SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Subcutaneous Implantable Defibrillator

Device Trade Name: Cameron Health Subcutaneous Implantable Defibrillator S-ICD® System:
SQ-RX® Pulse Generator, Model 1010
Q-TRAK® Subcutaneous Electrode, Model 3010
Q-TECH™ Programmer, Model 2020
Q-GUIDE™ Electrode Insertion Tool Model 4010

Device Procode: LWS, NVY

Applicant's Name and Address: Cameron Health, Inc.
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San Clemente, CA 92673

Date of Panel Recommendation: April 26, 2012

Premarket Approval Application (PMA) Number: P110042

Date of FDA Notice of Approval: September 28, 2012

Expedited: Granted expedited review status on June 23, 2011 because the S-ICD® System represents breakthrough technology. The system also offers a clinically meaningful advantage over existing alternative treatments with the use of a subcutaneous lead.

II. INDICATIONS FOR USE

The S-ICD® System is intended to provide defibrillation therapy for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia, incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing.

III. CONTRAINDICATIONS

Unipolar pacemakers are contraindicated for use with the S-ICD® System.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the S-ICD® User Manuals.

V. DEVICE DESCRIPTION

The S-ICD® system is a subcutaneous defibrillation system which employs the following:

- SQ-RX® Model 1010 Implantable Pulse Generator with Firmware Version 2.3.308
- Q-TRAK® Subcutaneous Electrode Model 3010
- Q-GUIDE™ Electrode Insertion Tool (EIT) Model 4010
- Q-TECH™ Programmer Model 2020 with Software Version 1.90.00
- Accessories (programmer telemetry wand Model 4510, Magnet Model 4520, suture sleeve, torque wrench, patient screening tool, and SD memory card)

The S-ICD® system also offers a surface ECG based "screening tool" which is used to determine the adequacy of sensing. The S-ICD system uses a subcutaneously placed electrode and an active can for sensing and detecting ventricular arrhythmias and delivering biphasic defibrillation shocks. The device is capable of delivering high energy defibrillation shocks as well as bradycardia demand mode cardiac pacing at a rate of 50 ppm for a period up to thirty seconds following defibrillation therapy (The post-shock pacing waveform is a constant current, 200 mA, biphasic pulse with a pulse width of 7.5 ms). When the device senses a ventricular tachyarrhythmia it charges up to 5 maximum energy shocks (80J). The defibrillation waveform is a truncated exponential, 50% biphasic pulse delivered between the coil and can. Shock energy is non-programmable except for the shocks delivered manually or during induction testing (The device has a shock polarity algorithm which selects the polarity for the first shock delivered based on the polarity of the last delivered successful shock). The pulse generator has what is called an Internal Warning System – Beeper Control that emits a tone to alert the patient to device conditions, e.g., ERI (Elective replacement Indication), EOL (End of Life), electrode impedance and prolonged charge times. The pulse generator is programmable with a "shock rate zone" and a "conditional shock zone", which incorporates arrhythmia discrimination algorithms. Ambulatory shocks are delivered at 80 Joules (non-programmable). The sponsor has provided information which indicates that the battery has a capacity of over 100 shocks at the time of manufacture and approximately 21 shocks over a service life of 5 years.

The SQ-RX® Model 1010 pulse generator weighs approximately 145 grams and has a volume of about 69cc. The inner assembly of the pulse generator is enclosed in a hermetically sealed can with a pre-molded polyurethane header for connecting the Q-TRAK® electrode. See Figure 1 and Figure 2.

Figure 1: SQ-RX® Pulse Generator

The Q-TRAK® electrode is a single use device with an operational life of at least 7 years. The electrode comprises one high voltage defibrillation coil for the purpose of providing defibrillation energy. The sensing electrodes are electrically insulated from the defibrillation coil. The electrode has a proximal and distal ring electrode on each side of an 8 cm coil electrode.

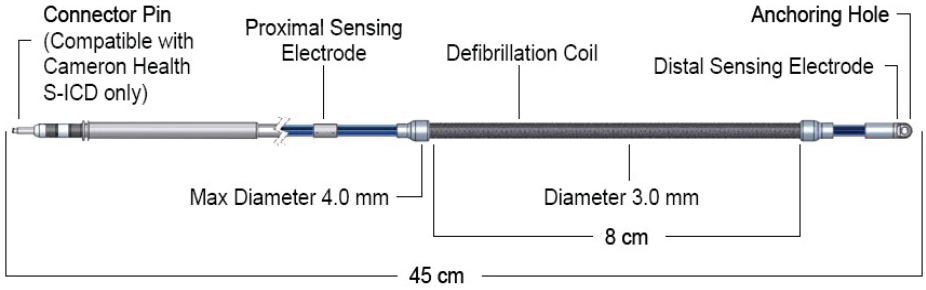


Figure 2: Q-TRAK® Subcutaneous Electrode

Defibrillation is delivered between the coil on the electrode and the active can. Sensing is accomplished using both or any one of the proximal and distal ring electrodes on the electrode and the electrically conductive pulse generator enclosure. This design allows the S-ICD® System to use one of three unique sensing vectors, which may be selected non-invasively using the Q- TECH™ programmer.

The proximal termination of the electrode comprises a multi-pole connector to plug into the header of the SQ-RX® pulse generator. This connector is designed to be compatible

with the SQ-RX® pulse generator only. The electrode is designed to be subcutaneously tunneled from the pulse generator pocket to an incision near the xiphoid process and then superiorly from the xiphoid process such that the distal tip is approximately 14 cm above the xiphoid incision. The electrode is designed to be implanted using anatomical landmarks only without the need for fluoroscopy or other medical imaging systems during the surgical implant procedure. Also in contrast to transvenous leads, the electrode is not stylet driven and therefore does not require a central lumen. Instead, the electrode design includes an inner multi-strand MP35N cable connected to the distal and proximal tips that allows the electrode to be safely pulled during the implant procedure or in the event that extraction is subsequently required. Each electrode is permanently and visibly marked with the device model and serial number. Additionally, the electrically active portions of the electrode are radio-opaque which enables identification of implanted electrodes via x-ray or fluoroscopic imaging. See Figure 3.

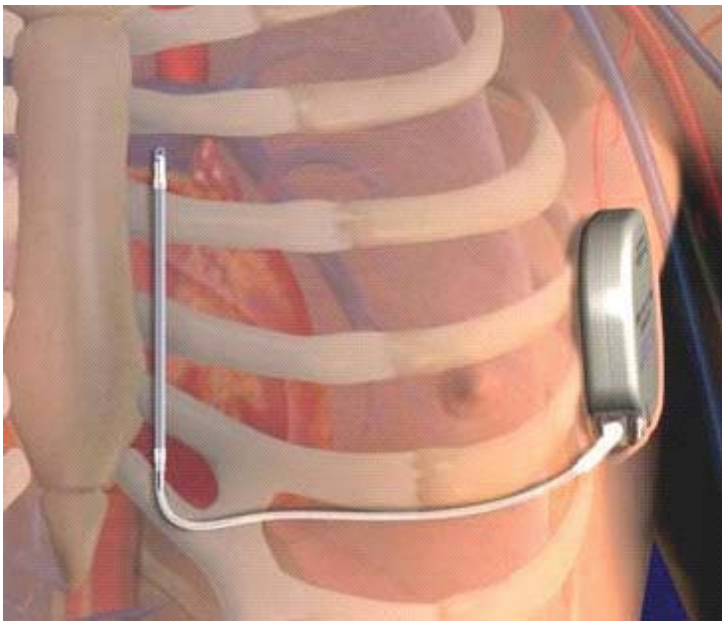


Figure 3: SQ-RX® Pulse Generator and Q-TRAK®

The Q-GUIDE™ Electrode Insertion Tool ("EIT") is a single use, disposable subcutaneous tunneling tool which is used to facilitate placement of the electrode. The EIT is designed to create an appropriately sized subcutaneous sinus for the electrode such that the electrode will fit securely and not loosely in the subcutaneous sinus. The tip of the EIT and the tip of the electrode are equipped with suture holes which enable the two devices to be temporarily sutured together during the implant procedure. Once the two devices are sutured together, the EIT can be used to pull the electrode through a subcutaneous sinus.

The Q-TECH™ Programmer ("programmer") is a completely self-contained, non-sterile, non-implantable, lightweight, dedicated computer. The programmer implements a graphical user interface (GUI) design which gathers user input via touch screen and/or keyboard. It has a 600 x 800 pixel resolution display (high quality SVGA size) and is 9.25 x 7.24 x 1.38 inches when closed, weighing 2.55 pounds. The programmer operates off of a rechargeable

lithium ion battery pack or AC power via its wall power source. The programmer is equipped with an SD Card port for collecting device diagnostics when necessary.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The S-ICD® System is designed to provide life sustaining therapy to patients experiencing ventricular tachyarrhythmias. Alternative therapies for the treatment of life-threatening ventricular tachyarrhythmias include the use of antiarrhythmic drug therapy, electrical ablation, cardiac surgery and transvenous ICD therapy, or a combination thereof.

