duo Ablation Catheter, Safire BLU Duo Ablation Catheter, and 1500T9-CP V1.6 Cardiac Ablation Generator met the product specifications.

A. In Vitro Bench Studies

Table 1 below summarizes the bench testing for the Therapy Cool Path Duo Ablation Catheter including reliability, mechanical and electrical integrity, and performance test results.

Table 1. In vitro Engineering Studies with Therapy Cool Path Duo

Test	Acceptance Criteria	Result
Thermocouple Temperature Response	Thermal Response < 3 seconds, Thermal Accuracy < 3° C	Pass
Inflow Pressure and Flow Rate Test	Catheter will maintain a pressurized lumen of 25 psi for 30 seconds	Pass
Noise Test	Electrocardiogram (ECG) signals with no excessive interfering Noise	Pass
Di Electric Strength Break Down Test	No electric breakdown at 500 VAC for 60 seconds	Pass
Tissue Temperature Study	For characterization purposes to access lesion dimension as well as tissue temperature at different depths	Pass
Fluid Pressurization Test	No leaks in catheter lumen at a pressure of 10 PSI for a duration of 30 Seconds	Pass
Buckling	The buckling load shall be less than 200g	Pass
Flow Test	The pump flow rate shall be within ±10% of the flow rate at the Cool Path Duo tip at a flow rate of 13ml/min and a maximum pressure of 15psi	Pass

Test	Acceptance Criteria	Result
Deflection / Flexion and Insertion / Withdrawal	After 40 repetitive deflection cycles, the catheter shall demonstrate electrical continuity and joint integrity (note: joint integrity is tested under Tip Bond). Note: The deflection testing was conducted after 5 insertion and withdrawal cycles in the introducer sheath.	Pass
Torque	The catheter shall withstand 2 complete rotations (720°) or 1.6 ozf-in before mechanical failure occurs	Pass
Pull & De-Curve	Pull force (non-deflected): <1 lb. Decurving force (fully deflected): < 2 lbs.	Pass
Air Pressurization Test	No pressure drop greater than 0.2 psi at a test pressure of 25psi and test time of 30 seconds.	Pass
High Freq Leakage Current	Must pass ANSI/AAMI HF 18 section 4.2.5.2 requirements: < 4.02 mA/cm	Pass
Tip Bond	Tip to distal tubing should withstand a minimum of 3.37 lbs (15N) pull force with no mechanical failure per ISO 10555-1, Section 4.5.	Pass
Handle to Shaft Bond	3.37 lbs (15N) pull force with no mechanical failure per ISO 10555-1, Section 4.5.	Pass

Table 2 below summarizes the bench testing for the Safire BLU Duo Ablation Catheter including reliability, mechanical and electrical integrity, and performance test results.

Table 2. In Vitro Engineering Studies with Safire BLU Duo

Test	Acceptance Criteria	Result
Thermal Accuracy & Response Test	- Tip temperature accuracy must be within ± 3°C of the reference thermocouple temperature. The results of X ± (K*σ) must be within ± 3°C of the reference thermocouple temperature. - The pre-ablation and post-ablation response time of the catheter must be less than or equal to 3 seconds. The results of X+ (K*σ) must be ≤ 3 seconds.	Pass
Catheter Flow Test	- The inflow pressure must be equal to or less than 15 PSI when the catheter is in the fully deflected position (without the rubber stopper). The results of X + (K*σ) must be less than 15 PSI. - The measured flow rate of the catheters shall be within ± 10% of the average of 5 data points for flow without catheters at settings of 13 ml/min. The results of X± (K*σ) must be within ± 10% of 13 ml/min.	Pass
Fluid Lumen Pressure Test	- The catheter shall not leak liquid when pressurized to 25 psi for 30 seconds.	Pass
Buckling Test	- The buckling force must be < 96 g. The results of X+ (K*σ) must be < 96g.	Pass
Deflection and Flexion Test	- Deflection Test: Catheters must pass curve template and electrical continuity before and after deflection and flexion cycles. Catheters must be able to deflect 40 times. During deflection, Auto-Lock must function properly. - Visual Inspection: Catheter must be free from exposed braids, bumps, or breaks/cracks in tubing, after 40 deflections and flexion cycles. - HIPOT: Must pass HIPOT in both directions.	Pass

Test	Acceptance Criteria	Result
Insertion and Withdrawal test	- Visual Inspection: Catheter must be free from damage to shaft, band, and adhesives after insertion and withdrawal from an 8F introducer sheath.	Pass
Torque Test	- The electrical integrity of the catheter sample set must withstand torque up to 1.6 ozf-in. measured on the torque gauge or 720° of rotation. - During visual inspection the catheter sample set must be free from exposed braid, bumps, or breaks/cracks in tubing, after torque.	Pass
High Frequency Leakage Current Test	- High frequency leakage current shall not exceed 4.02mA/cm of catheter length.	Pass
Lumen Bond Test	- Tip Electrode – Lumen Bond must be > 3.37lbs. The results of $X-(K*\sigma) \geq 3.37$ lbs. -Tip Electrode – Combination Bond must be > 3.37lbs. The results of $X-(K*\sigma) \geq 3.37$ lbs.	Pass
Tip Bond Test	- Tip bond must withstand a minimum of 3.37 lbs. before mechanical failure occurs. The results of $X- (K*\sigma)$ must be greater than 3.37 lbs.	Pass
Handle to Shaft Bond Test	- Handle to Shaft Bond: Must withstand a minimum of 3.37 lbs. before mechanical failure occurs. - The results of $X- (K*\sigma)$ must be greater than of 3.37 lbs.	Pass
Catheter Tubing Pressure Test	- Catheter (subassembly) shall not leak air > 0.050 PSI when a positive pressure of 6.2 PSI is applied to the outside of the distal portion of the catheter shaft and maintained for 20 seconds.	Pass
Meat Ablation (Electrical Short) Test	- The catheter should only ablate through the tip electrode and not any band electrodes.	Pass
Electrical Connector Test	- Retention Force: Connector shall withstand 40N/min without either the end cap from the handle or the connector from the end cap separating. - Impulse: Connector shall maintain electrical continuity and temperature function after being subjected to an impulse resulting from a 260 gram mass dropped from a height of 25 cm.	Pass
Pull and De-Curve Test	- The pull force shall be ≤ 1 lb. - The de-curving force shall be ≤ 2 lbs. - The results of $X + (K*\sigma)$ must be less than or equal to 1 lb. and 2 lbs.	Pass