VII. MARKETING HISTORY

The S-ICD® System has been distributed commercially outside the United States since July, 2009. Specifically, the S-ICD® System has been commercially distributed in the following countries: Denmark, Germany, Italy, Netherlands, Czech Republic, Slovakia, Portugal, Ireland, the United Kingdom, Belgium, Sweden, Austria and New Zealand. The S-ICD System has not been withdrawn from these markets for any reason.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse events related to implantation of the S-ICD System may include, but are not limited to the following:

- Acceleration/induction of atrial or ventricular arrhythmia
- Improper electrode connection to the device, e.g., inappropriate sensing, therapy or surgical revision to correctly insert the electrode
- Inability to defibrillate or pace
- Adverse reaction to induction testing, e.g., failure to defibrillate, atrial fibrillation, acute hypotension
- Inappropriate post-shock pacing
- Allergic/adverse reaction to system
- Inappropriate shock delivery
- Infection
- Bleeding
- Conductor fracture
- Keloid formation
- Migration or dislodgement
- Cyst formation
- Death
- Muscle stimulation
- Nerve damage
- Delayed therapy delivery
- Pneumothorax
- Discomfort or prolonged healing of incision
- Post-shock/post-pace discomfort
- Premature battery depletion
- Electrode deformation and/or breakage

• Random component failures
• Electrode insulation failure
• Stroke
• Erosion/extrusion
• Failure to deliver therapy
• Surgical revision or replacement of the system
• Syncope
• Fever
• Hematoma
• Tissue redness, irritation, numbness or necrosis
• Hemothorax
• Inability to communicate with the device
• Subcutaneous emphysema

IX. SUMMARY OF PRECLINICAL STUDIES

The following is a summary of the preclinical studies performed for the S-ICD System. Preclinical testing included design verification (finished device and software), biocompatibility, sterilization, packaging and shelf life, and animal studies.

A. Laboratory Studies

Biocompatibility

All tissue and non tissue contacting materials of the Cameron Health S-ICD® System have been assessed for biocompatibility and meet the requirements of ISO 10993-1 "Biological Evaluation of Medical Devices Part 1". All biocompatibility studies were performed in compliance with Good Laboratory Practice (GLP) regulations (21 CFR, Part 58). The biocompatibility studies for the SQ-RX® pulse generator, and Q-TRAK® subcutaneous electrode were conducted based on their classification as permanent implant devices (>30 days). The implantable suture sleeve accessory is a commercially available device that has been cleared by FDA for marketing under a 510(k) notification, K041809. The biocompatibility studies for the non-implantable components were conducted based on their classification as external contacting devices made of materials with limited contact duration (≤ 24 hr). The results summarized in Table 1 and Table 2 support the biocompatibility of the S-ICD® System materials for their intended uses.

Table 1: Summary of Biocompatibility Testing of Implantable Components: SQ-RX® Pulse Generator and Q-TRAK® Subcutaneous Electrode

Test Performed	Standard Method	Conclusion
Cytotoxicity using the ISO Elution Method	ISO 10993-5	No evidence of toxicity (met test requirements)
ISO Maximization Sensitization	ISO 10993-10	No evidence of sensitization (met test requirements)
Genotoxicity: Bacterial Reverse Mutation	ISO 10993-3	Non-mutagenic (met test requirements)
Genotoxicity: Mouse Lymphoma Assay	ISO 10993-3 and ASTM guideline E1280-97	Non-mutagenic (met test requirements)
Genotoxicity: Mouse Peripheral Blood Micronucleus	ISO 10993-3	Non-mutagenic (met test requirements)
ISO Subcutaneous Implantation – Two Week	ISO 10993-6	No evidence of irritation or toxicity (normal)
ISO Subcutaneous Implantation – Four Week	ISO 10993-6	No evidence of irritation or toxicity (normal)
ISO Subcutaneous Implantation – 12 Week	ISO 10993-6	No evidence of irritation or toxicity (normal)
ISO Subcutaneous Implantation – 26 Week	ISO 10993-6	No evidence of irritation or toxicity (normal)

Table 2: Summary of Biocompatibility Testing for Non-Implantable Components: the Q-GUIDE™ Electrode Insertion Tool (EIT) and Torque Wrench

Test Performed	Standard Method	Conclusion
Cytotoxicity Using the ISO Elution Method	ISO 10993-5	No evidence of toxicity (met test requirements)
Maximization Sensitization	ISO 10993-10	No evidence of sensitization (met test requirements)
Intracutaneous Reactivity	ISO 10993-10	No abnormal erythema or edema (met test requirements)
Systemic Toxicity	Guidelines of the United States Pharmacopeia (USP)	No mortality or systemic toxicity (met test requirements)

Sterilization, Packaging and Shelf Life Information

All processes used to sterilize the S-ICD® System sterile components were validated according to internationally recognized standards. The SQ-RX® pulse generator and the Q-TRAK® subcutaneous electrode use a 100% ethylene oxide (EO) sterilization process. The suture sleeve accessory, Model LS-21, uses a 6-8.5% EO sterilization process. The cycles were validated using the "half cycle method" to ensure a minimum Sterility Assurance Level (SAL) of 10^{-6}. The Q-GUIDE® electrode

insertion tool (EIT) uses a minimum 25 kGy Gamma dose to ensure a minimum Sterility Assurance Level (SAL). Package design verification tests were performed on the S-ICD® System components to ensure suitability of the package to protect the device and maintain the sterility of the device contents throughout the labeled shelf-life period shown below.

Table 3: Shelf Life of the S-ICD® System Components

S-ICD System Component	Shelf Life
SQ-RX® Pulse Generator, Model 1010	Expiration dating for this device has been established at 13 months after the date of battery attach or 12 months after sterile tray seal, whichever is sooner.
Q-TRAK® Subcutaneous Electrode, Model 3010 with packaged suture sleeve	Expiration dating for this device has been established at 2 years from the date of sterilization.
Q-GUIDE™ Electrode Insertion Tool (EIT), Model 4010	Expiration dating for this device has been established at 690 days from the date of pouch seal.
Sterile Accessory: Suture Sleeve, Model LS-21	Expiration dating for the suture sleeve accessory has been established at 3 years from the date of sterilization.

Software and Firmware Testing

Comprehensive verification and validation (V&V) activities were performed for the SQ-RX® pulse generator Firmware (FW) and Q-TECH programmer software (SW) in accordance with Cameron Health's Quality System and IEC 62304 "Medical device software – Software life cycle processes". The test results summarized in Table 4 supports that the design requirements have been properly implemented and that the end users' clinical needs will be met.

Table 4: Summary of S-ICD® System Software and Firmware Testing

Test Performed	Results
Unit Testing and Design Analysis (Integration)	Supports clinical release
Programmer Software Verification	Supports clinical release
Pulse Generator Firmware Verification	Supports clinical release
System Level Verification	Supports clinical release
Algorithm Validation	Supports clinical release
General System Simulated User Validation	Supports clinical release

Mechanical and Electrical Verification Testing:

Non-clinical testing of the S-ICD® System was conducted to ensue that the components of the S-ICD® System perform in accordance with their established design criteria/requirements. All mechanical and electrical evaluations were successfully completed demonstrating the electrical and mechanical testing met its requirements.

The testing conducted is presented in Table 5 through Table 10. "Pass" as used below denotes that the device met pre-established performance criteria and/or specifications, or was in conformance with the requirements of the applicable standard.

Table 5: Summary of Pulse Generator Design Verification Testing

Test Name	Objective	Results
SQ-RX® Pulse Generator Mechanical Design Verification: physical requirements, shock and vibration, rib compression, header peel, header electrical, header impedance, environmental pressure, operational, sharp features or edges, electrical isolation, release of particulate matter, marking indelibility	Verify the pulse generator's mechanical design requirements are met.	Pass
SQ-RX® Pulse Generator Electrical Design Verification: high voltage shock, pacing therapy, VF induction, shock electrode sub- threshold impedance, sensing, annunciator, magnetic reed switch, high voltage external	Verify the pulse generator's electrical design requirements are met.	Pass
SQ-RX® Pulse Generator Therapy Output Characterization: high voltage shock	Characterize the therapy output of the pulse generator into the load resistance ranges.	Results met expected parameters for therapy output
SQ-RX® Pulse Generator Electrical PC69 Design Verification: protection from AC magnetic field exposure in the range 1 to 140 kHz, performance during RF interference 450-3,000 MHz	Verify the requirements of Sections 4.8.2 and 4.9 of the 2007 PC69 AAMI Electromagnetic Compatibility Compliance Standard are met.	Pass

SQ-RX® Pulse Generator Electrical CENELEC Design Verification: measurement of ICD output voltage, measurement of ICD delivered pulse energy, electrical neutrality, AC leakage current, DC leakage current, case temperature, ERI/EOL rundown, internal defibrillation protection, external protection, high frequency surgical equipment exposure, induced lead current, protection from persisting malfunction due to continuous wave sources, temporary response to continuous wave sources, modulated EMI 16.6 Hz to 150 kHz, modulated EMI 150 kHz to 10MHz, modulated EMI 10 MHz to 450 MHz, weak static magnetic fields, strong static	Demonstrate compliance with the remaining applicable sections of PC69 AAMI Electromagnetic Compatibility Compliance Standard, as well as applicable sections of EN 45502-2-2:1998.	Pass

Test Name	Objective	Results
SQ-RX® Pulse Generator Electrical CENELEC Supplement Device Verification: high frequency surgical equipment exposure, induced lead current, weak static magnetic fields, strong static magnetic fields, external protection, protection from persisting malfunction due to continuous wave sources from 16.6 Hz to 10 MHz, protection from persisting malfunction due to continuous wave sources from 10 MHz to 450 MHz, protection from persisting malfunction due to continuous wave sources from 450 MHz to 3 GHz, CMRR characterization, unmodulated EMI test 16.6 Hz to 1 kHz	Demonstrate compliance with the updated CENELEC standard 45502-2-2:2008.	Pass
SQ-RX® Pulse Generator Ultrasound Exposure per EN 45502-1 Section 22.1	Demonstrate that no change occurs to the pulse generator due to exposure of diagnostic levels of ultrasonic energy.	Pass
SQ-RX® Pulse Generator Battery Longevity Characterization: shelf life simulation, implant procedure simulation, unmonitored run-down phase, monitored run-down to ERI phase	To characterize the expected battery longevity of the pulse generator.	The nominal battery longevity of the pulse generator is 5.1 years.

Q-TRAK® Electrode Supplemental Design Verification: CPR compression, conductive paths between proximal connector and distal end, weight, dimensional, 5-lb transition point tensile, 10° flexural stress, cyclic fatigue, electrical continuity, high voltage	Verify the electrode mechanical and electrical design requirements continue to be met following a design modification.	Pass
Q-TRAK® Electrode with Tecothane Connector Design Verification: transportation exposure, temperature cycling, environmental pressure, physical, connector insertion and withdrawal force, dielectric insulation impedance, 5-lb tensile test	Verify the electrode design requirements continue to be met following a change in the electrode connector seal material.	Pass

Table 6: Summary of Electrode Design Verification Testing

Test Name	Objective	Results
Q-TRAK® Electrode Mechanical Design Verification: proximal connector tri-polar, conductive paths between proximal connector and distal end, abrasion, radiopacity, suture feature, CPR compression, connector seals, weight, dimensional, connector setscrew, 5-lb tip-to-tip tensile, 20-lb tip-to-tip tensile, 5-lb transition point tensile, 10° flexural stress, 90° flexural stress, 45° flexural stress, cyclic fatigue, trans-axial compression force, connector insertion and withdrawal force, sharp feature, particulate release, marking and identification	Verify the electrode mechanical design requirements are met.	Pass
Q-TRAK® Electrode Electrical Design Verification: electrical current carrying capability, electrical continuity, lead connector electrical isolation, high voltage insulation, dielectric insulation impedance, defibrillation shocks over operational life.	Verify the electrode electrical design requirements are met.	Pass
Q-TRAK® Electrode Supplemental Design Verification: CPR compression, conductive paths between proximal connector and distal end, weight, dimensional, 5-lb transition point tensile, 10° flexural stress, cyclic fatigue, electrical continuity, high voltage insulation, dielectric insulation impedance	Verify the electrode mechanical and electrical design requirements continue to be met following a design modification.	Pass

Test Name	Objective	Results
Q-TRAK® Electrode with Tecothane Connector Design Verification: transportation exposure, temperature cycling, environmental pressure, physical, connector insertion and withdrawal force, dielectric insulation impedance, 5-lb tensile test	Verify the electrode design requirements continue to be met following a change in the electrode connector seal material.	Pass
Q-TRAK®: Stability of Polyurethane Tubing	Demonstrate biostability of the electrode tubing material.	Pass

Table 7: Summary of Electrode Insertion Tool Design Verification Testing

Test Name	Objective	Results
Q-GUIDE™ Electrode Insertion Tool (EIT) Mechanical Design Verification: physical, dimensional, mechanical, environmental, safety,	Verify the mechanical design requirements of the EIT are met.	Pass

Table 8: Summary of Programmer Design Verification Testing

Test Name	Objective	Results
Q-TECH™ Programmer Mechanical Design Verification: programmer mechanical and dimensional properties, wand surface temperature, wand connector set engagement/disengagement life and force, wand cable connector set rotational life, wand cable and connector parallel and perpendicular transverse pull forces and vertical and horizontal transverse pull forces, cable-to-wand and cable- to-connector pull tests , wand cable pull/programmer radio card non-removability, PCMCIA interface with the programmer radio card (PRC) card, programmer and wand external surface safety test, programmer and wand free fall/drop, programmer and wand push safety, wand multiple-drop test, programmer and wand high temperature safety and impact safety tests, programmer ball impact safety, and programmer and wand label/marking durability.	Verify the mechanical and mechanical safety requirements of the operating programmer are met.	Pass
Q-TECH™ Programmer Telemetry Wand to PRC Connector Redesign Regression Design Verification: wand connector housing cleaning, wand cable length verification, wand connector verification, wand cable connector set engagement/disengagement life and force, wand cable and connector parallel and perpendicular transverse pull forces and vertical and horizontal transverse pull forces, connector termination, cable-to-connector	Verify the mechanical design requirements for the telemetry wand connector continue to be met following a change to the Telemetry Wand-to-PRC connector configuration.	Pass
Q-TECH™ Programmer EMC / Safety Design Verification: Testing to meet the safety requirements of EN 45502-1:1997, EN 45502-2-2:1998, IEC 60601-1:1990 + A1:1993 + A2:1995 + A13:1996, IEC 60601-1-1:2005, EN 55022:1998 (CISPR22), EN 61000-3-2:2001, EN 61000-3-3:2002, IEC 60601-1-2:2005	Demonstrate compliance with recognized safety standards for medical electrical equipment and medical electrical systems.	Pass

Q-TECH™ Programmer ESD Testing Design Verification	Verify that no irreversible change will be caused by an electrostatic discharge that could occur during handling.	Pass

Table 9: Summary of Suture Sleeve and Magnet Verification Testing

Test Name	Objective	Results
Suture Sleeve Design Verification: retention force, particulate release	Verify suture sleeve retention force and particulate design Requirements are met.	Pass
Magnet Mechanical Design Verification: physical and dimensional, drop, operational, marking, transportation, label indelibility, humidity	Verify the mechanical design requirements of the magnet are met.	Pass

Table 10: Summary of S-ICD® System Level and Radio Frequency Telemetry Verification Testing

Test Name	Objective	Results
Telemetry Design Verification: Bit Error Rate (BER), range, direction and operating surfaces; BER in the presence of an interferer; scan, link and episode download integrity, data link layer	Verify that the pulse generator telemetry performance requirements are met.	Pass
Medical Implant Communication Service (MICS)	Verify the MICS requirements for the S-ICD System are met.	Pass
Numerical Specific Absorption Rate (SAR) Analysis of Pulse Generator: Testing to meet the requirements of 47 CFR 2.1093(d)(2)	Determine the maximum 1gram average SAR exposure generated by the pulse generator.	Pass

B. Animal Studies

A series of animal studies (summarized in Table 11) were conducted to demonstrate the acute and chronic *in vivo* functionality of the S-ICD® System prior to first use in humans. Histology studies assessed injury to tissue following shock delivery, and targeted animal studies verified particular design requirements when bench testing was not appropriate. All test results met the pre-defined test criteria and support the safety and effectiveness of the S-ICD System for its intended use.

Table 11: Summary of Animal Studies

Animal Study	Animal Model	Test Article(s)	Objective	Results
Chronic Canine	Canine	Pulse Generator, Electrode, and Programmer	To evaluate performance of the implanted S-ICD® System, as well as algorithm operation, in a canine model.	The study has successfully demonstrated the continued operation of the implanted S-ICD System through 34 months.
Histology	Canine	Pulse Generator and Electrode	To assess the gross and histological effect on subcutaneous tissue associated with the mechanical implant of the electrode, and combined effect of the mechanical implant of the electrode and shocks delivered by the S-ICD® System.	All findings in the tissues surrounding the devices are typical in tissues surrounding foreign material implanted at surgery.
Acute Implant Performance	Porcine	Pulse Generator, Electrode, EIT, and Programmer	To evaluate the acute use of the S-ICD® System in a porcine model prior to use in the Initial Chronic Human Validation Study.	All tests passed without exception.
Acute GLP Validation Study	Porcine	Pulse Generator, Electrode, and Programmer	To validate the *in vivo* functionality of the S-ICD® System.	All tests passed without exception.
24-Hour Histology	Porcine	Pulse Generator, Electrode, and Programmer	To assess the potential for acute cardiac, lung, skeletal muscle and adjacent tissue injuries associated with shock delivery from the S-ICD® System.	The shocks delivered by the S-ICD® System do not cause more injury to tissues than those delivered by the transvenous system.

Animal Study	Animal Model	Test Article(s)	Objective	Results
EIT / Electrode Performance Verification	Porcine	Electrode and EIT	To verify the EIT performance during an implant procedure.	All tests passed without exception.
X-Ray ID Verification	Canine	Pulse Generator	To verify that an implanted pulse generator can be identified via x-ray.	All requirements passed without exception.
Electrode Modification Analysis	Porcine	Modified and Unmodified Coil Electrodes	To evaluate the performance of a modification to the electrode design.	The modified electrodes outperformed the unmodified electrodes and demonstrated acceptable post-shock and post-pace ECG recovery characteristics.
Acute Testing for Software Maintenance Release	Porcine	Programmer, Electrode, Pulse Generator, and EIT	To validate the acute use of the S-ICD® System following a software maintenance update.	All tests passed without exception.
Validation of User's Manual for Software Maintenance Release	Porcine	Pulse Generator, Electrode, EIT, and Programmer	To confirm that by following the Instructions for Use the S-ICD® System can be successfully upgraded with software maintenance updates, implanted and followed-up.	All tests passed without exception.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a series of six acute human studies to evaluate the feasibility of subcutaneous defibrillation in humans and to determine the optimum system configuration. The S-ICD® System configuration was chosen after completion of the first three studies. Studies four through six were conducted to compare the chosen configuration to standard transvenous systems and to test two additional refinements to the final S-ICD® System configuration.

The first clinical study of fully functional chronic S-ICD® System implants in humans was a single-arm, non-randomized study at 2 centers in New Zealand that enrolled 6 patients who were followed for 30 days. The S-ICD System appropriately sensed and converted more than 12 episodes of induced ventricular fibrillation (VF). All patients

met the effectiveness criterion of 2 consecutive, successful conversions of induced VF episodes in either standard or reverse polarity. All patients were discharged from the hospital on the day following surgery. All patients attended the follow-up visits at 7 and 30 days. There were 4 adverse device events in this study. One patient had two (2) inappropriately paced beats following an undersensed beat post shock. Three (3) patients had pulse generator rotation by 180 degrees observed at 30 days compared with images from the pre-discharge visit. None of these events have had any undue effects on the patients involved and the S-ICD® System performed as expected throughout the study.