Biocompatibility Testing

Biocompatibility testing of the Duo was conducted in accordance with the ISO 10993 "Biological evaluation of medical devices" standard and FDA/CDRH/ODE Blue Book Memorandum G95-1, "Use of International Standard ISO-10993" using a representative catheter. Based on ISO-10993, the catheters are externally communicating devices, which contact circulating blood for "limited" duration (less than 24 hours). A summary of the results are reported in Table 3: Biocompatibility Testing Summary and demonstrate that the Therapy Cool Path Duo Ablation Catheter and Safire BLU Duo Ablation Catheter are biocompatible as per ISO 10993.

Table 3: Biocompatibility Testing Summary

Test	Result
Cytotoxicity Using the ISO MEM Method	Pass
Sensitization Using the ISO Maximization Test	Pass
Irritation or Intracutaneous Reactivity Using ISO Intracutaneous Study	Pass
Systemic Toxicity Using the ISO Test (Intravenous and Intraperitoneal)	Pass
USP Pyrogen Study (Material-Mediated Pyrogenicity)	Pass
Hemolysis and Coagulation Study (ASTM Blood Compatibility Method)	Pass
In-Vivo Thromboresistance Study	Pass
C3a Complement Activation Assay	Pass
SC5b-9 Complement Activation Assay	Pass
C5 Complement Activation Assay	Pass

Patient contacting materials of the Therapy Cool Path Duo Ablation Catheter and Safire BLU Duo Ablation Catheter are listed in Table 4 below:

Table 4: List of Blood/Fluid Contact Components & Materials

Description	Proposed Unidirectional Variant Catheter	Proposed Bidirectional Variant Catheter	Patient Contact
Tip and Band Electrodes	Platinum -Iridium	Platinum-Iridium	Direct Tissue and Blood
Catheter tubing	Pebax	Pebax	Direct Tissue and Blood
Internal Lumen	Polyimide	Polyimide	Fluid contact indirect
Tip and Band Adhesive	Loctite, Urethane	FDA2 Epoxy, Urethane	Direct Tissue and Blood
Luer/Hemo Hub Component	Polycarbonate	ABS and Pebax	Fluid contact indirect

B. Animal Studies

Acute and Chronic Good Laboratory Practice (GLP) *in vivo* animal testing was conducted using the Therapy Cool Path Duo Ablation Catheters and Safire BLU Duo Ablation Catheters in conjunction with an SJM RF ablation generator. Testing demonstrated that catheters successfully delivered RF energy to target endocardial locations in canine and porcine tissue. Creation of myocardial lesions was verified in various cardiac locations at multiple ablation parameters including at maximum power & maximum temperature settings. There were no procedural complications, such as stroke, embolism, myocardial infarction, myocardial perforation resulting in cardiac tamponade, pulmonary vein stenosis, or esophageal injury, with any of the test subjects in the *in vivo* GLP testing. A summary of the *in vivo* animal studies is presented in Table 5.

Table 5: *In vivo* animal studies

Animal Model	Procedure	Number of Animals	Catheter
Canine	Acute	3	Therapy Cool Path Duo Ablation Catheter
Porcine	Acute	4	
Canine	Chronic	3	
Porcine	Chronic	6	
Canine	Chronic	2	Therapy Cool Path Duo Ablation Catheter and Safire BLU Duo Ablation Catheter
Porcine	Chronic	6	

C. Additional Studies

Sterilization, Packaging, and Shelf Life

The Therapy Cool Path Duo™ Ablation Catheters and Safire BLU Duo™ Ablation Catheters are supplied sterile, single use, and are ready for use. The 1500T9-CP Cardiac Ablation Generator is not sterile, is reusable, and is placed in the non-sterile field during the procedure. The catheters are sterilized using ethylene oxide (EO) sterilant gas to a sterility assurance level (SAL) of 10^{-6}. The sterilization cycle uses the same process as for the current irrigated catheters and is validated according to *ISO 11135-1:2007, Medical devices – Validation and routing control of ethylene oxide sterilization, Method C.* Adoption of the catheters into the current SJM sterilization cycle is supported by resistance study data and formal product assessment. Catheters meet the ISO allowable limits for sterilant gas residuals as set forth in ISO 10993-7 *Biological Evaluation of Medical Devices – Part 7: Ethylene oxide sterilization residuals.* Catheters are routinely tested for pyrogens of non-material mediated origin and meet the USP criteria for devices in contact with blood.

The packaging materials are commonly used throughout the medical device industry and are the same as those used in currently approved devices (P060019/S002 and S009). The device is packaged in a double sterile barrier system consisting of a molded tray with a Tyvek lid and a Tyvek/Mylar pouch.

Expiration dating is 6 months for the Therapy Cool Path Duo™ Ablation Catheter and 3 years for the Safire BLU Duo™ Ablation Catheter.

Software

The RF Generator utilizes non-volatile, preprogrammed firmware. During development, the firmware was tested independently and then integrated into the hardware and tested at the system level. The 1500T9-CP V1.6 RF Generator uses version 1.6 (V1.6) software. Software validation and verification testing was conducted and demonstrates that the software-controlled 1500T9-CP RF Generator adequately detects, controls, and interfaces with the connected catheter and compatible irrigation pump and accessories

X. SUMMARY OF PRIMARY CLINICAL STUDY

The sponsor performed a clinical study to establish a reasonable assurance of safety and effectiveness of creating endocardial lesions during cardiac ablation procedures (mapping, stimulation and ablation) with the Therapy Cool Path Duo Ablation Catheter and 1500T9-CP Cardiac Ablation Generator for the treatment of typical atrial flutter in the U.S. and Canada under IDE # G090109, the Duo FLAIR Study. 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 treated between October 21, 2009 and July 19, 2010. The database for this PMA reflected data collected through January 24, 2011 and included 188 patients. There were 22 investigational sites.

The study was a prospective, multi-center, open-label, non- randomized, clinical study. All patients, who signed the consent form and who were verified to meet the inclusion/exclusion criteria, received ablation therapy for typical atrial flutter using the Duo catheter. Line-level historical data from PMA # P060019 (Therapy Cool Path Catheter Ablation System study) was used for control comparisons in this study. The study was designed to demonstrate that safety and effectiveness of the Therapy Cool Path Duo catheter was equivalent (not inferior) to that of the Therapy Cool Path catheter (a legally marketed ablation catheter approved for the treatment of typical atrial flutter).

Clinical Endpoints

Primary Safety
Primary safety was defined as the incidence of composite, serious adverse events (SAEs) within 7 days post-procedure, regardless of whether a determination can be made regarding device relatedness.

Primary Effectiveness
Primary effectiveness or acute success was defined as the achievement of bidirectional block in the cavo-tricuspid isthmus and non-inducibility of typical atrial flutter at least 30 minutes following the last RF application with the investigational catheter.

Secondary Effectiveness
Secondary effectiveness or chronic success was defined as freedom from recurrence of typical atrial flutter up to three months post ablation. Repeat ablations, new medication or increase in the dosage of existing class I/III anti-arrhythmic medication for typical atrial flutter during the three month follow-up were considered chronic failures. Acute failures were counted as chronic failures.

Sample Size

The required study sample size was determined based on the two primary endpoints. Sample sizes were conservatively calculated for two sample tests of non-inferiority of proportions with SAS PROC POWER version 9.2. Calculations are based on a one-sided 5% level of significance and 80% power.

Primary safety (Procedural safety)
A non-inferiority limit of 8.0% (δ =0.08), and a procedural safety rate of 8.0% for both the Duo system (test) and the Cool path system (control) results in a sample size of 120 subjects to be treated with the Therapy Cool Path Duo system to be compared to the 174 subjects treated with the Cool Path catheter for whom primary safety data is available.

Primary effectiveness (Acute Success)
A non-inferiority limit of 7.5% (δ =0.075), and an acute success rate of 92.5% for both the Therapy Cool Path Duo system (test) and the Cool Path system (control) results in a sample size of 140 subjects to be treated with the Therapy Cool Path Duo catheter to be compared to the 174 subjects treated with the Cool Path catheter for whom acute success data is available.

The maximum required sample size for the Therapy Cool Path Duo group to perform the above tests was 140 subjects for the primary endpoints. However, based on statistical, clinical, and logistical considerations, a sample size of 169 evaluable patients was planned. This would supply approximately 85% power for the two endpoints. After adjusting for 10% attrition, the total sample size of the study (i.e. the minimum number of enrolled patients treated with the Therapy Cool Path Duo system) was determined to be 188 subjects.

Hypothesis Testing

The hypothesis tests for the primary endpoints and the secondary effectiveness endpoint was formulated as follows:

Primary safety (Procedural safety)
For the primary safety hypothesis:
H_0: $\pi 1 - \pi 2 \geq \delta$
H_A: $\pi 1 - \pi 2 < \delta$
where $\pi 1$ and $\pi 2$ are the proportions of patients with procedural safety events in the Therapy Cool Path Duo and Cool Path groups respectively. The non-inferiority limit was set at 8.0% (δ=0.08). The test will be performed at a one-sided 5% level of significance. The null hypothesis would be rejected if the one-sided 95% confidence limit for the difference in proportions was less than the non-inferiority limit of 0.08.

Primary effectiveness (Acute success)
For the primary effectiveness hypothesis:
H_0: $\pi 2 - \pi 1 \geq \delta$
H_A: $\pi 2 - \pi 1 < \delta$
where $\pi 1$ and $\pi 2$ are the proportions of patients with acute success in the Therapy Cool Path Duo and Cool Path groups respectively. The non-inferiority limit was set at 7.5% (δ=0.075). The test will be performed at a one-sided 5% level of significance. The null hypothesis will be rejected if the one-sided 95% confidence limit for the difference in proportions was less than the non-inferiority limit of 0.075.

Secondary effectiveness (Chronic success)
For the secondary effectiveness hypothesis:
H_0: $\pi 2 - \pi 1 \geq \delta$
H_A: $\pi 2 - \pi 1 < \delta$
where $\pi 1$ and $\pi 2$ are the proportions of patients with chronic success in the Therapy Cool Path Duo and Cool Path groups respectively. The non-inferiority limit was set at 12% (δ=0.12). A rate of 78.5% was observed for the Cool Path group and a similar rate was expected for the Therapy Cool Path Duo group. The test was performed at a one-sided 5% level of significance. The null hypothesis would be rejected if the one-sided 95% confidence limit for the difference in proportions was less than the non-inferiority limit of 0.12. The confidence interval for the difference in proportions was based on the normal approximation to the binomial distribution, i.e. Wald confidence limits. This is appropriate given the relatively large sample size and the expected event rates.

Success/Failure Criteria
Overall study success is defined as the rejection of the null hypothesis for both the primary safety and the primary effectiveness endpoint.

External Evaluation Group

Clinical Event Committee
The Clinical Event Committee (CEC) consisted of a medical monitor who was a practicing electrophysiologist. The CEC adjudicated reported adverse events for the study. The CEC was appointed prior to study enrollment and was independent from the sponsor and participating investigators. The CEC member completed financial disclosure and was cleared of significant conflicts of interests with the sponsor. In addition the member was not involved in the conduct of the trial in any other role than that of CEC.

Data Safety Monitoring Board
An independent Data Safety and Monitoring Board (DSMB) which consisted of two practicing electrophysiologists, one practicing cardiologist and one biostatistician, was established. All members were independent from the sponsor and the

participating investigators. DSMB members completed financial disclosures and were cleared of significant conflicts of interests with the sponsor. In addition members could not be involved in the conduct of the trial in any other role than that of DSMB. The DSMB reviewed the progress of the clinical study, including CEC adjudicated adverse events. The members of CEC and DSMB did not overlap. The DSMB was established to make recommendations regarding the continuation, suspension or termination of this clinical study.