The CE Study, the second clinical study of fully functional chronic S-ICD® System implants in humans, was a multi-center, single-arm, non-randomized study, conducted at 8 centers in New Zealand, the Netherlands the United Kingdom and Italy. Data from this study supported the CE mark approval for the device. Fifty five (55) patients were enrolled and followed for 180 days. The patient cohort enrolled in this study had a mean age of 56 years and mean left ventricular ejection fraction of 34%. Forty-three patients had a primary prevention indication and 12 patients had a secondary prevention indication.

The induced ventricular fibrillation (VF) conversion effectiveness rate with the S-ICD® System in the CE Study was 52 of 53 episodes [98.1%] in patients with evaluable tests. In one patient, conversion testing was not completed due to hemodynamic instability during testing; however, this event was classified as a conversion failure due to a number of individual failed conversion attempts. The detection sensitivity of the S-ICD® System was 100% for all induced conversion attempts, as there were no failures to appropriately sense and classify VF or VT. Nineteen patients experienced 26 reported clinical events. More than one event was reported for the following: 6 for inappropriate shocks; 4 for electrode movement; 2 for infection; 2 for discomfort and 2 for worsening heart failure. A single event was reported for each of the following: worsening VT; local tissue reaction; adverse reaction to medication; dislocated hip; palpitations; hemodynamic instability during conversion testing; and x-ray that revealed a mass on the lung, shortness of breath; hematoma; and suboptimal electrode position. All system related events were resolved without any long term clinical sequelae.

The S-ICD® Clinical Investigation (pivotal clinical trial) was performed to establish a reasonable assurance of safety and effectiveness of the S-ICD® System for the treatment of life-threatening ventricular tachyarrhythmias in patients who do not have symptomatic bradycardia; incessant ventricular tachycardia, or spontaneous, frequently recurring ventricular tachycardia that is reliably terminated with anti-tachycardia pacing. The study was performed in US, New Zealand, the Netherlands and the United Kingdom under IDE G090013. A summary of the clinical study is presented below.

A. Study Design

Patients were enrolled between January 27, 2010 and May 20, 2011. The database for this PMA/PMA supplement reflected data collected through February 14, 2012 and included 330 patients. There were 33 investigational sites. All sites followed the same Clinical Investigational Plan and methods to collect data.

The study was a single-arm, prospective, non-randomized, multicenter clinical study conducted in patients age 18 or older who had an existing transvenous ICD, or who met guideline indications for ICD therapy, and had an appropriate pre-operative ECG that met the pre-specified ECG screening tool criteria. Each implant was preceded by use of the S-ICD® surface ECG based "screening tool" to assure adequacy of QRS sensing. Patients with documented spontaneous and frequently recurring ventricular tachycardia (VT) that was reliably terminated with anti-tachycardia pacing were excluded unless they were not a candidate for a transvenous ICD system. A full list of inclusion/exclusion criteria is provided below.

Co-primary endpoints for safety and effectiveness were tested in hierarchical sequence to maintain a family-wise significance level of 0.025 (one-sided) with 80% power. The safety endpoint (180-day S-ICD® System (Type I) Complication-Free Rate) was tested first for superiority to the safety performance goal (79%). The statistical plan pre-specified that if superiority was declared for the first test, the effectiveness endpoint (VF Conversion Efficacy Rate) would be tested for superiority to the effectiveness performance goal (88%). The sample size of 330 patients provided 80% power.

Chronic (≥ 150 days post-implant) induced VT/VF conversion data was collected for a target minimum of 125 subjects at 18 of the 33 investigational sites that participated in the Chronic Conversion Substudy. A target minimum of 100 implants was to be followed at least 360 days, as well as target minimum of 25 subjects' CPK, Creatinine and Chest X-rays before and immediately after implant, and a target minimum of 50 reviewable spontaneous device-treated VT/VF events.

A clinical events committee (CEC) was established prior to study commencement and consisted of three voting members who are independent experts in the field of cardiology, including individuals with expertise with implantable defibrillators, and broad experience with clinical trials and no vested interest in the S-ICD® System. The primary responsibilities of the CEC include:

Review and adjudication of all deaths;
Review and adjudication of all clinical events; and
Review and adjudication of all spontaneous episodes pertaining to therapy appropriateness.

A Data and Safety Monitoring Board (DSMB) was established prior to study commencement and was responsible for safeguarding the interests of study participants and helping to ensure the quality and integrity of the study. The DSMB consists of three voting members who are independent experts in the fields of cardiology and biostatistics, including individuals with expertise with implantable defibrillators, and broad experience with clinical trials (and no vested interest in the S-ICD® System).

1. Inclusion Criteria

Patients who met the following criteria were considered for inclusion in this study.

- Patient meets Class I, Class IIa or Class IIb indications/recommendations for ICD with implantation per the current published guidelines at the time of enrollment (Criterion only applicable to patients with an existing transvenous ICD system).
- Patient requires replacement or revision of an existing implanted transvenous ICD system (Criterion only applicable to patients with an existing transvenous ICD system),
- Patient's age is ≥ 18 years.
- Patient has had an appropriate pre-operative ECG.

2. Exclusion Criteria

Patients who met any one of the following criteria were excluded from this study:

- any condition that precludes the subject's ability to comply with the study requirements, including completion of the study;
- females who are pregnant or lactating and pre-menopausal women who are unwilling to use adequate birth control for the duration of the study;
- Participation in any other investigational study without prior written consent from the study sponsor;
- patients with a serious medical condition and life expectancy of less than one year;
- patients with documented spontaneous and frequently recurring ventricular tachycardia (VT) that is reliably terminated with anti-tachycardia pacing, unless the patient is not a candidate for a transvenous ICD system;
- patients with existing epicardial patches or subcutaneous electrodes in the left thoracic quadrant;
- patients with unipolar pacemakers or implanted devices that revert to unipolar pacing; and
- patients with severely impaired kidney function as measured by a Cockcroft-Gault Glomerular Filtration Rate (GFR) with an estimated GFR ≤ 29.

3. Follow-up Schedule

All patients were scheduled to return for follow-up examinations after the implant procedure and pre-discharge follow-up at 30, 90 and 180 days post implant, and semi-annually thereafter. Data collected at each follow-up visit are summarized in 12, below. Clinical events were recorded at all scheduled and unscheduled visits throughout the study.

As planned at least 100 implants were followed for at least 360 days. Also 50 subjects had CPK, Creatinine and Chest X-rays collected before and immediately after implant, meeting the target of a minimum of 25 subjects.

Table 12: Summary of Testing and Data Collection at Each Visit

Activity	Enrollment	Implant	Pre-Discharge	30 ± 7 days Post-implant	90 ± 14 days Post-implant	180 ± 30 days Post-implant	Semi-Annual*	Additional Visits
Pre-operative ECG	X							
Creatinine Level	X		X					
CPK Level	X							
Enrollment Data	X							
Current Medications		X	X	X	X	X	X	If Applicable
Conversion Testing	N/A	X**						
Device Evaluation and Spontaneous Episodes	N/A	X	X	X	X	X	X	If Applicable
A/P x-ray	N/A	X						
P/A and Lateral chest x-rays			X	X	X	X	X***	If Applicable
Clinical Events and Deviations	X	X	X	X	X	X	X	X

* Every 180 days (±45 days) until device is explanted or study closure
** Conversion testing is required for all patients implanted with an S-ICD System and may be performed as part of the implant procedure or prior to hospital discharge
*** X-rays are required at every other semi-annual follow-up visit beginning with the 360 day visit.
X Indicates evaluation required
N/A Not Applicable

Patients consenting to participate in the chronic conversion substudy also underwent induced ventricular arrhythmia conversion testing on or after 150 days post implant.

Primary Safety and Effectiveness Endpoints

The primary safety endpoint was defined as the 180 day S-ICD® System (Type I) complication-free rate, evaluated by comparing the lower confidence bound of the observed rate to the performance goal of 79%.Type I complications were those clinical events specifically caused by the S-ICD® System and requiring invasive intervention. In this trial, the primary safety endpoint did not include complications caused by the S-ICD® System user's manual or labeling of the S-ICD® System (Type II) or complications not caused by the S-ICD® System, but would not have occurred in the absence of the implanted S-ICD® System (Type III) or those caused by a change in the patient's condition (Type IV). Some examples of complications classified as Type II and III and not included in the primary endpoint included electrode or PG movement and sub-optimal position requiring revision, hematoma and infection. However, a worst case analysis which included Type I-III complications showed that the performance goal of 79% was also met

The primary safety endpoint was assessed in all patients with an attempted S-ICD® System implant (N=321) during the period between the implant procedure and 180 days post implant.

The primary effectiveness endpoint was defined as the Acute Ventricular Fibrillation Conversion Effectiveness Rate of induced episodes, evaluated by comparing the lower confidence bound of the observed rate to the performance goal of 88%. A conversion success was defined as two consecutive 65 J shock conversions in the same polarity out of 4 attempts. Any test that did not exhaust all attempts in each polarity was considered non-evaluable. The potential impact of non-evaluable tests on the analysis was assessed in two additional sensitivity analyses.

Chronic performance was also assessed from spontaneous episodes and chronic conversion of induced episodes. Both were summarized using descriptive statistics.

Spontaneous episodes of VT/VF were collected throughout the study and independently adjudicated for therapy appropriateness by the CEC. Spontaneous episodes were assessed for first-shock conversion success and for overall episode conversion.