The following key areas evaluated by the DSMB to determine if the study is suspended or terminated were:

- Occurrence of unanticipated adverse device effects
- Occurrence of serious adverse events as defined in the protocol
- Safety and effectiveness trends
- Benefits versus risks of the study

Control Group

The control group was historical data from a prospective, multicenter, randomized pivotal clinical study for the evaluation of safety and effectiveness of the Therapy™ Cool Path™ Ablation Catheter System for the treatment of typical atrial flutter, a legally marketed alternative approved under PMA # P060019. One hundred and seventy four (174) subjects from this study were used as the control group.

Design Discussion

Subsequent to the approval of the Therapy Cool Path Ablation Catheter, a modified version of this catheter, the Therapy Cool Path Duo Ablation Catheter, was designed. This modified catheter was similar in terms of the design and the functionality to the Cool Path catheter. The Therapy Cool Path Duo Ablation catheter is different in that the tip includes 12 irrigation ports (6 on the distal end of the tip and 6 on the proximal end of the tip) as opposed to the 6 distal irrigation ports in the Cool Path catheter.

Considering the design similarities between the proposed Duo catheter and the approved Cool Path catheter, a clinical study design which used line-level data from the Cool Path PMA as a historical control was formulated. In order to achieve the comparability with the historical control, similar inclusion/ exclusion criteria, study methods, follow up duration and endpoints were used in the proposed clinical study. In addition, FDA guidance document on "Clinical Study Design For Catheter Ablation Devices for Treatment of Typical Atrial Flutter" (issued on August 05, 2008), and the response from the FDA on the IDE application were used to finalize the study design.

Overall, this design was thought to be appropriate because this study:

- Utilized standard, widely used methods for the assessment of the primary endpoints,

- Utilized historical line-level data from a control device which was similar in design, operation and intended use when compared to the proposed device, and
- Was powered, in terms of sample size, to establish the safety and effectiveness of the Therapy Cool Path Duo catheter.

There were two differences between the definition of chronic success used in the Cool Path and Duo FLAIR studies:

1) In the Cool Path study, subjects who were acute failures were not considered as chronic failures. In the Duo FLAIR study, acute failures were considered as chronic failure.

2) In the Cool Path study, subjects who received new or increased dosage of an existing anti-arrhythmic medication (irrespective of arrhythmia) were considered chronic failures. In the Duo FLAIR study, only those subjects who received new or increased dosage of an existing anti-arrhythmia medication specific to typical atrial flutter were considered chronic failures.

Clinical Inclusion and Exclusion Criteria

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

- A signed written Informed Consent
- Presence of typical atrial flutter (cavo-tricuspid isthmus dependent)
- If subjects are receiving antiarrhythmic drug therapy (Class I or Class III AAD) for an arrhythmia other than typical atrial flutter, then the subject needs to be controlled on their medication for at least 3 months. If the subject had typical atrial flutter before starting the AAD(s) (Class I or Class III) and then subsequently had another arrhythmia (i.e. atrial fibrillation), then the 3 month AAD criteria did not apply.
- One documented occurrence of the study arrhythmia documented by ECG, Holter, telemetry strip, or transtelephonic monitor within the past 6 months
- In good physical health
- 18 years of age or older
- Agree to comply with follow-up visits and evaluation

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

- Prior typical atrial flutter ablation treatment
- Pregnancy
- Atypical flutter or scar flutter (non isthmus dependent)
- Have significant coronary heart disease or heart failure; that is unstable angina pectoris and/or uncontrolled congestive heart failure (NYHA Class III or IV) at the time of enrollment
- A recent myocardial infarction within 3 months of the intended procedure date

- Permanent coronary sinus pacing lead
- Tricuspid valvular disease and/or a prosthetic tricuspid heart valve requiring surgery (i.e. significant)
- Evidence of intracardiac thrombus or a history of clotting disorders
- Participation in another investigational study
- Cardiac surgery within 1 month of the intended procedure date
- Allergy or contraindication to Heparin

Follow-up Schedule

Subjects were required to sign the IRB / CEC approved informed consent prior to participation in the clinical study. Subjects who met inclusion/exclusion criteria were treated with the investigational system. After completing the procedure, the investigator verified that bi-directional block and non –inducibility of typical atrial flutter was achieved at least 30 minutes following the last RF application with the investigational system, for assessment of acute efficacy. Any adverse events that occurred during the procedure were collected on the appropriate CRF.

Post procedure, the subjects were discharged after completing the pre-discharge evaluation. All treated subjects were required to return for 10 day (+/- 3 day) follow-up visit for the assessment of primary safety. Subjects who were acute failures were discontinued from the study after the 10 day follow up visit. In addition, those who had recurrence of typical atrial flutter, as well as those who had repeat ablation or new/ increased dosage of AAD for atrial flutter were discontinued from further follow up . The rest of the subjects were followed up for 3 month (+/- 14 day) visit for the assessment of chronic efficacy. Table 6 below describes the schedule of visits.

Table 6: Schedule of visits

Study Period	Pre-Ablation	During Procedure	Pre-Discharge	10 Days[d]	3 Months[d]	Not Scheduled[d]
Consent	X					
Medical History	X					
TTE	X[a]		X			
TEE	X[b]					
12-Lead ECG	X		X	X	X	X[e]
Confirmation of bidirectional block in cavotricuspid isthmus and non-inducibility of typical atrial flutter		X[c]				
Assessment of current AAD medication	X		X	X	X	X[e]
Assessment of current anti-coagulation medication	X[b]		X[f]	X[f]	X[f]	
Adverse Event		X	X	X	X	X

Key To Abbreviations

TTE=Transthoracic echocardiogram

TEE= Transesophageal echocardiogram

a = A baseline TTE within 6 months prior to ablation procedure is permissible

b= For patients with chronic/persistent typical atrial flutter ONLY a pre-ablation trans-esophageal echocardiogram

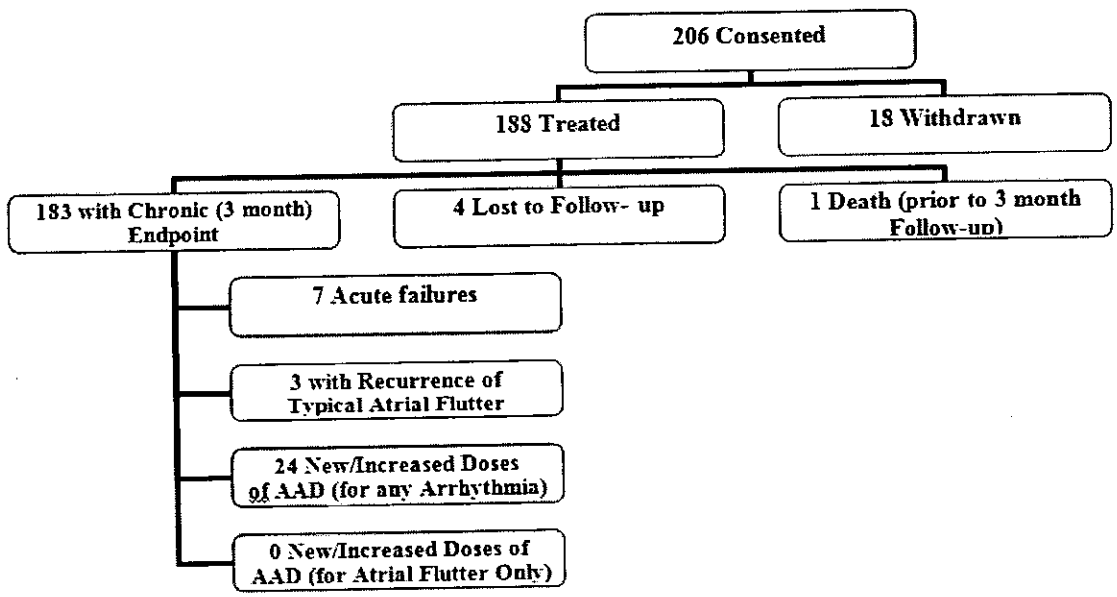
(TEE) is required within 7 days prior to the ablation procedure, unless the subject has received therapeutic anticoagulation for a period of at least three weeks prior to the procedure.
c= At least 30 minutes after the last RF application with the investigational system.
d= To accommodate patient referrals from distant hospitals, the referring physician may conduct the indicated follow-up visits. In such cases, the investigator may contact the referring physician's office and/or obtain the appropriate source documents to complete the appropriate Case Report Forms (CRFs).
e= This assessment during unscheduled visit may be done if required based on physician's judgment of patient's medical condition.
f= Anticoagulants are recommended only for the subjects are who are in atrial flutter during the procedure

Adverse events and complications were recorded at all visits.

B. Accountability of PMA Cohort

At the time of database lock (January 24, 2011), of 206 patients who were consented in the PMA study, 188 patients were available for analysis. Of the 18 subjects withdrawn from the study, 17 were considered late screen failures because their isthmus dependent atrial flutter could not be confirmed and 1 subject withdrew at his own request. Figure 2 below describes the accountability of subjects studied:

Figure 2. Patient Accountability Tree



C. Study Population Demographics and Baseline Parameters

A total of 206 subjects were consented at 22 investigational sites (20 in the US and 2 in Canada). Out of 206 subjects, 188 subjects were treated with the investigational system and 18 subjects were withdrawn prior to the use of the investigational system.

Of the 188 subjects treated with the investigational system, 160 subjects (85.1%) were male and 28 subjects (14.9%) were female. A pre-dominance of atrial flutter was noted in males when compared to females during this study. This was consistent with the control data that reported 81% males in the study. A meta-analysis performed by Pérez et. al which summarized 158 studies on clinical outcomes of atrial flutter ablation over a period of 20 years further indicated the predominance of atrial flutter in males (1).

The mean age of treated subjects was approximately 67.0 years and the mean weight was 212.8 pounds.

The demographics of the study population are typical for a study of patients with atrial flutter performed in the US. Subject demographics are shown in Table 7

Table 7: Subject demographics

	Treatment Group n=188
Gender	
Female	28 (14.9%)
Male	160 (85.1%)
Age	
Mean	66.5
Standard Deviation	11.2
Range	33-86
Weight	
Mean	213
Standard Deviation	47.9
Range	110-370

Cardiac history of treated subjects is summarized in Table 8. The most common cardiac history was Hypertension (77.7%), Atrial Fibrillation (34.6%) and Coronary Artery Disease (28.2%).

Table 8: Cardiac history of treated subjects

Cardiac Condition	**Therapy Cool Path Duo Ablation System**
Hypertension	77.66% (n=146)
Atrial Fibrillation	34.57% (n=65)
Coronary artery disease	28.19% (n=53)
Coronary Artery Intervention	19.15% (n=36)
Valve Disease	14.36% (n=27)
Congestive Heart Failure	13.83% (n=26)
Pacemaker/ICD Implant	10.64% (n=20)

Valve Surgery	10.64% (n=20)
Myocardial Infarction	9.04% (n=17)
Stroke/TIA	6.91% (n=13)
Ventricular Tachycardia	3.72% (n=7)
Atypical Atrial Flutter	3.19% (n=6)
Pericarditis	1.06% (n=2)

Procedural Data

Table 9 provides procedural parameters for the subjects treated with the Therapy Cool Path Duo ablation system.

Table 9: Procedural parameters

Parameter	N	Mean +/- SD
# Applications Per Procedure	188	14.49 ± 12.05
RF Time (min) Per Procedure	188	18.18 ± 11.65
Procedure Time (min) Per Patient	188	105.79 ± 45.50
Total Fluid Administered (mL) Per Patient	185[¥]	851.16 ± 458.00
Total pump saline (mL) Per Patient	186[¥]	408.45 ± 194.63
RF Time (Sec) Per Application (*)	2,713[†]	75.58 ± 68.64
Temperature (°C) Per Application	2,715[†]	34.64 ± 2.27
Mean Power (Watts) Per Application	2,717[†]	32.69 ± 7.62
Impedance (Ohms) Per Application	2,714[†]	96.89 ± 15.04

[†] A total of 2,725 RF applications were delivered, however the procedural data could not be collected by the site for some RF applications. The percentage of such instances is less than 0.5%.

[¥] A total of 188 subjects were treated with the investigational system, however the total fluid administered or total pump saline administered could not be collected for some subjects. The percentage of such instances is less than 0.4%.