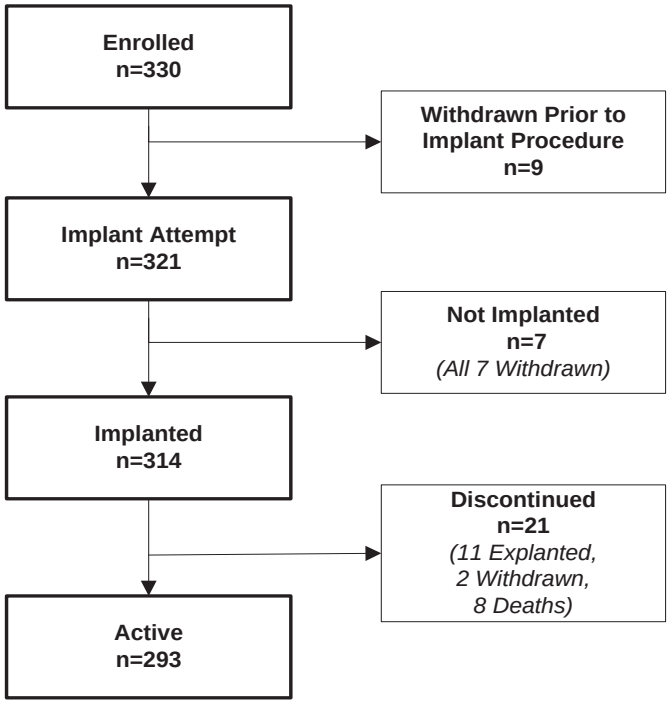
The Chronic Ventricular Arrhythmia Conversion Effectiveness Rate of induced episodes on or after 150 days post implant was also reported. A chronic conversion success was defined as a single successful 65 J shock conversion in either polarity.

B. Accountability of PMA Cohort

Of 330 patients enrolled in PMA study, 321 underwent an implant procedure, of whom 314 were implanted with the S-ICD® System. There were 293 patients still active at the time of database lock on February 14, 2012. The mean follow-up duration for all patients implanted was 330 days with a range of 17 to 715 days.

Cumulative time of follow-up for all implanted patients was 3,410 months. The disposition of all study participants is summarized in Figure 4 below.

Figure 4: Summary of Patient Status as of 14 February, 2012



The primary safety endpoint analysis cohort includes all patients who underwent an implant attempt for the S-ICD® System (N=321). The primary effectiveness endpoint cohort includes all patients undergoing an implant attempt with complete acute induced VF conversion tests (N=304). A total of 17 patients did not undergo (N=1) or complete (N=16) acute induced VF conversion testing, 7 of which were ultimately not implanted (These 7 patients were implanted and underwent DFT testing but then were explanted and did not leave the hospital with a S-ICD® device. Since the device was explanted without completing the acute induced VF conversion testing per protocol, they were considered non-evaluable and not included in the primary endpoint). The single patient who did not undergo any testing had a left ventricular thrombus. Five subjects with incomplete testing had difficulty inducing VF. Eleven subjects with incomplete testing had at least one failed shock

1. Study Population Demographics and Baseline Parameters

The population consisted of 238 males (74.1 percent) and 83 females (25.9 percent; mean age (51.9 +/-15.5 years with a range of 18.5-85.2 years.

Forty-three (13.4 percent) patients had a prior transvenous ICD, including 33 with prior infection, all of whom had prior system explant. Five of the remaining 10 had explant of the entire previously implanted transvenous ICD system. Five had a capped, remaining transvenous ICD lead in place.

The demographics of the study population are similar for an ICD study performed in the U.S. in most aspects although age tended to be younger and a relatively high proportion of enrollees had atypical cardiomyopathies or primary VT or VF arrhythmia syndromes such as ARVD (3), LQTS (12) and Brugada syndrome (10). Cardiovascular history included congestive heart failure (61.4%), hypertension (58.3%), and myocardial infarction (41.4%). Secondary prevention ICD indications represented 20.6% of the population. Subject demographics (Table 13), baseline characteristics (Table 14) and ICD Indications (Table 15) are described below.

Table 13: Subject Demographics

Demographic	Statistic/Category	N=321
Age (years)	Mean ± SD (Median) Range	51.9 ± 15.5 (53.8) 18.5-85.2
Gender (n, %)	Male	238 (74.1)
	Female	83 (25.9)
Race (n, %)	White or Caucasian	208 (64.8)
	Black or African American	76 (23.7)
	Hispanic or Latino	23 (7.2)
	Asian	6 (1.9)
	Asian Indian	3 (0.9)
	Maori	3 (0.9)
	Pacific Islander	2 (0.6)
Height (cm)	Mean ± SD (Median) Range	174.3 ± 10.2 (175.0) 142.2-200.7
Weight (kg)	Mean ± SD (Median) Range	90.5 ± 25.2 (86.6) 42.6-230.9
BMI	Mean ± SD (Median) Range	29.7 ± 7.2 (29.0) 15.2-69.0

Table 14: Baseline Characteristics

Attribute	Statistic/Category	N=321
Creatinine (mg/dL)	Mean ± SD (Median) Range	1.1 ± 0.4 (1.0) 0.3-3.7
Ejection Fraction (%) (n=299)	Mean ± SD (Median) Range	36.1 ± 15.9 (31.0) 10.0-82.0
NYHA Classification at Enrollment (n, %)	I: No Physical Limitations	68 (21.2)
	II: Slight Physical Limitations	146 (45.5)
	III: Marked Physical Limitations	55 (17.1)
	IV: Total Physical Limitations	1 (0.3)
	Unknown/Not Assessed	51 (15.9)
Co-morbidities History (n, %)	Atrial Fibrillation	49 (15.3)
	COPD	27 (8.4)
	Cancer	31 (9.7)
	Congestive Heart Failure	197 (61.4)
	Diabetes	90 (28.0)
	Hypertension	187 (58.3)
	Myocardial Infarction	133 (41.4)
	Stroke	18 (5.6)
	Valve Disease	42 (13.1)
Cardiac Surgical History (n, %)	Ablation	16 (5.0)
	CABG	48 (15.0)
	Defibrillator	43 (13.4)
	Pacemaker	4 (1.2)
	Percutaneous Revascularization	92 (28.7)
	Valve Surgery	18 (5.6)

Table 15: Indications According to ACC/AHA/HRS Guidelines

Indication Details	N=321 Patients n (%)
Left ventricular ejection fraction (LVEF) less than 35% due to prior MI who are at least 40 days post-MI and are in NYHA functional Class II or III	88 (27.4)
Non-ischemic DCM and an LVEF less than or equal to 35% and is in NYHA functional Class II or III	76 (23.7)
Survivor of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes	40 (12.5)
Hypertrophic Cardiomyopathy with risk for SCD	28 (8.7)
Structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable	15 (4.7)
Left Ventricular (LV) dysfunction due to prior MI and is at least 40 days post-MI, has an LVEF less than 30%, and is in NYHA functional Class I	13 (4.0)
Cardiomyopathy with risk for SCD	13 (4.0)
Long-QT syndrome with risk of SCD	12 (3.7)
Brugada syndrome with risk for SCD	10 (3.1)
Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced at electrophysiological study	7 (2.2)
Familial cardiomyopathy associated with SCD	6 (1.9)
Cardiac sarcoidosis or Chagas disease	4 (1.2)
Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) with risk for SCD	3 (0.9)
Nonsustained VT due to prior MI, LVEF less than 40%, and inducible VF or sustained VT at electrophysiological study	2 (0.6)
LV noncompaction	1 (0.3)
Catecholaminergic polymorphic VT	1 (0.3)
Sustained VT and normal or near-normal ventricular function	1 (0.3)
Symptomatic ventricular arrhythmia	1 (0.3)

2. Implant Information

The S-ICD® is intended and designed to be implanted with anatomical landmarks and not with fluoroscopy. According to the protocol, medical imaging systems (e.g.

fluoroscopy, x-ray, etc.) were not to be used during the implant procedure for placement of the S-ICD® System. Of the 321 implant procedures, 304 (94.7%) were completed using anatomical landmarks only and 17 (5.3%) used medical imaging. Of note, 8 of 17 (47.1%) uses of medical imaging occurred at a single investigational center. In all 17 cases, medical imaging was used to assess the position of the system after difficulty inducing or converting the patient during conversion testing. Of the 17 cases, eleven (11) resulted in successful implants and 7 were not implanted.

C. Safety and Effectiveness Results

1. Safety Results

The 180-day Type I complication-free rate was assessed in all patients with an attempted S-ICD® System implant (N=321) for the primary safety endpoint. A Type I complication was defined as any clinical event caused by the S-ICD® System that required invasive intervention. The Type I complication-free rate at 180 days was 99.0% with a lower 95% confidence bound of 97.9%. These results meet the primary safety endpoint performance goal of 79% and demonstrate the safety of the S-ICD® System. Details of the Kaplan-Meier analysis are in Figure 5 and Table 15.