* The maximum RF application time for a drag lesion was 689 seconds. The Inter Quartile Range was 36 to 89 seconds.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the treated cohort of 188 subjects and available data on composite serious adverse events within 7 days post procedure. Out of 188 subjects treated with the investigational system, 12 subjects had composite serious adverse events within 7 days of the procedure. The rate of composite serious adverse events was 6.38% (12/188). The 95% confidence limit

(CL) for the difference between the treatment group (Therapy Cool Path Duo catheter) and the control (Therapy Cool Path catheter) was 5.49%. The CL was less than the pre-specified non inferiority margin of 8%. Thus, based on the quantitative assessment, the Duo FLAIR study demonstrated that the Therapy Cool Path Duo Cardiac Ablation system was equivalent (non-inferior) to the market approved Therapy Cool Path Catheter System (control) with respect to safety for its intended use.

No unanticipated adverse device effects (UADE) were reported. None of the adverse events were adjudicated as device related by the Clinical Events Committee. The key safety outcomes for this study are presented in Tables 10, 11 and 12.

Table 10: Primary Safety Comparison

Measure	Therapy CoolPath Duo Ablation System	Control	Hypotheses	95% CL[1]	Decision	Conclusion
Composite Serious Adverse Events (Primary Safety)[2]	12/188 (6.38%)	13/174 (7.47%)	H_0: $\pi_1 - \pi_2 \geq 8\%$ H_A: $\pi_1 - \pi_2 < 8\%$	5.49%	Reject H_0	Equivalent Safety

[1] Based on one-sided asymptotic confidence limits for differences in proportions.

[2] The Cool Path submission reported 12/174 subjects with a major complication, which did not include stroke and TIA events. The Composite SAE definition in the Duo FLAIR study includes stroke and TIA. There was one subject among the Cool Path patients that had a stroke.

Table 11: Composite serious adverse effects that occurred within 7 days post-procedure:

Event	Number of Subjects
Ventricular Arrhythmia	3 / 188 (1.6%)
Hypotension	3 / 188 (1.56%)
Congestive Heart Failure (CHF) Exacerbation	2 / 188 (1.06%)
Pericarditis	1 / 188 (0.53%)
Syncope	1 / 188 (0.53%)
Coronary Artery Disease	1 / 188 (0.53%)
Atrial fibrillation	1 / 188 (0.53 %)

Table 12: Time course of major complications

Number of Subjects	Event	Days Post Procedure
3	Hypotension	0
1	Ventricular Arrhythmia	0
1	Ventricular Arrhythmia	1
1	Atrial Fibrillation	6
1	Ventricular Arrhythmia Requiring Defibrillation	0
1	Congestive Heart Failure (CHF) Exacerbation	1
1	Congestive Heart Failure (CHF) Exacerbation	2
1	Pericarditis	1
1	Syncope	3
1	Coronary Artery Disease	0

There was one (1) death reported during the course of the clinical study, the causality of which was attributed to the subject's underlying disease by the Clinical Events Committee. Below is a description of this event:

The subject was a 65 year old male with a history of congestive heart failure, GI bleed, hypertension and peripheral vascular disease. The subject was successfully treated for the study arrhythmia with the investigational system on March 25, 2010. The procedure was completed without event and the subject was discharged the following day. Thirty (30) days post procedure, he presented to the emergency room with episodes of vomiting, seizure in his left arm, and decreased responsiveness and consciousness. These symptoms were attributed to a large intracerebral hemorrhage with associated intra ventricular hemorrhage. Three (3) days later, the subject passed away peacefully. In the opinion of the CEC, this event was not device related, but was related to the subject's underlying disease condition.

2. Effectiveness Results

Primary Effectiveness
The analysis of primary effectiveness was based on the procedural success of 188 subjects treated with the investigational system. Out of 188 subjects treated, 181 subjects had acute procedural success and 7 subjects were acute failures. Therefore, the acute procedural success rate in this study was 96.28% (181/188). The 95% upper confidence limit (CL) for the difference between the treatment group (Therapy Cool Path Duo catheter) and the control (Therapy Cool Path catheter) was 0.24%. The CL was less than the pre-specified non inferiority margin of 7.5%. Thus based on a quantitative assessment, the Duo FLAIR study

demonstrated that the Therapy Cool Path Duo Cardiac Ablation system was equivalent (non-inferior) to the market approved Therapy Cool Path Catheter System (control) with respect to safety for its intended use. Table 13 illustrates the primary effectiveness results.

Table 13: Primary Effectiveness

Measure	Therapy Cool Path Duo Ablation System	Control	Hypothesis	95% CL[1]	Decision	Conclusion
ACUTE PROCEDURAL SUCCESS (PRIMARY EFFECTIVENESS)	181/188 (96.28%)	161/174 (92.53%)	H_0: $\pi_2 - \pi_1 \geq 7.5\%$ H_A: $\pi_2 - \pi_1 < 7.5\%$	0.24%	Reject H_0	Equivalent Effectiveness

[1] Based on one-sided asymptotic confidence limits for differences in proportions.

Secondary Effectiveness

Out of 188 subjects treated with the investigational system, there were 4 subjects lost to follow up and 1 death. Out of the 183 subjects who were evaluated for the chronic endpoint, 3 subjects had a recurrence of the study arrhythmia and 173 met the chronic success endpoint criteria. The chronic success rate was 94.54% (173/183).

In the Cool Path PMA (control study), the chronic success was presented as freedom from recurrence of typical atrial flutter or new/increased dose of any Class Ia, Ic or III antiarrhythmic medication for any arrhythmia up to 3 months follow-up. Acute failures were excluded from the chronic efficacy analysis.

To maintain consistency with the control study, another secondary efficacy analysis was performed. In the Duo FLAIR study, and of 188 subjects who were treated with the investigational system, 7 subjects were acute failures, 4 subjects were lost to follow up and 1 subject died. Out of 176 subjects evaluated for the chronic endpoint, a total of 149 subjects had freedom from recurrence of typical atrial flutter or new/increased dose of any Class Ia, Ic or III antiarrhythmic medication for any arrhythmia up to 3 months follow-up. Hence the chronic success rate as per this definition was 84.66% (149/176). The 95% confidence limit (CL) for the difference between the treatment group (Therapy Cool Path Duo catheter) and the control (Cool Path catheter) was 0.98%. The CL was less than the pre-specified non inferiority margin of 12%.