Figure 5: Primary Safety Endpoint Kaplan-Meier Analysis

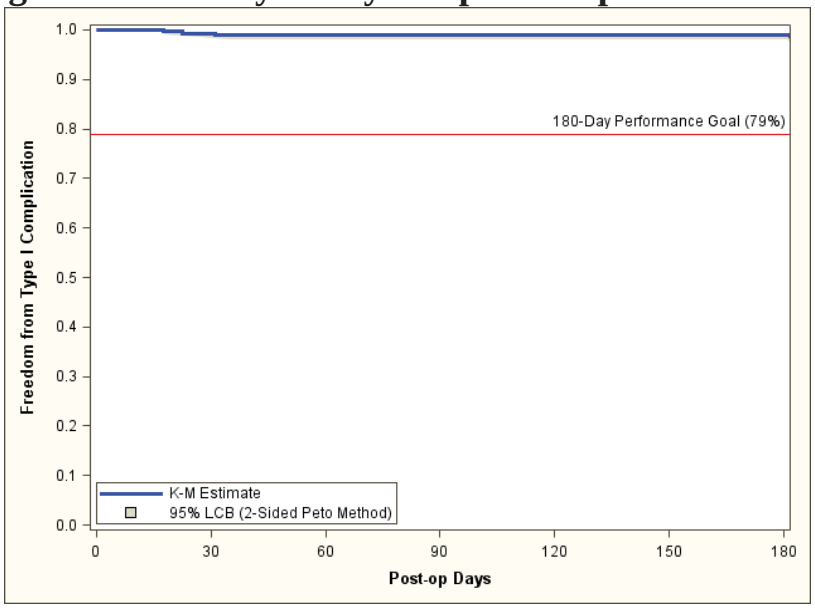


Table 16: Kaplan-Meier Estimates for Primary Safety Endpoint

	Start of Interval (Days from Implant)				
Statistic	0	30	90	180	360
Number Remaining at Risk	319	311	308	274	119
Cumulative Patients Censored	2	8	10	44	194
Cumulative Patients with Events	0	2	3	3	8
KM Estimate of Patients Free from Event (%)	100	99.4	99.0	99.0	96.6
95% Lower Confidence Bound	100	98.5	98.0	97.9	93.5

The prespecified primary safety endpoint was met. As mentioned above, the primary endpoint includes only Type I Complications. Therefore, it does not include other clinical events that merit mention as additional information in interpreting the S-ICD® primary safety endpoint such as:

- eleven subjects with incomplete implant VF induction shock conversion testing with at least one failed shock;
- forty-six clinical events for inappropriate shocks, 3 of which required surgery for SVT with rates in the VF zone;
- four Infections requiring explant, 1 infection requiring wound revision and 13 infections treated medically (type III);

- six Inadequate lead position or movement requiring surgery (2 were type II and 4 were Type III); and
- one discomfort requiring invasive intervention (Type III).

However, the sponsor performed a worst case analysis to include Type I, II and III complications, the endpoint was also met (92.1% at 180 days, LCB – 88.9%).

2. Clinical Events

A Clinical Event is defined as any untoward medical occurrence in a patient. An Observation is a clinical event that does not result in invasive intervention and a Complication is a clinical event that results in invasive intervention. All clinical events were classified by type based on the cause of the clinical event, according to the following definitions:

Type I: Caused by the S-ICD® System

Type II: Caused by the S-ICD® System user's manual or labeling of the S-ICD® System

Type III: Not caused by the S-ICD® System, but would not have occurred in the absence of the implanted S-ICD® System

Type IV: Caused by a change in the patient's condition

Table 17 summarizes all 211 clinical events reported from 139 patients, followed by a full listing of all Type I, II and III clinical events in Tables 18, 19 20, respectively.

Table 17: Clinical Event Summary by Type and Observation/Complication
All patients with an implant attempt (N=321)

Clinical Event	Complications		Observations		Total	
	Events	Patients (%)	Events	Patients (%)	Events	Patients (%)
Type I	12[i]	11 (3.4)	35	30 (9.3)	47	3 (12.1)
Type II	4	4 (1.2)	0	0 (0.0)	4	4 (1.2)
Type III	25	24 (7.5)	83	71 (22.1)	108	88 (27.4)
Type IV	16	15 (4.7)	36	33 (10.3)	52	44 (13.7)
All Clinical Events	57	48 (15.0)	154	116 (36.1)	211	139 (43.3)

Table 18: Type I Clinical Events
All patients with an implant attempt (N=321)

Clinical Event	Complications		Observations		Total	
	Events	Patients (%)	Events	Patients (%)	Events	Patients (%)
Discomfort	3	3 (0.9)	8	7 (2.2)	11	11 (3.4)
Inability to Communicate with the Device	2	2 (0.6)	0	0 (0.0)	2	2 (0.6)
Inappropriate Shock: Oversensing	5	5 (1.6)	25	21 (6.5)	30	25 (7.8)
Numbness at Device Site	0	0 (0.0)	1	1 (0.3)	1	1 (0.3)
Premature Battery Depletion	2	2 (0.6)	0	0 (0.0)	2	2 (0.6)
Subcutaneous Emphysema	0	0 (0.0)	1	1 (0.3)	1	1 (0.3)
All Type I Clinical Events	12	11 (3.4)	35	30 (9.3)	47	39 (12.1)

Table 19: Type II Clinical Events
All patients with an implant attempt (N=321)

Clinical Event	Complications		Observations		Total	
	Events	Patients (%)	Events	Patients (%)	Events	Patients (%)
Electrode Movement	2	2 (0.6)	0	0 (0.0)	2	2 (0.6)
Inappropriate Electrode Connection to the Device	1	1 (0.3)	0	0 (0.0)	1	1 (0.3)
Sub-optimal Electrode Position	1	1 (0.3)	0	0 (0.0)	1	1 (0.3)
All Type II Clinical Events	4	4 (1.2)	0	0 (0.0)	4	4 (1.2)

Table 20: Type III Clinical Events
All patients with an implant attempt (N=321)

Clinical Event	Complications		Observations		Total	
	Events	Patients (%)	Events	Patients (%)	Events	Patients (%)
Acute Hypoxic Respiratory Failure	0	0 (0.0)	1	1 (0.3)	1	1 (0.3)
Adverse Reaction to Medication	3	3 (0.9)	5	5 (1.6)	8	8 (2.5)
Atrial Fibrillation / Flutter	0	0 (0.0)	14	14 (4.4)	14	14 (4.4)
Bleeding	0	0 (0.0)	1	1 (0.3)	1	1 (0.3)
Discomfort	1	1 (0.3)	12	12 (3.7)	13	12 (3.7)
Electrode Movement	1	1 (0.3)	0	0 (0.0)	1	1 (0.3)
Fever	0	0 (0.0)	3	3 (0.9)	3	3 (0.9)
Hematoma	1	1 (0.3)	5	4 (1.2)	6	5 (1.6)
Inadequate/Prolonged Healing of Incision Site	3	3 (0.9)	2	2 (0.6)	5	5 (1.6)
Inappropriate Shock: SVT Above Discrimination Zone (Normal Device Function)	4	4 (1.2)	17	14 (4.4)	21	16 (5.0)
Incision/Superficial Infection	1	1 (0.3)	13	13 (4.0)	14	14 (4.4)
Keloid	1	1 (0.3)	0	0 (0.0)	1	1 (0.3)
Local Tissue Reaction	0	0 (0.0)	1	1 (0.3)	1	1 (0.3)
Numbness at Device Site	0	0 (0.0)	1	1 (0.3)	1	1 (0.3)
PG Movement/Revision	1	1 (0.3)	0	0 (0.0)	1	1 (0.3)
Phantom Shock	0	0 (0.0)	5	3 (0.9)	5	3 (0.9)
Redness/Irritation	0	0 (0.0)	2	2 (0.6)	2	2 (0.6)
Stroke	0	0 (0.0)	1	1 (0.3)	1	1 (0.3)
Sub-optimal PG and Electrode Position	3	3 (0.9)	0	0 (0.0)	3	3 (0.9)
Sub-optimal Pulse Generator Position	1	1 (0.3)	0	0 (0.0)	1	1 (0.3)

Clinical Event	Complications		Observations		Total	
	Events	Patients (%)	Events	Patients (%)	Events	Patients (%)
Suspected Worsening of Ischemia	1	1 (0.3)	0	0 (0.0)	1	1 (0.3)
System Infection	4	4 (1.2)	0	0 (0.0)	4	4 (1.2)
All Type III Clinical Events	25	24 (7.5)	83	71 (22.1)	108	88 (27.4)

Device Explants

Eleven (11) patients exited the study after the S-ICD® System was removed for: system infection (4), oversensing (2), pre-mature battery depletion (1), transvenous device implanted to provide overdrive pacing for ventricular arrhythmia trigger suppression (1), elective explant due to the development of an indication for biventricular pacing (1), elective explant due to development of high defibrillation threshold (1), and elective due to patient request (1).

Patient Deaths

Eight (8) deaths were documented in the study. One (1) subject died of pneumonia; although device interrogation was not obtained, the following physician's assessment was that arrhythmias or S-ICD activity did not occur in this subject. One (1) subject died during travel and details for this subject's death are not available. Review of data for 7 of 8 deaths showed no association with the device function or procedure.

Discomfort

Four (4) of 321 subjects with implant attempts had discomfort requiring surgery, all of which resolved. Eighteen (18) of 321 had discomfort that resolved without surgery. The inframammary crease was cited in 2 cases of female discomfort and the interface between the device site and the patient's bra was cited in another case.

Infections

303 of 321 implant attempts were not associated with infection. Eighteen subjects with infection included thirteen (13) subjects whose infection was resolved with antibiotics and five (5) subjects who required explant or wound revision.

Explants Without Replacement

Eleven (11) S-ICD® Systems were explanted without replacement: four (4) for infection, two (2) to address inappropriate shocks for oversensing, one (1) subject developed high defibrillation thresholds, one (1) requested explant and was performed against medical advice, one (1) subject needed a CRT device, one (1) subject had a premature battery depletion without replacement and one (1) subject required overdrive pacing to suppress/prevent VT.

Inappropriate Shocks

The study included a total of 204 treated episodes for any cause in 56 subjects. Seventy-eight were confirmed episodes of VT/VF and 41 were presumed appropriately treated VT/VF episodes in a single subject with multiple shocks for which the device memory limit was exceeded. One hundred and nineteen episodes of 204 were considered appropriately treated VT/VF, or 58.3%.

In the case of the subject with 41 presumed episodes that were part of a VT/VF storm where the data exceeded the memory of the device, all episodes in this storm that had full data recorded showed appropriately detected and treated VT/VF.

Efforts employed to prevent recurrence of inappropriate shocks in subjects who had inappropriate shocks during the study included reprogramming the device in 32 of 41 subjects or 78.0%. Nine (9) of 41 subjects, or 22.0% required more than simple reprogramming: one (1) needed thyroidectomy; one (1) needed EPS/VT ablation; one (1) needed pulse generator revision; one (1) needed a MAZE procedure for atrial fibrillation; two (2) required an EP study; and two (2) needed S-ICD® explants.