Thus based on a quantitative assessment using both the pre-specified and retrospective criteria, the pivotal study demonstrated that the Therapy Cool Path Duo Cardiac Ablation system was equivalent (non-inferior) to the market approved Therapy Cool Path Catheter System (control) with respect to chronic efficacy for its intended use.

Comparability of historical control – Propensity Score Analysis

This study was designed to minimize the potential for differences between enrolled subjects and those from the historical control data. Additionally, a propensity score analysis was performed to reduce the potential for bias created by possible differences between groups. This pre-specified analysis used covariates considered to be clinically important (i.e., age, height, weight, gender, history of coronary artery disease, history of atrial fibrillation, history of congestive heart failure (CHF) and Class I or Class III AAD therapy at the time of enrollment) to calculate a probability, or propensity, of subjects to be in the current study or in the historical control group. Technically, an automatic step-wise selection procedure was used to select the best fitting model from these covariates. The final model for the propensity score included the following variables: history of atrial fibrillation and history of coronary artery disease. The propensity score generated from this model was then used as a covariate in a regression approach to control for differences between the groups while producing the same comparisons between the Therapy Cool Path Duo and historical data (Therapy Cool Path PMA) as in the unadjusted primary analysis. This regression approach to propensity score analysis has the advantage of utilizing all the available data for which the covariate information is available. The propensity score adjusted analysis was performed separately for each of the primary endpoints, the secondary effectiveness endpoint as well as the alternative definitions of the secondary effectiveness endpoint. These results were consistent with the primary analyses and support the conclusion that the Therapy Cool Path Duo data was equivalent to the historical control data. While it cannot be ruled out that there are other potential differences between the historical control group and the current study population, this propensity score analysis enhances the validity of the primary results.

Missing Data

To supplement the primary analyses, sensitivity analyses were performed that examined the impact of missing data on the conclusions. There were no missing data for the primary endpoints, so no sensitivity analysis was performed. For the secondary endpoint of chronic effectiveness, three separate analyses were performed.

The first analysis treated subjects with acute failures as chronic failures, the second analysis treated subjects with missing 3 month status as chronic failure, and the third analysis treated both the acute effectiveness failures and the subjects with missing 3 month status as chronic failures. The comparison to the historical data was performed for all three analyses; all three were consistent with the primary analyses and all led to the same conclusion that the Therapy Cool Path Duo data were equivalent to the historical control data.

Assessment of Consistency by Center

For the acute and chronic success endpoints, results were consistent across the investigational sites with no evidence of a statistically significant difference ($p=0.699$ for acute success and $p>0.96$ for either definition of chronic success, from Fisher's exact test). For the primary safety endpoint of procedural safety, there is some evidence of variation in the results by site ($p=0.0412$ from Fisher's exact test).

To account for this, a random effects logistic regression model was used to produce an overall estimated rate of primary safety events that incorporates site variation. For comparison purposes, a logistic regression model that does not incorporate site variation was also used to produce an overall estimated rate of primary safety events. Results from these two models were consistent. It can be concluded that potential variation between investigational sites does not have a large impact on the primary safety results.

3. Gender & Subgroup Analyses

The primary and secondary endpoints were calculated separately by subgroups defined by baseline characteristics including the following variables pre-specified in the protocol: age, height, weight, gender, history of coronary artery disease, history of atrial fibrillation, and history of congestive heart failure. The subgroup analyses described in this section are considered descriptive in nature. The p-values presented are not adjusted for multiple comparisons.

For continuous variables such as age, subjects were divided into two groups based on the median value. Differences in event rates between subgroups were quantified by producing a two-sided 95% confidence interval for the difference in event rates and a p-value from Fisher's Exact test was used to assess statistical significance of differences.

For the primary safety endpoint, there were no significant differences in the occurrence of composite SAEs within 7 days post procedure for any other subgroup (age, height, weight, gender, history of coronary artery disease, history of atrial fibrillation, and history of congestive heart failure) except *weight*. There was a statistically significant difference in event rates by weight at the 0.05 level ($p=0.0328$). The event rate was 10.53% (10/95) in those subjects with a weight at or above the median value of 205 lbs as compared to those with a weight below the median value who had an event rate of 2.15% (2/93). Out of 10 subjects whose weight was above the median value, 7 subjects (70%) had composite serious adverse events (SAEs) that were related to the underlying disease and unrelated to the device or the ablation procedure. Please refer to Table 14.

Table 14: Composite Serious Adverse Events by Subgroup

Subgroup	N	Subjects with 1+ Events	Percent	Difference (95% CI)	P-Value
Age					
<68 (Median)	94	4	4.26%	-4.26 (-18.9 to 10.53)	0.3717
≥68 (Median)	94	8	8.51%		
Height					
<70in (Median)	78	5	6.41%	0.05 (-14.41 to 14.51)	1.0000
≥70in (Median)	110	7	6.36%		
Weight					
<205lb (Median)	93	2	2.15%	-8.38 (-22.44 to 6.26)	0.0328
≥205lb (Median)	95	10	10.53%		
Gender					
Male	160	11	6.88%	3.30 (-16.71 to 23.28)	1.0000
Female	28	1	3.57%		
Coronary Artery Disease					
No History	135	6	4.44%	-6.88 (-22.60 to 9.07)	0.1005
History	53	6	11.32%		
Atrial Fibrillation					
No History	123	6	4.88%	-4.35 (-19.22 to 10.60)	0.3464
History	65	6	9.23%		
Congestive Heart Failure					
No History	162	11	6.79%	2.94 (-17.7 to 23.60)	1.0000
History	26	1	3.85%		

All of these subjects were either obese or overweight (BMI of >25). It is known that there is a higher incidence of cardiovascular disease in overweight/ obese population (2).

For the primary effectiveness endpoint, there were no notable differences in acute procedural success rate for any subgroup (age, height, weight, gender, history of coronary artery disease, history of atrial fibrillation, and history of congestive heart failure). Table 15 displays acute procedural success by subgroup analyses.