Undersensing

The time from detection of an arrhythmia to shock delivery is slightly prolonged in the S-ICD® device compared to transvenous ICDs and is typically in the range of 12 to 18 seconds. However, occasionally the time to treatment was noted to be further prolonged, i.e. greater than 20 seconds, due to undersensing of the tachyarrhythmia. In 6.8% (57/839) of VF induction tests, including implant and chronic testing, time from arrhythmia onset to device therapy was equal to or greater than 20 seconds. For the chronic testing alone, the time to treatment was $\geq$20 seconds in 9.9% of inductions (8/81). There were two instances where the charge time was greater than 30 seconds and the patient received an external shock. Based on the clinical studies, undersensing can be readily identified with VF conversion testing by evaluating the sensing markers during the induced rhythm.

Battery Performance

The device battery has the capacity for delivering over 100 full energy shocks at the time the device is connected to the battery. The device is projected to last for 5 years

assuming normal energy usage and 3 full energy charges per year for device maintenance, plus an additional capacity to deliver 21 therapy shocks over that period.

3. Effectiveness Results

The effectiveness of the S-ICD® System was assessed by the proportion of patients with successful acute (induced) VF conversion in all patients with an attempted S-ICD System implant (N=321). A successful VF conversion test required two consecutive VF conversions at 65 J from four induction attempts within a given shock polarity. One (1) patient did not undergo testing at the discretion of the physician.

Of the 320 patients who underwent acute VF conversion testing, 16 patients had non-evaluable results, due to incomplete protocol testing. Of the 304 evaluable results, the S-ICD® System acute VF conversion success rate was 100% with a lower 95% confidence bound of 98.8% (Table 21). These results met the primary effectiveness endpoint performance goal of 88% and demonstrate the effectiveness of the S-ICD® System.

Table 21: Effectiveness Endpoint Result - Acute VF Conversion Rate
Patients undergoing acute VF conversion testing (N=320)

Non-evaluable Results	Evaluable Results		Estimate (%)	95% Clopper-Pearson Interval (%)
	Successful	Failure		
16	304	0	100.0	(98.8-100.0)

Of the 16 non-evaluable patients, 11 were associated with at least one failed conversion attempt at 65 J and, due to physician discretion, did not exhaust all of the protocol defined induction attempts in both shock polarities. A sensitivity analysis was performed to impute these patients as failures despite incomplete testing, resulting in an imputed VF conversion success rate of 96.5%. This met the pre-specified performance goal of 88%.

Time to Therapy

Sensing was evaluated during VF induction testing to identify any undersensing leading to extended time to therapy. The S-ICD® System is designed to reduce unnecessary therapy delivery by allowing for spontaneous arrhythmia termination and treating sustained ventricular tachyarrhythmias with an extended time to therapy. Time to therapy encompasses the total time to detect a ventricular arrhythmia, charge the capacitors, confirm the sustained nature of the ventricular arrhythmia and deliver the shock. The mean time to therapy for all inductions during the clinical study was 14.6+/-2.9 seconds with 93.2% of induction tests resulting in a time to therapy less than 20 seconds.

Spontaneous Episodes

A total of 119 spontaneous VT/VF episodes in 21 patients were treated by the S-ICD® System through February 14, 2012. A VT/VF episode refers to a device-declared episode in which device rate/discrimination criteria were met in response to a ventricular tachyarrhythmia and therapy was delivered. A single episode may contain up to 5 shocks. The episode ends when the rolling average of the rate falls below the lowest programmed rate zone for 24 consecutive intervals.

For analysis, episodes were sub-divided into two classes: 1) discrete episodes that were temporally independent (<3 within 24 hours); and, 2) VT/VF storms that comprise 3 or more treated VT/VF episodes within 24 hours in the same patient. Of the 38 discrete device episodes, 35 (92.1%) were converted with the first shock and 37 (97.4%) were converted by any shock (Table 22). One episode terminated spontaneously after an unsuccessful first shock (MVT). Four (4) VT/VF storms from 2 patients resulted in 81 total device episodes, 40 of which were VF and stored in S-ICD® System memory with the remaining 41 episodes not stored due to memory capacity limitations. Three (3) storms were ultimately converted by the S-ICD® System and 1 was ultimately converted with an external defibrillation shock (Table 23).

Table 22: Conversion Effectiveness of Discrete Device Episodes (non-Storm)
Patients with discrete episodes (N=16); Discrete device episodes (N=28)

Rhythm	Patients	Device Episodes	Episode Converted by 1st Shock (%)	Episode Converted by Any Shock (%)
MVT	13	22	21 (95.5)	21 (95.5)
PVT/VF	11	16	14 (87.5)	16 (100.0)
Total	**21**	**38**	**35 (92.1)**	**37 (97.4)**

Table 23: Conversion of VT/VF Storms
Patients with VT/VF Storms (N=2), Storm events (N=4), Stored Device episodes (N=40)

Patients	VT/VF Storms	Device Episodes	Final Storm Conversion Method (%)
2	4	40	**S-ICD: 3 (75)**
			External: 1 (25)
			Spontaneous Conversion: 0 (0)

Chronic Conversion Substudy

The chronic performance of the S-ICD® System was assessed by the proportion of patients with successful conversion of induced VT/VF ≥150 days post-implant in all implanted patients who provided informed consent for this testing (N=78). Three (3) patients were excluded from the analysis because they met the pre-specified definition of a non-evaluable test (did not complete testing in the opposite polarity after a failed 65J shock, as required by the protocol). All three were converted with a subsequent 80J S-ICD® System shock.

The rate of successful conversion by a sub-maximal (65J) S-ICD® System shock was 72/75 (96.0%). All 3/75 (4.0%) patients who failed to convert with a sub-maximal (65J) S-ICD® System shock in either polarity were successfully converted with a subsequent higher-energy S-ICD® System shock.

Chronic (≥ 150 days post-implant) induced VT/VF conversion data was collected for less than the target minimum of 125 subjects, however more than the target minimum of 50 reviewable spontaneous device-treated VT/VF events was collected in this study.

More than 86% of successful implant testing succeeded on shocks #1 and #2 in standard polarity.

Implant Without Medical Imaging

Implant without medical imaging was accomplished as intended in 304 of 321 implant attempts.

Pacing

The S-ICD® can demand pace at 50 ppm up to 30 sec post-shock. This was programmed "On": all but 5 cases of VT/VF Conversion testing. In this IDE there were 183 instances of documented appropriate pacing and capture. There was one beat of inappropriate pacing without clinical consequences. This data was interpreted to mean that post-shock pacing functioned as intended.

4. Subgroup Analyses

Stepwise logistic regression models (backward elimination with a threshold p-value of 0.20) were used to evaluate basic demographic characteristics (age, gender, African American race) and baseline device programming (dual zone programming at hospital discharge) for statistical associations between with following safety-related outcomes:

- All Inappropriate shocks (n=41)
- Inappropriate shocks for oversensing (n=25)
- Inappropriate shocks for SVT (n=16)
- Discomfort (n=22)
- System and Superficial/Incision Infection (n=18)
- Type I-III Complications (n=35)

Age

Age was a significant predictor for inappropriate shocks. Patient who experience inappropriate shocks were younger with a mean age of 47 compared to a mean age of 53 for patients who did not received any inappropriate shocks.

Gender

Female gender was significantly associated with a higher risk for device or procedure related discomfort. Although the numbers are very small, it is notable that the inframammary crease was cited in 2 cases of female discomfort and the interface between the device site and the patient's bra was cited in another case.

Race

African American race was not associated with device or procedure related complications.

Dual Zone Programming at Discharge

Dual zone programming at the time of hospital discharge was associated with significantly fewer inappropriate shocks than those programmed with a single zone. There was a 70% relative reduction of incidence for inappropriate shocks due to SVT with heart rates in the Shock only zone and a 56% relative reduction of incidence for inappropriate shocks due to oversensing, when compare to single zone programming.

5. Conclusion

The purpose of the S-ICD® System Clinical Investigation was to evaluate the safety, effectiveness and chronic performance of the S-ICD® System. There were 330 patients enrolled in the study and 321 underwent an implant procedure. The 314 patients implanted with the S-ICD® System generated 3,410 months of patient data.
The data demonstrate that the S-ICD System operates appropriately per design for the S-ICD® System's intended uses and as described in the S-ICD® System's labeling.

Safety

- The S-ICD® study met its Primary Safety Endpoint. The 95% lower confidence bound (LCB) of the Type I complication free rate (CFR) at 180 days (99%) was 97.9%. The primary safety endpoint therefore met its performance goal of > 79%.
- Shocks did not appear to cause myocardial or organ damage by perioperative serum creatine kinase (CPK), creatinine (Cr) or chest x-ray.
- Discomfort occurred in 22, or approximately 6.9% of 321 subjects; 4 (1.2%) required surgery.
- Infections occurred in 18 (5.6%) of subjects; 5 (1.6%) required surgeries (4 explants).

- Explants for reasons other than infection (battery depletion, CRT needed, ATP needed) were noted in 7 subjects.
- 51 clinical events comprising 85 episodes with inappropriate shocks occurred in 41 (13.1%) of subjects.
- 25 episodes for 9 inappropriate shocks were due to SVT detected in the shock zone, which is considered normal device function. 60 episodes occurred due to oversensing the cardiac signal or external noise.
- Inappropriate shocks occurred more frequently with borderline screening EKG or single zone programming.
- Reprogramming to dual zone programming reduced inappropriate shocks.
- 9 of 41 subjects with inappropriate shocks required surgery; the remaining 32 were resolved by reprogramming.
- Overall 85 of 204 episodes in the IDE study (41.7%) were inappropriate for SVT detected in the shock zone (12.3%) and oversensing (29.4%).