Table 15: Acute Procedural Success Subgroup Analyses

Subgroup	N	Successes	Percent	Difference (95% CI)	P-Value
Age					
<68 (Median)	94	88	93.62%	-5.32 (-19.94 to 9.47)	0.1180
≥68 (Median)	94	93	98.94%		
Height					
<70in (Median)	78	76	97.44%	1.98(-12.53 to 16.43)	0.7014
≥70in (Median)	110	105	95.45%		
Weight					
<205lb (Median)	93	90	96.77%	0.98 (-13.57 to 15.33)	1.0000
≥205lb (Median)	95	91	95.79%		
Gender					
Male	160	155	96.88%	4.02 (-16.09 to 23.97)	0.2796
Female	28	26	92.86%		
Coronary Artery Disease					
No History	135	130	96.30%	0.07 (-15.73 to 15.87)	1.0000
History	53	51	96.23%		
Atrial Fibrillation					
No History	123	119	96.75%	1.36 (-13.65 to 16.36)	0.3464
History	65	62	95.38%		
Congestive Heart Failure					
No History	162	156	96.30%	0.14 (-20.55 to 20.73)	1.0000
History	26	25	96.15%		

For the chronic success endpoint, there were no notable differences in event rates for any subgroups (age, height, weight, gender, history of coronary artery disease, history of atrial fibrillation, and history of congestive heart failure) for the definition that counts events for recurrence of typical atrial flutter or new/increased dosage of Class I/III antiarrhythmic medications for typical atrial flutter only.

For the definition based on recurrence of atrial flutter or new/increased dosage of Class I/III antiarrhythmic medications changes for any arrhythmia, there were no notable differences in the event rate for any other subgroup (age, height, weight, gender, history of coronary artery disease, history of atrial fibrillation, and history of congestive heart failure) except the *baseline history of atrial fibrillation.* There was a difference between those with and without a baseline history of atrial fibrillation (p=0.0016). The chronic success rate was 72.13% (44/61) in those subjects with a history of AF and 91.30% (105/115) in those without a history of AF. A total of 34.5% of the study subjects had a history of atrial fibrillation. Table 16 illustrates these data.

Table 16: Chronic Success Subgroup Analyses Freedom from Recurrence of Typical Atrial Flutter or New/Increased Dose of any Class I/III Antiarrhythmic Medication Up to 3 Months Follow Up

Subgroup	N	Successes	Percent	Difference (95% CI)	P-Value
Age					
<68 (Median)	85	70	82.35%	-4.46 (-19.17 to 10.40)	0.5307
≥68 (Median)	91	79	86.81%		
Height					
<70in (Median)	72	60	83.33%	-2.24 (-17.18 to 12.80)	0.6775
≥70in (Median)	104	89	85.58%		
Weight					
<205lb (Median)	86	72	83.72%	-1.83 (-16.51 to 13.07)	0.8351
≥205lb (Median)	90	77	85.56%		
Gender					
Male	152	130	85.53%	6.36 (-15.27 to 27.73)	0.3781
Female	24	19	79.17%		
Coronary Artery Disease					
No History	126	106	84.13%	-1.87 (-18.01 to 14.49)	0.8211
History	50	43	86.00%		
Atrial Fibrillation					
No History	115	105	91.30%	19.17 (3.70 to 34.02)	0.0016
History	61	44	72.13%		
Congestive Heart Failure					
No History	153	127	83.01%	-12.65 (-34.24 to 9.34)	0.2096
History	23	22	95.65%		

A literature search was performed on pre-existence of atrial fibrillation in subjects with typical atrial flutter. A meta analysis reporting clinical outcomes after catheter ablation of atrial flutter published between January 1988 and July 2007 by Perez et al. (2) reported that 42% of subjects had a history of atrial fibrillation and that the overall occurrence rate of atrial fibrillation after atrial flutter ablation was 33.6% (CI 29.7 - 37.3%).

Results by US / OUS Sites

Two sites in the study were located outside the United States. There were a total of 26 subjects enrolled at these two sites. To assess the consistency of sites within and outside the US (OUS), the summary statistics for the endpoints were calculated separately for the US and OUS sites.

For the primary safety endpoint, there were no notable differences between the US and OUS sites (p=1.000 from Fisher's exact test). The rate of composite

serious adverse events within 7 days of the index procedure was 6.79% for the US sites and 3.85% for the OUS sites.

For the primary effectiveness endpoint, there was a difference between the US and OUS sites (p=0.0565 from Fisher's exact test). Rates of acute procedural success were 97.53% for the US sites and 88.46% for the OUS sites, with one OUS site having a success rate of 82.35% and the other a rate of 100%.

For the secondary effectiveness endpoint, there was a difference between the US and OUS sites (p=0.0373 from Fisher's exact test). The rate of chronic success was 96.18% for the US sites and 84.62% for the OUS sites. One OUS site had a chronic success rate of 82.35% and the other a rate of 88.89%.

The exact 95% confidence interval for chronic success for only the US sites was 91.87% - 98.58%, which are consistent with the results for all sites combined. The differences in chronic success between the US and OUS sites are driven by one OUS site that had 3 chronic failures (2 of which were acute failures). The overall study results are consistent with those from the US sites.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) 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.

XII. CONCLUSION.S DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in the clinical study conducted to support PMA approval as described above. Thus, based on the quantitative assessment, the Duo FLAIR study demonstrated that the Therapy Cool Path Duo Cardiac Ablation system was equivalent (non-inferior) to the market approved Therapy Cool Path Catheter System (control) with respect to safety for its intended use.

B. Effectiveness Conclusions

The pivotal study demonstrated that the Therapy Cool Path Duo Cardiac Ablation system was equivalent (non-inferior) to the market approved Therapy Cool Path Catheter System (control) with respect to chronic efficacy for its intended use.

C. Overall Conclusions

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.

XIII. CDRH DECISION

CDRH issued an approval order on January 25, 2012. The final conditions of approval cited in the approval order are described below.

The applicant's manufacturing facility(ies) was/were 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.

XV. REFERENCES

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