Effectiveness:

- The Primary Effectiveness Endpoint was met; the lower confidence bound (LCB) of the observed success rate for conversion of induced VF at implant was 98.8% in 304 evaluable subjects. This met the pre-specified performance goal of 88%.
- 17 non-evaluable subjects included 11 with at least 1 failed shock. Sensitivity analyses counting these 11 and 17 subjects as failures, met the performance goal.
- More than 86% of successful implant testing succeeded on shocks #1 and #2 in standard polarity.
- Implant without medical imaging was accomplished as intended in 304 of 321 implant attempts.
- Mean shock delivery time was approximately 15 seconds with some responses as long as 30 seconds.
- 72 of 75 subjects were successful at repeat VF conversion testing at 150 days.
- 119 spontaneous VT/VF episodes occurred in the trial, 78 of which had fully evaluable recorded data showing S-ICD® conversion in all but one that terminated spontaneously after a single shock.

XI. Panel Meeting Recommendations and FDA's Post Panel Action

A. Panel Meeting Recommendation

At an advisory meeting held on April 26, 2012 the Circulatory System Devices Panel voted 8-0 that there is reasonable assurance that the device is safe and 7-1 that there is

reasonable assurance that the device is effective, and 7-1 that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication. Specific additional recommendations by the panel included:

- POST-APPROVAL STUDY: The panel recommended a 5 year post approval study with the ability to collect more spontaneous episodes to confirm arrhythmia detection and treatment in a more diverse "real world" population. The panel recommended that the prespecified goals of the complication free rate and effectiveness be more rigorous with the necessary adjustments for duration of study and the actual outcome of the IDE study.

- LABELING: The panel recommended that implant VF induction and 65J shock conversion testing be routinely performed and recommended in the implant instructions on the basis of this being performed in the IDE study to assure that the implant configuration was adequate and effective to allow implant. The panel also recommended use of dual zone programming or use of a high rate criterion to avoid SVT of rates less than VF rates receiving shocks. This was what the IDE study showed was helpful to reduce inappropriate shocks.

TRAINING: The panel recommended that the implanting physician be required to have training and experience sufficient to manage the appropriate selection of patients for the S-ICD as well as the long term device and arrhythmia management.

B. FDA's Post-Panel Action

Based on specific recommendations by the panel, FDA worked with the firm to make the following modifications:

- POST-APPROVAL STUDY: There will be a 5 year post-approval study with the ability to collect more spontaneous episodes to confirm arrhythmia detection and treatment in a more diverse "real world" population with a more rigorous performance goal. Type I complications will be included in the safety endpoint and will be compared to a more rigorous performance goal. In addition, complications, e.g., lead and pocket revisions and complications requiring explants will undergo a separate analysis. The prespecified goal of the complication free rate and effectiveness will be more rigorous with the necessary adjustments for duration of study, based on the actual outcome of the IDE study.

- LABELING: Implant VF induction and 65J shock conversion testing be routinely performed and recommended in implant instructions on the basis of this being performed in the IDE study to assure that the implant configuration was adequate and effective to allow implant. Use of the ECG screening tool will be emphasized to identify patients appropriate for the device. Dual zone programming or a high rate criterion will be recommended in labeling to avoid SVT of rates less than VF rates receiving shocks. This was what the IDE study showed was helpful to reduce inappropriate shocks. VF induction and conversion testing should be routinely performed to ensure adequate sensing.

- TRAINING: All implanting physicians will receive training based on the formal program as set forth by the manufacturer prior to implanting the S-ICD® System.

XII CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The S-ICD® study assessed the effectiveness of the S-ICD® System for treating induced VF at implant in 320/321 subjects undergoing an implant procedure. The 95% lower confidence bound of the successful conversion rate in 304 evaluable subjects was 98.8%, meeting the performance goal of 88%.

Sensitivity analyses of the primary endpoint including either 17 non-evaluable subjects or 11 with at least 1 failed shock also met the pre-specified performance goal. Most implant testing succeeded on shocks #1 and #2 in standard polarity, implant without medical imaging was accomplished as intended in most subjects and mean shock delivery time was approximately 15 seconds with some responses as long as 30 seconds. Most subjects undergoing repeat VF conversion testing at 150 days were successfully converted. Of 119 spontaneous VT/VF episodes all but one were converted by the S-ICD, including one (1) that terminated spontaneously and one (1) that required external shock for VT/VF storm. Undersensing did not cause any reduction in overall effectiveness; however, it did cause a prolongation in time to therapy (> 20 sec.) in 6.8 percent of the subjects.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and/or animal studies as well as data collected in clinical studies conducted to support PMA approval as described above. The S-ICD study assessed the Type I complication free rate (CFR) at 180 days. The 95% lower confidence bound (LCB) was 97.9%, which met the performance goal of > 79%.

The tests performed before and after device implant did not reveal evidence of shock damage to the heart, lung or kidneys. Discomfort occurred in 21, or approximately 7% of 321 subjects; 4 required surgery. Infections occurred in 18, or approximately 6% of subjects; 5 required surgeries (4 explants). Explants for reasons other than infection were noted in 7 subjects. Fifty-one (51) clinical events comprising 85 episodes occurred in 41 (13.1%) subjects. Twenty-five (25) inappropriate episodes occurred due to SVT detected in the shock zone, which is considered normal device function. Sixty (60) inappropriate shocks occurred due to oversensing of the cardiac signal and external noise. Inappropriate shocks occurred more frequently with borderline screening EKG or single zone programming. Reprogramming to dual zone programming reduced inappropriate shocks. Nine of 41 subjects with inappropriate shocks required surgery; the remaining 32 were resolved by reprogramming. Overall

85 of 204 treated episodes in the IDE study (41.7%) were inappropriate for SVT with ventricular rates in the shock zone (12.3%) and oversensing (29.4%).

C. Benefit-Risk Conclusions

The benefits and risks of this new SICD® were demonstrated in acute and long term clinical studies including the IDE study which was a prospective single arm trial that followed subjects for a minimum of 6 months with over a 100 patients followed for a year. The S-ICD® demonstrated high effectiveness for terminating induced VF episodes at the time of implant. It also demonstrated high effectiveness for terminating induced VF episodes at 150 days post implant in a subset of the study cohort as well as terminating the ventricular tachyarrhythmia in subjects who had spontaneous ventricular arrhythmias. The design of the S-ICD® allows it to be implanted subcutaneously without the need for intravascular lead placement and in most cases without the need for fluoroscopy imaging at implant.

The premarket prospective study was well designed and well conducted. The safety profile appears favorable; the most common adverse events included patient discomfort, infections, and inappropriate shocks. There were also uncommon instances of inability to defibrillate VF and undersensing of VF resulting in a prolonged time to therapy in which two instances were greater than 30 seconds. Inappropriate shocks can be somewhat mitigated by appropriate programming of the device parameters and dual zone programming. Detection of inability to defibrillate VF and undersensing of VF can be determined with defibrillation threshold testing at implant. The ECG screening tool minimizes risk of inappropriate shocks due to double counting of sensed beats. One of the benefits of the S-ICD® compared to transvenous ICD systems is the nonvascular location of the implant which lessens the risk of the implant procedure complications and also lessens the long term risk of systemic infection involving cardiac structures. The S-ICD® however does not have certain capabilities that transvenous ICD systems can perform such as recording all tachyarrhythmia episodes rather than only recording those that result in a shock, providing long term bradycardia pacing or antitachycardia pacing which is effective in terminating arrhythmias and preventing shocks. The overall results are generalizable to patients who meet ICD implant criteria and do not require anti-bradycardia or anti-tachycardia pacing.

In conclusion, the data support the use of the S-ICD® in patients who are indicated for an ICD and do not have bradycardia requiring pacing or ventricular tachycardia that can be terminated with anti-tachycardia pacing. The benefit of successfully terminating a ventricular rhythm and restoring normal rhythm outweigh the probable risks of the implant procedure and long term risks of the S-ICD.

The Circulatory System Devices panel members agreed with restricting the device to patients who do not need either anti-bradycardia or anti-tachycardia pacing. The panel also stated that implanting physicians should have sufficient training and experience to appropriately select patients for the S-ICD, as well as implant the device and provide long-term management of the device and arrhythmias.

D. Overall Conclusions

The data in this application provide a reasonable assurance of safety and effectiveness of the S-ICD® System when used in accordance with the indications for use. The primary safety and effectiveness endpoints were both met. The preclinical and clinical testing demonstrated that the design requirements of the device were met. The data provided reasonable assurance through response to induced and spontaneous episodes that the device functioned as intended. Also regarding device longevity, the test data showed that the number of available shocks to patients over the life of the S-ICD® system was sufficient. Regarding safety, the incidence of inappropriate shocks was found to be comparable to that of transvenous ICDs. Infection and discomfort rates occurred at acceptable levels.

XIII. CDRH DECISION

CDRH issued an approval order on September 28, 2012. The final conditions of approval cited in the approval order are described below.

The conditions of approval consist of the "Conditions of Approval for Implantable Defibrillators and Programmers". The results of on-going reliability tests will be provided for review in the annual reports. In addition a post-approval study which will consist of continued follow-up of patients who participated in the S-ICD® clinical investigation and prospective enrollment of patients newly implanted with the S-ICD® System will be conducted. The patients will be followed for a period of 5 years. The post-approval study will provide performance data in the treatment of induced and spontaneous episodes of ventricular tachyarrhythmias and provide an analysis of procedure and system related adverse events.

The applicant's manufacturing facilities 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.

Post-approval Requirements and Restrictions: See approval order.